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COMMENTARY

Chronic Abdominal Discomfort Syndrome (CADS): A Narrative Review of Treatment Strategies

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Abstract: Chronic Abdominal Discomfort Syndrome (CADS) is a recently proposed term that is a subclassification of Chronic Abdominal Pain, characterized by symptoms affecting clinical, diagnostic, and functional domains. Patients with CADS often have a history of abdominal surgery and experience chronic gastrointestinal symptoms such as nausea, bloating, vomiting, and dyspepsia. This review explores the underlying pathophysiology of CADS, emphasizing the role of the sympathetic and parasympathetic nervous systems in pain transmission. Various pharmacological treatments are discussed, including acid suppressants, antispasmodics, and analgesics, highlighting their effectiveness and limitations. Non-pharmacological approaches such as intrathecal pumps, nerve blocks, peripheral nerve stimulation, and spinal cord stimulation are also examined, providing insights into interventional pain management strategies. The review underscores the necessity of an individualized treatment algorithm due to the complexity of CADS and the multiple pain generators involved. Ultimately, this paper advocates for a structured approach to CADS treatment, incorporating both emerging and established therapeutic options.

Keywords: chronic abdominal pain, abdominal discomfort, abdominal pain treatment

Introduction

Chronic Abdominal Discomfort Syndrome (CADS) is a diagnostic subclassification of Chronic Abdominal Pain that was proposed in the article "Chronic Abdominal Discomfort Syndrome (CADS): Defining and Discussing a Novel Diagnosis".[1] Approximately, 1–2% of adults live with some form of chronic abdominal discomfort.[1] The diagnosis is supported by signs or symptoms across three domains (clinical criteria, diagnostic criteria and functional criteria) having greater than fifty percent positive clinical criteria and one-hundred percent positive diagnostic and functional criteria. Clinical criteria include items such as abdominal bloating, nausea and vomiting. Diagnostic criteria include no findings of acute pathology and good response to anesthetic blocks. Functional criteria are measured through the Short-Form 36 survey showing decrease in daily function (Figure 1). Individuals suffering from CADS often endorse histories of previous abdominal surgery with or without potential neuronal injury secondary to entrapment, adhesions or neuroma formation. These patients may concomitantly carry additional gastrointestinal diagnosis comorbidities and report symptoms consistent with those of chronic pancreatitis, suffer from abdominal bloating, nausea, vomiting or dyspepsia.[1]

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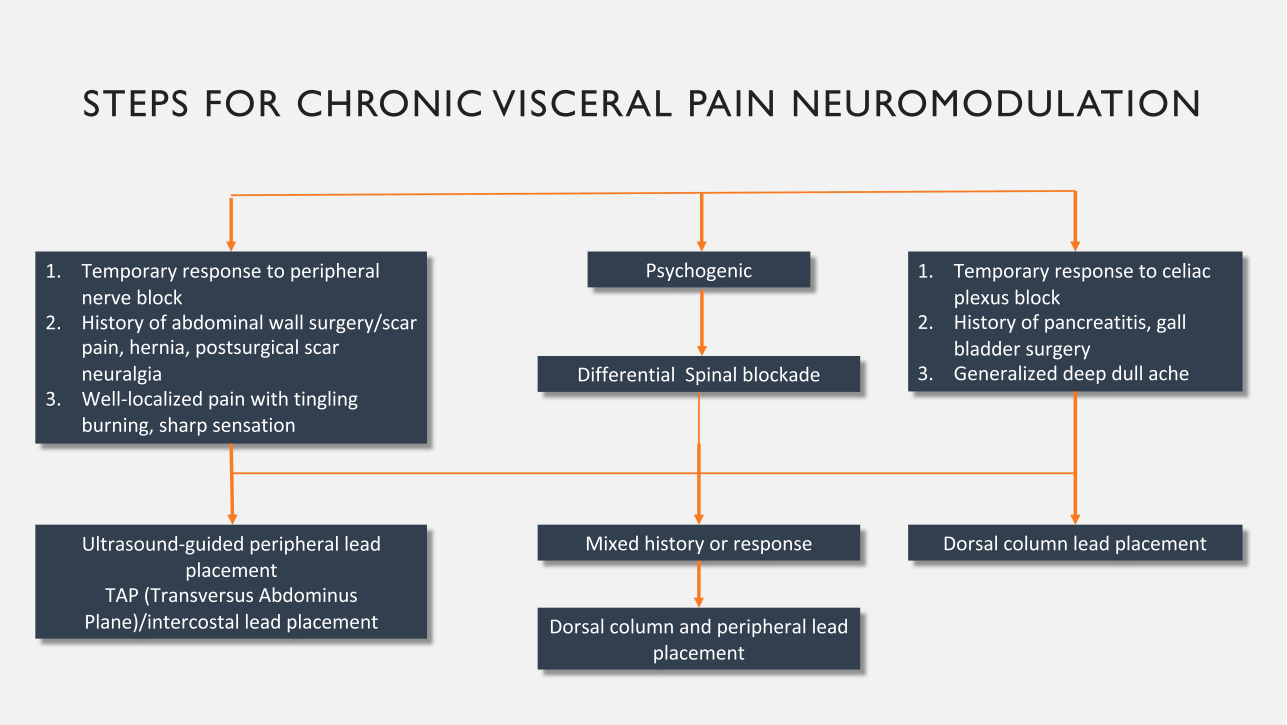

Figure 1 A proposed neuromodulatory approach to visceral pain predominant patient presentation.

In this review, we explore treatment modalities and propose a treatment algorithm for CADS. As outlined in the first paper, "Chronic Abdominal Discomfort Syndrome (CADS): Defining and Discussing a Novel Diagnosis",[1] the nerves involved in the pathophysiology of CADS include the visceral sympathetic, parasympathetic and spinal nerves that ascend via the spinal cord up to the brain.

It is important to recognize the sympathetic ganglia as a collection of sympathetic fibers arranged in a chain on either side of the vertebral column.[2] This network of fibers extends the region of sympathetic fibers beyond spinal cord levels T1-L2. These fibers can merge together to form prevertebral ganglia which are located along the anterior surface of the abdominal aorta, eventually extending to innervate structures such as smooth muscle and glands.

It is also important to note the phenomenon of referred pain, which occurs secondary to the close proximity of the visceral and somatic fibers within the abdomen. Clinically, this manifests as pain from internal organs referring to sites on the body wall and elsewhere.[3] Understanding the basic neural pathway of the abdomen and its contents is imperative, as this provides therapeutic targets. Viscero-visceral, viscero-somatic, viscero-cutaneous chronic pain convergence may be confusing for the patients, and frequently, discovering the source of abdominal pain may difficult for clinicians. Furthermore, approximately 50% of abdominal pains remains to be of unknown source.

Methods

Treatment approaches were broadly split into sections based on published literature and clinical utility. Selected approaches include: pharmacological agents, intrathecal pumps, nerve blocks, peripheral nerve stimulation, vagus nerve stimulation and spinal cord stimulation. Databases including PubMed, Google Scholar and Cochrane Library were searched for literature pertaining to each treatment approach. Preliminary search terms included the selected approach followed by "for chronic abdominal discomfort OR pain." When possible, randomized control trials were preferentially cited in addition to meta-analyses and systematic reviews. Due to the exploratory nature of this narrative review, case series and reports were also mentioned for novel treatment modalities. It is important to note that one aim of this article to present all known treatment approaches while acknowledging limitations of specific modalities at a larger scale without further randomized control trials.

Pharmacological Approaches

Pharmacological approaches to treatment of Chronic Abdominal Discomfort Syndrome are generally determined by suspected etiology. Typically, this involves generalized tenderness of the abdomen, bloating, nausea, vomiting or dyspepsia. In addition, objective imaging via radiology or direct vision may play a role in decision-making.

Symptoms of abdominal pain accompanied by sensations of burning, bloating, belching are indicative of concurrent dyspepsia. Current popular over-the-counter medications include calcium carbonate and bismuth subsalicylate. Calcium carbonate may reduce discomfort by decreasing the relative amount of acid present in the stomach via neutralization.[4] Bismuth subsalicylate acts by forming a protective coating around the intestinal mucosa and increasing water absorption in the large intestine.[5] If the patient fails these first-line therapeutics, one can consider acid suppressants such as H2-receptor blockers (cimetidine) and Proton Pump Inhibitors (pantoprazole). Proton Pump Inhibitors demonstrate superior response rates compared to H2 blockers and placebo.[6] These medications can be used in addition to direct management of the abdominal discomfort and pain.

Typically, if abdominal pain has a more chronic nature and can be attributed to either irritable bowel syndrome, functional dyspepsia or centrally mediated abdominal pain syndromes (CADS included), antispasmodics have demonstrated strong efficacy.[7] Medications with antispasmodic mechanisms of action include anticholinergic medications, calcium channel blockers and direct smooth muscle relaxants.[8] Commonly utilized anticholinergic/antimuscarinic agents used in treatment for irritable bowel syndrome in the United States include dicyclomine, hyoscine and hyoscyamine. These medications have been reported to decrease abdominal cramping and pain when compared to placebo.[9,10] Although commonly used in irritable bowel syndrome management, generalized abdominal cramping can be treated with anticholinergic medications, which are often also prescribed for acute distress such as secondary to viral gastritis. Direct smooth muscle inhibitors include Mebeverine, which did not demonstrate significant benefit when compared to placebo in controlling spasmodic symptoms of IBS.[11] Less frequently utilized, calcium channel blockers such as alverine citrate have also demonstrated only minimal difference compared to placebo in controlling cramping and spasming abdominal pain.[12]

Given the frequent gastrointestinal side effects associated with opioids, the use of opioids is typically avoided as the first line of treatment with acute abdominal pain. One paper discusses a treatment algorithm for pain associated with inflammatory bowel disease (IBD) and reports the efficacy of opioid use for acute pain, but also discusses the limited evidence presented on the use of opioids for IBD or other chronic abdominal pain conditions.[13] Several research studies have demonstrated that opioids do not improve quality of life scores in patients with chronic abdominal pain conditions.[13] Given the vast number of side effects associated with opioid use, atypical opioids have garnered new interest as a possible treatment option. Partial opioid receptor agonists, such as buprenorphine, offer reduced withdrawal effects and have a better safety profile.[14] Additionally, several studies have noted the use of buprenorphine in chronic abdominal pain conditions such as IBD to have better pain control with decreased side effects compared to traditional opioids.[15] Another review conducted on the use of opioids for chronic abdominal pain identified limited clinical evidence for the use of long-term opioids for the treatment of chronic abdominal pain.[16]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesic medications appreciated for their antipyretic and anti-inflammatory properties. The primary mechanism of action of NSAIDs is inhibition of the cyclooxygenase enzyme, which functions to convert arachidonic acid into substances such as prostaglandins that play a role in nociception.[17] There are two separate types of cyclooxygenases: COX–1 and COX–2, both of which are important in maintaining gastrointestinal mucosa, kidney function and platelet aggregation.[18] Subsequently, inhibition of COX–1 and COX–2 can lead to detrimental effects manifesting as gastric ulcers, worsening kidney function and difficulty with blood clotting. At present, the most prescribed NSAIDs on market are ibuprofen, aspirin and naproxen, the last of which is a selective COX–2 NSAID that primarily decreases inflammation while minimizing damage to gastric mucosa.[19] It is not recommended that patients be treated with NSAIDs long term for pain management, as approximately one-third of patients consuming NSAIDs will develop symptoms such as dyspepsia and gastroesophageal reflux disease.[20] The most common and potentially dangerous complication of NSAID usage is peptic ulcer development, which can often occur with no prior warning symptoms. Compared to non-users, the risk of complications secondary to gastroduodenal peptic

ulcers are 5 times more frequent among those consuming NSAIDs long term.[21] Considering the neuropathic etiology of CADS, the question of whether NSAIDs in general have any benefit for use in chronic neuropathic pain. In a Cochrane review published in 2015, two studies involving 251 participants with neuropathic etiology of pain were administered NSAIDs and monitored for pain score improvement. Results produced no evidence to support or refute the use of oral NSAIDs to treat neuropathic conditions, with only third tear evidence (very low quality) supporting usage.[22] Given increased risk versus benefit for the use of NSAIDs and treatment of general chronic pain, it is not advised that NSAIDs be prescribed for treatment of suspected CADS.

Intrathecal Pumps

An option to consider in the management of chronic pain that is intractable to oral pharmacological therapy, injection therapy and surgical correction is intrathecal analgesic administration. This is accomplished through an implantable device which consists of a reservoir containing opiates or non-opioid intrathecal drugs that are then delivered by way of a silastic catheter into the intrathecal space. In doing so, the medication is directly targeted to the central nervous system and can reduce adverse effects or side effects seen in escalated doses of oral medications. It is important to note that only 3 medications have been approved and labeled by the United States Food and drug administration for intrathecal delivery: Morphine, ziconotide and baclofen. Despite this labeling, several other agents have been used as adjuvants to these drugs, including bupivacaine and clonidine. These drugs are within the standard of care and well supported in the literature.[23] Specifically for pain management, morphine and ziconotide are most often used in intrathecal pumps to assist in dampening ascending pain-related neural activity. Contraindications to consider prior to intrathecal pump implantation for chronic pain include unresolved coagulopathy, immunosuppression, active untreated drug addiction, active suicidal or homicidal ideation, use and systemic or localized infection.[23] In addition, ziconotide is contraindicated in those with a history of psychosis.[23] A stringent selection criterion should be utilized, as intrathecal pumps are not indicated for use for widespread pain, headaches or fascial pain.[23]

Low dose initiation of intrathecal drugs is an important strategy to reduce side effects and prevent the change of tolerance. In the past, the recommendation of using a dosage of intrathecal morphine of approximately $1/300^{th}$ of the patient's total oral morphine dosage has been theorized, although new dosing strategies include more specific dosing quantities.[23,24] Like oral morphine, adverse effects of which to be wary include respiratory depression, histamine release mediated pruritus and nausea or vomiting. One must also be wary of urinary retention secondary to inhibition of the sacral parasympathetic system leading to relaxation of the detrusor muscle.[25]

Nerve Blocks

In patients who fail oral medications or other analgesic interventions, a celiac plexus block may be performed for management of intractable abdominal pain. Although this is a therapy most studied in abdominal cancer patients, the involvement of nerve pathways makes this a reasonable target for the treatment of CADS. The targets of this block are the visceral afferent pain fibers which innervate multiple abdominal organs such as the liver, gallbladder, stomach, pancreas, spleen, kidneys, and small bowel.[26]

The celiac plexus itself is composed of the celiac, superior mesenteric and aorticorenal ganglia, all of which contribute to create a neural network known as the solar plexus.[27] Sympathetic and parasympathetic nerves originating from the anterior lateral horns at levels T5 and T12 of the spinal cord also contribute to the celiac plexus.[28,29] Given its complexity, this plexus serves many functions; however, most relevant is a conduit for transmitting visceral pain signals from the abdominal organs to the central nervous system – serving as a prime target for neurolytic blocks.

In those with cancer or at end of life, a neurolysis is commonly performed by injecting 50–100% ethanol in addition to a long-acting anesthetic such as bupivacaine per patient tolerance.[30] Anatomically, the ganglia are located in the retroperitoneal fat, anterolateral to the aorta and posterior to the stomach and pancreas at the level of T12 or L1 just below the celiac artery.[31] The celiac plexus can be accessed either through a posterior or anterior approach, with posterior being more common. Within the posterior approach, variations include antecrural, retrocrural, trans-intervertebral disc and transaortic. Interestingly, analgesic outcomes have not been demonstrated to differ based on approach, and therefore should be optimized to each patient's anatomy and comorbidities.[32]

A systematic review and meta-analysis was published in 2023 concerning the efficacy and safety of celiac plexus neurolysis for the treatment of chronic pain in the abdomen secondary to oncological pathology. A total of 744 publications were reviewed, and it was concluded that celiac plexus neurolysis for the treatment of severe chronic abdominal pain provided pain relief similar to that of conventional pharmacological therapies.[33]

A component of the celiac plexus is the splanchnic nerve, which has also been a common target for neurolysis. In a retrospective study performed on patients with distorted celiac axis and anatomy not amenable to plexus neurolysis, splanchnic nerve blocks were determined to provide significant pain relief, decreased opiate intake, improved functional status, and overall improved quality of life for up to 3 months.[34] The primary benefit of targeting the splanchnic nerve is increased specificity. In a study of 16 patients with chronic abdominal pain who received both celiac and greater and lesser splanchnic nerve blocks, Kapural et al identified improvement of pain scores from a baseline of 7.24 to 4.1 with celiac plexus blocks versus 7.8 to 2.9 following T11 bilateral splanchnic nerve blocks at 4 weeks postinjection. Duration of pain relief was also reported for a median of 56 days with splanchnic nerve blocks versus 21 days for celiac plexus blocks in the same patients who received both procedures.[35] Currently, there are only case reports of positive responses to radiofrequency ablation of the splanchnic nerve and superior hypogastric plexus for chronic abdominal pain after abdominal surgery. Noor et al published a case report in 2020 that suggested significant pain relief in a patient with chronic abdominal pain status post Whipple procedure for pancreatic cancer.[36] A recent propensity matched retrospective analysis of 62 patients receiving either RFA of splanchnic nerves or spinal cord stimulation suggested that most of the patients benefited greatly from RFA. Post RFA, a majority of patients reported >50% of pain relief at up to 6 months following RFA, with 30% endorsing effect up to one-year post ablation. Eventually, repeated RFA would be needed.[35]

Role of PNS

The mechanism of action of Peripheral Nerve Stimulation (PNS) is hypothesized to relate to the gate control theory. Essentially, the dorsal horn at the spinal cord, which receives sensory input, is in a balance between non-nociceptive and nociceptive input that is regulated by gates. The main conduction pathway for nociceptive input comes from small-diameter fibers which open the gate for nociceptive input. PNS stimulate large-diameter fibers that are the pathway for non-nociceptive gate activation. Thus, using PNS to drive non-nociceptive stimuli should skew gate balance against pain.[37]

The ideal candidate for a PNS implant should satisfy the following criteria:

1. Pain consistent with the sensory distribution of a single peripheral nerve, with exceptions for generalized pain conditions (such as CADS) that overlap two peripheral nerve targets.
2. A positive diagnostic peripheral nerve block can be supportive, although this has not demonstrated correlation with long-term outcomes. Therefore, a negative diagnostic peripheral nerve block does not completely disqualify a patient from PNS implantation.
3. Exclusion of treatable nerve entrapment neuropathies.
4. The patient is stable in issues such as severe anxiety and depression, is not suicidal and has no untreated substance addiction issues.
5. The patient or caregiver can operate the peripheral nerve stimulator independently and has access to routine follow-up with a pain specialist who can assess and treat long-term outcomes or complications.
6. The patient has no adhesive allergies or skin issues that make it difficult to use wearables when required.

These recommendations were adapted from "An Advanced Practice Provider Guide to Peripheral Nerve Stimulation" by Hoffmann et al.[38]

Targeting

Transverse Abdominis Plane (TAP) blocks are a primary approach for providing analgesia to the parietal peritoneum, muscles and overlying skin of the anterior abdominal wall.[39] Often, this procedure is reserved for pre- or post-abdominal procedure pain management, and can result in appreciable decreases in nausea, vomiting and opiate utilization.[40] In a retrospective chart review by Abd-Elsayed et al, ninety-two patients with chronic abdominal pain were determined to

experience a 50.3% improvement in pain scores for up to one-hundred eight days.[41] Reports in the extant literature also exist of inserting continuous flow catheters within the TAP, providing continuous, long-term pain relief for up to nine months following a two-week catheter implantation period.[42] It has been hypothesized that long-term analgesic and therapeutic effects can result from neuromodulation of the nerves within the transverse abdominis plane. Although lacking broad clinical deployment, this technique has been outlined by Lam et al with placement of a peripheral nerve stimulator just below the internal oblique using ultrasound.[43] Initial programming parameter recommendations are a frequency of 80 hertz, pulse width of 400 microseconds and amplitude between 1500 and 3000 milliamps.[43]

Nerve roots T7-T11 (thoraco-abdominal nerves) extend anteriorly to form the thoracic intercostal nerves which are found in the intercostal spaces and extending into the abdominal wall.[44] In a case study, implantation of PNS at the T11 level of the thoraco-abdominal nerve programmed to 500ms, 80Hz, 2–3mA was determined to reduce opioid usage by approximately 50% at the four week mark. By the 10 month follow-up period, the patient was completely pain free and not on any pharmacotherapeutics.[45] However, systematic study of this finding will be necessary in order to determine efficacy beyond anecdote.

The subcostal nerve is another target of TAP blocks, providing anesthesia to the upper and lower abdomen, depending on the selected approach.[46] Although there is a paucity of literature on targeting the subcostal nerve with PNS, a feasibility study describes subcostal nerve stimulation-guided TAP blocks. The targeted region was at the midpoint between the costal margin and iliac crest in the midaxillary line. Confirmation was provided through observed twitches of the abdominal wall following nerve stimulation and an overall success rate 75%.[47] Using such targeting, pain relief would be primarily in the lower abdomen, as the technique has similarity to lateral or posterior TAP blocks.

The iliohypogastric nerve (T12-L1) originates from the superior branch of the ventral ramus of the L1 spinal nerve, emerging from the lateral border of the psoas major muscle posteriorly and extending laterally to pierce the transverse abdominis muscle superior to the iliac crest. Pain targets should include the inferior portions of the transversus abdominis, external and internal oblique muscles.[44] Elahi and colleagues have published a case series in which they used PNS for treatment of intractable abdominal pain following inguinal herniorrhaphy. The stimulation parameters were 1mV amplitude with 300 pulse width and 80 Hz frequency. Results suggested a reduction in pain scores from an average of 9/10 prior to implantation with reduction to 1–2/10 3–5 years post-procedure.[48] Again, systematic research is needed in order to further the assess the efficacy of this procedure.

Nerve Field Stimulation

As an alternative to implanting PNSs in proximity to an identified nerve, Paicius and colleagues demonstrated benefits in pain reduction with implantation of PNSs within the general distribution of abdominal pain.[49] Their rationale was that the nerves mediating pain signals from the abdomen synapse were in the same spinal cord segments as the somatic spinal nerves.[50] Each lead was placed under the dermis, sufficiently superficial to be palpated through the skin. Patients' feedback was used to implant the leads in the area of maximal pain. Eight contact array leads were used, allowing for a greater area of coverage and programming options. In all implanted patients, the most effective programming involved continuous cycling of stimulation with a five-minute on and five-minute off. This method should be approached with caution, however, as there is currently minimal evidence of long-term efficacy.

Measures of Efficacy

Some commonly used measurable outcomes of efficacy include:

1. Patient reported decrease in pain Visual Analog Pain Score
2. Improvement in SF36 Quality of Life Score
3. Reduction in pharmacotherapy dose
4. Resolution of secondary symptoms (nausea, dyspepsia, abdominal bloating)
5. Length of time symptoms have remained improved after implantation

Vagus Nerve Stimulation

A potential target for neural control of the GI tract is the autonomic system, which is comprised of both the sympathetic and parasympathetic divisions. Focusing on the parasympathetic division, its primary role is excitatory and is communicated by the vagus nerve. The vagus nerve regulates both tone and volume of abdominal organs and vasculature primarily via communication with the myenteric motor neurons.[51] There has been considerable research on stimulating the vagus nerve (VNS) for pain of abdominal etiology. Bonaz et al discuss the bidirectional aspect of the vagus nerve, which allows communication between the nervous system and the digestive tract. They posit that there are two primary mechanisms of anti-inflammatory effects of vagus nerve – via activation of the hypothalamic pituitary adrenal axis and through vago-vagal inflammatory reflex (also known as the cholinergic anti-inflammatory pathway). The end result is inhibition of tumor necrosis factor (TNF) by macrophages, ie, the same pathway that is modulated by cytokines and is a pharmacological target for current therapeutics against Crohn's disease and ulcerative colitis.[52]

Vagus nerve stimulators are implanted in the left vagal nerve neck area at the carotid artery, as the left side bypasses any regulation of heart rhythm.[53] Stimulation parameters can vary from continuous to including OFF phases, typically at 0.25 milliamps at low frequency (1–10Hz) to prefer efferent stimulation of the vagus nerve.[54]

In a pilot study by Sinniger et al, 8 patients with Crohn's Disease were implanted with vagus nerve stimulators with severity of disease rated at moderate to severe and not taking any anti-TNF medications. Results suggested therapeutic effects from VNS, requiring three months to be effective per decreased inflammatory markers with a more robust effect identified at twelve months. Interestingly, VNS greatly decreased the perception of abdominal pain from a Visual Analog Score of 4 prior to VNS and 1 post-procedure.[55]

Specifically, focusing on the phenomena of abdominal pain, non-invasive vagal nerve stimulation (nVNS) may offer a therapeutic benefit. Non-invasive VNS generally targets the vagus nerve at the neck (cervical vagus) or the earlobe (auricular branch).[56] It is hypothesized that the nociceptive benefits of nVNS are due to the modulation of the ventral descending pathways of pain control.[57] In a study exploring withdrawal reflex to pain stimuli in the lower limb, healthy subjects reported better tolerance of pain at five and thirty minutes post-nVNS application.[58] Focusing on the abdomen, a single center, randomized, placebo-controlled trial in adolescents from ages 11–18 years diagnosed with functional gastrointestinal disorder suggested sustained abdominal pain relief with utilization of auricular nVNS.[59]

Pasricha et al have also explored nVNS for reduction of nausea and vomiting in gastroparesis and functional dyspepsia. In a study of forty-one patients, they determined that "as needed" use of nVNS decreased rescue medication utilization and also improved pain severity, constipation, depression and migraines.[60]

The vagus nerve is a formidable target for its regulatory effects in pain and associated symptom control. Many patients diagnosed with CADS should be considered for a trial of nVNS, as this is a non-invasive, "as needed" and safe modality of neuromodulation. Caution should be taken to monitor for over-utilization and unintended side effects, including ear pain, headache and tingling sensations.[61]

Spinal Cord Stimulation

Spinal cord stimulation is a technology that can be used to treat neuropathic pain in the trunk and limbs. Patients suffering from Chronic Abdominal Discomfort Syndrome may be good candidates for spinal cord stimulation therapy targeting analgesia, increased activity levels, and quality of life post-implantation. Implantation is done in a stepwise fashion, with an initial trial period ranging from 5–7 days followed by a permanent implantation. Care must be taken prior to proceeding with this therapy, as it is significantly more invasive than oral medications. Patients should have previously failed multiple more conservative interventions and demonstrate good understanding and cognitive capacity prior to proceeding.

At present, there are several small studies demonstrating significant long-term benefit of treating chronic visceral abdominal pain with spinal cord stimulation. Specifically, in a case published in 2021 by Shearin at al., the authors identified significant improvement in patients' pain and quality of life scores up to 12 years of post-paddle spinal cord stimulator implantation.[62] Kapural et al trialed SCS in 35 patients diagnosed with visceral pain, positioning the lead tips at T4/T5. The authors determined that 86% of patients reported at least 50% relief of pain following implantation.[63] It is

Table 1 Summary Approach to Treatment of Chronic Abdominal Discomfort Syndrome

Oral Medications	Nerve Blocks ± Peripheral Nerve Stimulator (PNS) Implantation	Vagal Nerve Stimulator	Spinal Cord Stimulation	Intrathecal Pumps
Dyspepsia symptoms - Calcium Carbonate - Proton Pump Inhibitors - H2 Receptor Blockers	**Thoraco-abdominal Nerves (T7-T11)** - One study showing opioid usage decreased by 50% at 4 weeks post implant with no pharmacotherapeutics being used at 10 month follow up	**Non-invasive Vagal Nerve Stimulation (nVNS)** - Single center randomized placebo-controlled trial in adolescents with functional gastrointestinal disorder show sustained abdominal pain relief - Study of 49 patients showed "as-needed" use of nVNS decreased rescue medication utilization amongst improvements in constipation, depression and migraines	**10KhZ stim between T4-T6** - Up to 12 months of relief in 19/24 patients	- Dampen ascending pain circuitry - Morphine dosing should be around 1/300th oral equivalent - Beware urinary retention due to sacral parasympathetic inhibition
Generalized abdominal pain - Acetaminophen - Non-Steroidal Anti-Inflammatory	**Iliohypogastric Nerves (T12-L1)** - Targeting the inferior transversus abdominis, external and internal obliques - Case series showing pain scores decreasing from 9/10 to 1–2/10 up to 3–5 years post implantation of PNS for intractable pain after inguinal herniorrhaphy	**Implanted Vagal Nerve Stimulator** - Shown to decrease inflammatory markers and pain up to one year post implant in 8 patients with Crohn's disease		
Cramping type abdominal pain - Anticholinergics (dicyclomine, hyoscine, hyoscyamine) - Direct smooth muscle inhibitors (mebeverine) - Calcium channel blockers (alverine citrate)	**Subcostal Nerves (T12)** - Addressed with a Transverse Abdominis Plane block, can alter targeting to address either upper or lower abdominal pain - No publications regarding PNS for this region			
	Nerve Field Stimulation - Sparse data supporting PNS lead placement in the general distribution of abdominal pain			

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important to note that the evidence-basis of the longevity of therapeutic efficacy is currently being developed. Researchers in a prospective study (IDE with FDA) have determined that stimulating spinal cord at 10 kHz between the T4-T8 level can provide up to 12 months of relief in 78.3% of subjects in a 24-patient cohort.[64] Clinical outcomes in the study were assessed in a comprehensive manner, with data not only on pain intensity but additionally on pain characteristics through the Short Form McGill Pain Questionnaire 2, mental health status using the Global Assessment of Functioning, and overall wellbeing using the Short Form Health Survey (SF-12). These are all important parameters to consider in the treatment of CADS given its broad implications. However, given the small study size, larger studies are certainly needed if longer-term efficacy is to be established.

Interestingly, in a comparison between 10 kHz spinal cord stimulation versus radiofrequency ablation of splanchnic nerves for chronic abdominal pain, a study of 62 patients (31 in each group) suggested significant improvement in pain scores in both groups at one year, with greater improvement in mean reduction of pain scores in the SCS group.[65] It is important to note that the goals of both therapies of decreasing overall opiate use as well as decreasing pain scores were achieved. Interventional therapies were part of a multidisciplinary approach which should be deployed in the treatment of CADS and tailored to the patients' goals. Additional prospective randomized studies are needed to better understand the best use of SCS in CAD syndromes.

A proposed summary of steps to approach chronic visceral pain per reviewed studies are outlined in Figure 1.

Conclusion

The use of many interventions exist to treat those who suffer from CADS. The current literature is mixed, with a complex issue of many pain generators causing this syndrome. This complexity suggests the need for a pain treatment decision tree that will improve patient care as we advance the therapies offered to each patient in an individualized fashion. The evidence presented in this review serves only to provide initial guidance. It is important to note that there is limited evidence for some discussed therapeutics which require further research. Specifically, an expansion of study caliber to support SCS and PNS in abdominal pain should be undertaken. A simplified diagram of available options is shown in Table 1 with progression of treatment from left to right. Finally, there is the need to update this guidance moving forward with prospective studies and consensus guidelines. We are confident that the body of empirical literature supporting such treatments will continue to grow and lead to better standardization of management.

Disclosure

Dr Peter Staats reports personal fees or grants from electroCore, nalu, saluda, AIS, Biotronik, outside the submitted work. In addition, Dr Peter Staats has a patent "Vagus Nerve Stimulation" licensed to electroCore. Dr Michael Schatman is a senior medical advisor for Apurano Pharma, outside the submitted work. Dr Hemant Kalia is a consultant for Abbott, nalu, curonix, Averitas, spr therapeutics, during the conduct of the study. Dr Dawood Sayed reports personal fees from PainTeq, Abbott, and Saluda; reports stock options from PainTeq and Surgentec, outside the submitted work. Dr Amol Soin reports research for Neuros medical, Avanos, and Neuronoff, outside the submitted work. In addition, Dr Amol Soin reports multiple patents related to neuromodulation issued to several pharmaceuticals. Dr Ganesan Baranidharan reports personal fees and/or grants from Nevro Corporation, Abbott, Mainstay Medical, Boston Scientific, and Saluda Medical, outside the submitted work. Dr Alaa Abd-Elsayed is a consultant for Medtronic, Curonix, Avanos and Averitas. Dr Timothy Deer reports personal fees for consultant, research and/or stock options from Abbott, SpineThera, Saluda Medical, Cornerloc, Boston Scientific, Pain Teq, Spinal Simplicity, SPR Therapeutics, Biotronik, Aurora, and Nervonik, during the conduct of the study. In addition, Dr Timothy Deer has a patent pending to Abbott. The authors report no other conflicts of interest in this work.

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