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Harnessing Our Knowledge About Voltage-gated Sodium Channels to Better Manage Disorders of Abdominal Pain Perception in Inflammatory Bowel Disease

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Abstract: Abdominal pain remains a major issue in health care. It is commonly associated with numerous conditions, frequently impacts individual quality of life, and is one of the most important determinants of healthcare expenditures and lost work hours in digestive disease, including inflammatory bowel disease (IBD).[1-5] Additionally, there are no analgesics that have been designed specifically to address visceral pain, and the most commonly used medications to address abdominal pain in IBD are all associated with serious potential side effects.[6] Patients and healthcare providers remain desperate to find new, safer and more effective analgesics. The pathological absence of abdominal pain in disorders such as Crohn's disease (CD) and ulcerative colitis (UC) (also known as hypoalgesic or silent IBD) also poses a significant problem, as those affected may be unaware of the presence of chronic inflammation, and this can lead to the development of serious complications that might otherwise have been avoided.[7,8] Growing evidence indicates that voltage-gated sodium channels (VGSCs) play a critical role in transmission of pain-related signals throughout the body. These channels have strong potential to provide critical insights into disorders of abdominal pain in IBD, as well as to help investigators develop new, more selective, safer, and effective analgesics to manage this symptom in these and other related disorders.

This article provides a brief overview of the role that VGSCs have related to pain, with a special focus on pain derived from the viscera. It also discusses what is known regarding the potential for specific channels to serve as novel diagnostic tools and/or analgesic targets in IBD, as well as other chronic digestive disorders. Additionally, it will summarize current management approaches to abdominal pain and the pathological absence of abdominal pain in IBD, and how our knowledge of VGSCs can help improve care for these patients.

Key words: Voltage gated sodium channel, abdominal pain, inflammatory bowel disease.

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Abbreviations used in this paper: PEP, pancreatic enzyme products; DC, digestive capacity; PERT, pancreatic enzyme replacement therapy; FE-1, fecal elastase; EPI, Exocrine Pancreatic Insufficiency; SIBO, small intestine bacterial overgrowth; H2, histamine receptor 2; MCTs, medium chain triglycerides.

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1. Background

What are voltage-gated sodium channels, and why are they important in pain?

Voltage-gated sodium channels are transmembrane proteins that help to regulate the membrane potential of cells.[9] In brief, they provide a hydrophilic corridor that permits regulated movement of sodium ions through the hydrophobic phospholipid bilayer of eukaryotic cells. Nine different VGSC isoforms have been identified in humans, designated $Na_v1.1$ through $Na_v1.9$, based upon the order in which each isoform was recognized.[10,11] VGSCs are differentiated based upon their alpha subunits, which contain six alpha-helical transmembrane segments that are folded into four domains that form the aforementioned pore.[12] Each isoform is made up of one alpha subunit and one or more beta subunits. The alpha subunits determine the specific function of each VGSC isoform, including ion selectivity, expression location, and overall channel function. Beta subunits affect gating and signaling functions of each channel, while also helping to anchor these channels within the cell membrane (Figure 1).[13,14] A more comprehensive review of the structure and physiology of each VGSC can be found in Coates et al.[15] and Heinle et al.[16] Of note, VGSCs are encoded by the *SCN* gene family, which are numbered 1-11A. These gene designations correspond in order with the isoforms described above, except for SCN6-7, which encodes Na_vx (a potential VGSC that is not yet fully characterized).[17,18]

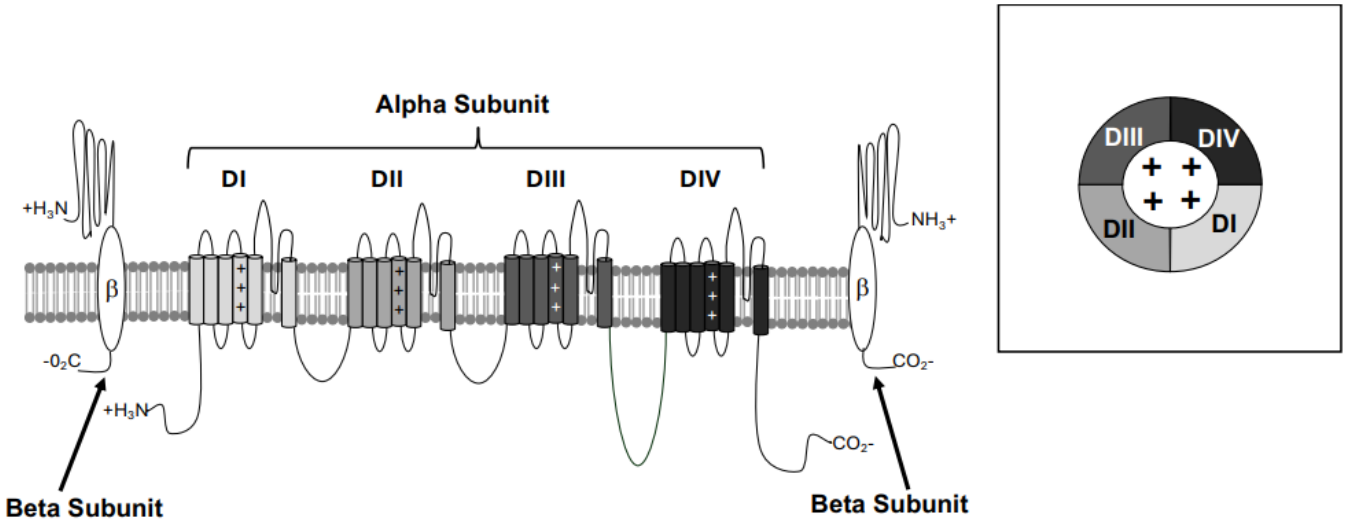
The precise functions of different channels vary. However, all of the VGSCs are critical determinants of the excitability of cells, including in neurons, muscles and endocrine cells, and they play important functions related to the contractions of muscle and the initiation and propagation of action potentials.[18] VGSCs are also expressed throughout the human body. Some isoforms appear to be preferentially expressed in either the central nervous system (CNS), or peripheral nervous system (PNS), but most of them are found in both (e.g., $Na_V1.1$ - $Na_V1.3$, $Na_V1.5$ and $Na_V1.6$).[19] Importantly, though, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are almost exclusively expressed in the PNS, and frequently on primary sensory neurons.[18, 20] In particular, $Na_v1.8$ is strongly associated with expression in dorsal root ganglion and trigeminal ganglion neurons[21], primarily in neurons that exhibit a major role in transmission of pain-related (nociceptive) signals.

How do we know that VGSCs play an important role in pain perception?

Genetics have played a particularly critical role in our understanding of VGSC function, particularly as it relates to pain in humans. For example, polymorphisms associated with the genes encoding Nav1.7 (*SCN9A*), Nav1.8 (*SCN10A*) and Nav1.9 (*SCN11A*) have been linked with significant alterations in pain perception. Some polymorphisms have been associated with "gain-of-function" changes. There are over a dozen SCN9A mutations associated with inherited erythromelalgia (a condition that causes intermittent pain with exposure to heat), while at least eight SCN9A missense mutations have been linked to the "paroxysmal extreme pain disorder" (PEPD), a rare but debilitating autosomal dominant disease characterized by recurrent bouts of rectal, perianal and facial pain).[22] SCN9A variants have also been associated with increased pain in osteoarthritis (rs6746030, R1150W), while SCN9A (rs12478318, M932L; rs71428908, I228M) and SCN10A (rs968515082, 5116A>G, I1706V) variants have been linked to small-fiber neuropathies.[22-24] Others result in "loss-of-function"

Figure 1. Basic Components of a Voltage-gated Sodium Channel.

Note: Inset demonstrates proposed "overhead" simple structure of the pore created by the alpha subunits. D = domain, + = positive charge.



phenotypes, including frame-shift and nonsense mutations of the SCN9A gene (c.774_775delGT and c.2488C>T respectively), and an SCN11A mutation (rs483352920; 2432T>C) implicated in congenital insensitivity to pain syndromes[23-25], Additionally, homozygosity for one SCN10A mutation (rs6795970; G>A; A1073V) has been associated with diminished mechanical pain sensitivity.[26]

How do we know that VGSCs play an important role in visceral (abdominal) pain perception?

A multitude of studies have demonstrated that VGSCs have a significant role in human abdominal pain experience. Protein and mRNA expression for all nine VGSC isoforms has been associated with sensory afferent neurons and other cell types associated with gut nociception.[27] Electrophysiological signatures consistent with several different types of VGSCs have been identified in nerves associated with each region of the gut.[28-33] Notably, though, some VGSC isoforms (e.g., $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, or $Na_V1.4$) have not yet been otherwise linked to visceral pain perception. At least one other has been linked to abdominal pain syndromes (e.g., multiple *SCN5A* ($Na_V1.5$) variants have been linked to increased risk of irritable bowel syndrome (IBS)), but has not demonstrated a clear physiological role to explain that association.[34-36]

The VGSC isoforms that have the strongest association with human abdominal pain, and that have demonstrated physiological relationships to gastrointestinal nociception and transmission of pain-related signals, are $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$. However, several details related to exactly how each of these channels impact human abdominal pain remain unclear. For example, studies of $Na_V1.7$ and its role in visceral pain perception have been somewhat contradictory in their findings. At least one prior investigation demonstrated that pharmacological antagonism of $Na_V1.7$ leads to reduced visceral pain perception.[37] However, studies of $Na_V1.7$ knockout models exhibited no discernible impact on visceral pain.[27] As indicated above, though, human studies utilizing biopsy samples from individuals diagnosed with idiopathic rectal hypersensitivity and PEPD (a.k.a. familial rectal pain), demonstrated that $Na_V1.7$-positive nerve fibers were more frequently observed in PEPD samples when compared to healthy controls.[38] Additionally, three polymorphisms associated with *SCN9A* (the gene encoding $Na_V1.7$) have been associated with PEPD (I1461T, T1464I, and M1627K).[39]

$Na_V1.8$ appears to have a more definitive role in this regard. In fact, electrophysiological studies suggest that a large percentage of gut-innervating afferent nerves demonstrate characteristics that are most consistent with $Na_V1.8$ activity (e.g., high threshold, slowly inactivating, TTX-resistant).[40,41] Multiple animal studies demonstrated that systemic and gut-focused genetic or pharmacological antagonism of $Na_V1.8$ leads to reduction in several visceral pain modalities.[42-44] Human studies also support an important role for $Na_V1.8$ in this context (including in the setting of IBD). For example, several polymorphisms in the gene encoding $Na_V1.8$, *SCN10A* (e.g., 2884 A>G, 3218 C>T and 3275 T>C), are associated with a lower likelihood of developing visceral hypersensitivity disorders such as epigastric pain syndrome, functional dyspepsia, and postprandial distress syndrome.[45] Separate studies investigating hypoalgesic (or "silent") IBD have demonstrated that these patients are significantly more likely to demonstrate homozygosity for a different *SCN10A* mutation (1073 A>V).[7,46] Notably, no other VGSC polymorphisms (including any of those associated with insensitivity to pain described above), were associated with silent IBD. Additionally, this genotype has also been associated with reduced pain severity after sigmoidectomy surgery, as well as reduced abdominal discomfort to barostatic rectal balloon distension in healthy human beings.[46,47]

The evidence for the role that $Na_V1.9$ has in human abdominal pain function is predominantly based on animal studies. Gut-associated sensory afferent neurons in animal models incorporating knockouts of the $Na_V1.9$ gene, *SCN11A*, exhibit attenuated actional electrophysiological activity to noxious luminal distension.[48] These models also exhibit significantly reduced abdominal pain perception, particularly in the setting of inflammation.[49] Notably, no published studies to date have demonstrated a definitive association between a specific *SCN11A* variant and altered abdominal pain perception in human beings. However, $Na_V1.9$ has been linked to human intestinal motility, a factor that can influence patient abdominal pain experience. In one study of a patient bearing a *SCN11A* polymorphism causing chronic insensitivity to pain (811 L>P), they were found to have reduced GI motility during a surgery.[50]

How have these findings impacted management of disorders associated with abdominal pain?

Genetic testing is available to evaluate for the pain-related conditions and the associated polymorphisms outlined above. However, these tests are uncommonly employed in the clinical setting. This is particularly true in the context of IBD, and other disorders associated with altered abdominal pain perception. Additionally, even when these genetic tests are used, there are no therapeutic interventions currently available to address the related findings. In other words, the potential benefits of these genetic tests are currently only diagnostic.

There are recent therapeutic advancements related to VGSCs that offer hope to more effectively and safely manage abdominal pain. For example, the novel $Na_V1.8$ antagonist, suzetrigine, was approved this year for the management of moderate to severe acute pain.[51] To date, no studies have been published describing the efficacy of suzetrigine in addressing any form of chronic pain. Additionally,

and relevant to this discussion, there are no data describing its' ability to treat any form of visceral pain. There are also other $Na_V1.8$ antagonists that are either in development or being actively studied as potentially pain therapies. For example, LTGO-33 is a selective small molecule inhibitor of $Na_V1.8$, that reportedly is very specific for this channel, particularly in human tissue.[52] There are other drugs designed to target more than one VGSC. ANP-230 antagonizes $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$, and it has been found to have significant analgesic impact in a variety of animal pain models.[53] Existing analgesics also may have the potential to impact VGSC activity. As an example, the tricyclic antidepressant, amitriptyline, has demonstrated efficacy to improve chemotherapy-induced neuropathic pain, and electrophysiological studies suggests that it does so by diminishing activity of $Na_v1.8$.[54] Some cannabinoids, including anandamide, have also been shown to diminish $Na_v1.8$-associated currents in neurons.[55] Importantly, with the exception of amitriptyline, none of the targets or medications described above have been studied specifically for use in digestive disorders like IBD.

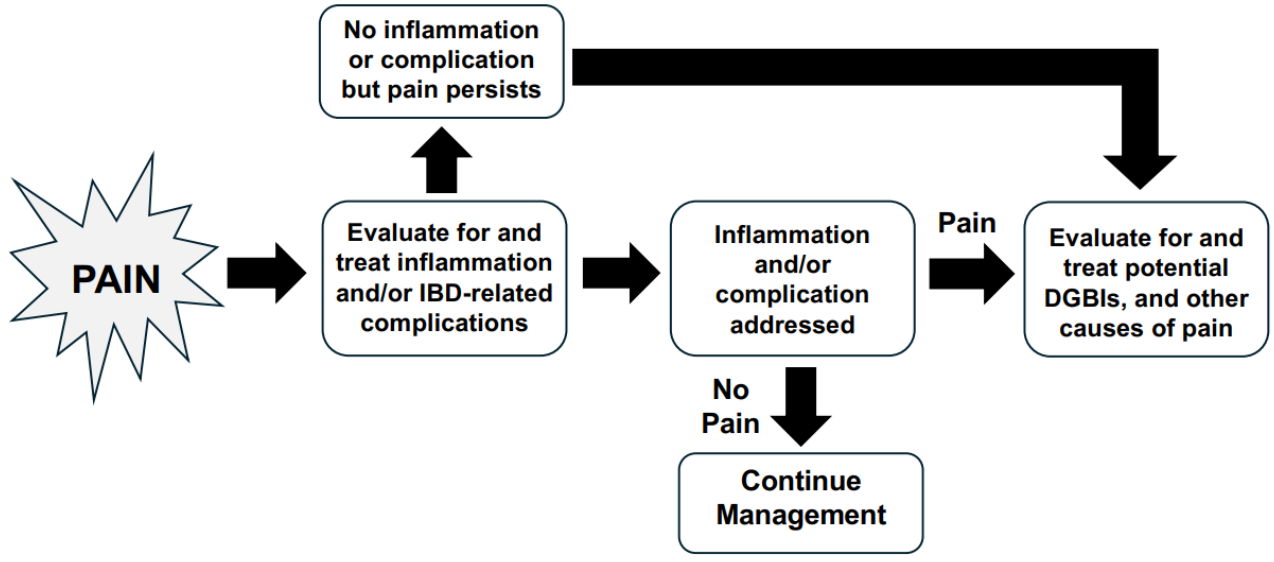
2. Clinical Pathway

Current approaches to manage abdominal pain in inflammatory bowel disease

While abdominal pain is recognized as a major problem in IBD[56], and other digestive disorders[2], there are currently no consensus guidelines describing how to effectively evaluate and manage abdominal pain in IBD. Instead, there have been several expert reviews and medical society-sponsored commentaries written to provide guidance on how to manage abdominal pain in these disorders[57-60], The associated recommendations include several common approaches to evaluate and manage abdominal pain in IBD. These include: a) obtaining a careful history to properly characterize the nature of the pain, and its potential contributing factors, b) thoroughly assessing for the presence of active disease and/or disease-related complications (e.g., strictures, fistulae, abscesses) using standard diagnostic testing (including endoscopic, histologic, radiologic and serological modalities), c) treating active inflammation and/or disease-related complications with appropriate anti-inflammatory medical therapy and/or surgery, d) prioritizing evaluation for and supportive treatment of disorders of gut-brain interaction (DGBI) in patients with abdominal pain in the absence of active inflammation, and e) employing a multi-disciplinary approach, particularly when initial efforts to manage abdominal pain fail (Figure 2a). Of note, utilization of each recommendation should be considered at each clinical encounter. Additionally, many of these steps can be employed simultaneously (i.e., they do not necessarily have to be used in sequential fashion). For example, it is always important to maintain a careful and updated history and characterization of the abdominal pain, and never too early to incorporate multi-disciplinary consultation.

These recommendations are largely uncontroversial as they are generally based in common sense principles that have been widely adopted. However, there are some important downsides associated with some of them. First, they necessarily represent a reactive approach to abdominal pain management. This is sensible from the standpoint that these recommendations are designed to make use of conventional, diagnostic strategies that most IBD providers currently have reasonable access to. However,

Figure 2a. Simplified Scheme for Current Management of Abdominal Pain in Inflammatory Bowel Disease
Simultaneous to these steps, providers are performing recurrent careful history and physicals, and employing a multi-disciplinary approach as appropriate. Note: DGBI = disorder of gut-brain interaction.



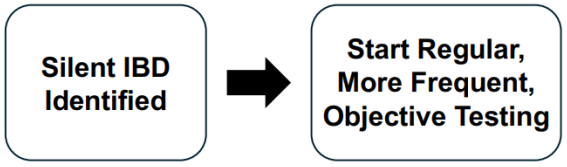
considering how common and impactful abdominal pain is in this setting, even during periods of quiescence for some patients, it would be highly advantageous to identify and utilize tools that help to predict the likelihood of developing this symptom in individual cases, in order to potentially mitigate future episodes as well as to reduce the often substantial associated healthcare costs. Second, and perhaps more importantly, there is a common tendency to conceptualize and manage persistent abdominal pain in quiescent IBD as part of a DGBI, such as IBS. While these conditions are relatively common, including in the setting of IBD, they are unlikely to explain most of the abdominal pain seen in this context.[6,58,61] Additionally, the analgesic therapies most often recommended in this context are the same as those used in DGBIs. These include tricyclic antidepressants, antispasmodics and other neuromodulatory therapies, none of which have actually demonstrated analgesic efficacy in IBD.[6] There remains a tremendous need to better understand the pathophysiology of abdominal pain in quiescent IBD, and to find safer and more effective ways to manage it.

Current approaches to manage hypoalgesic inflammatory bowel disease

There are also no currently available societal guidelines to help identify and manage hypoalgesic (silent) IBD. Expert recommendations on this topic have been published.[62,63] though it is important to note that these are largely based upon relatively limited and low quality evidence, as this condition is still understudied, inconsistently described and poorly understood. Importantly, there has also been no consensus regarding how to define silent IBD. This is part of the reason that it remains very challenging to identify this condition, particularly in individuals who have not already been formally diagnosed with a form of IBD. My colleagues and I have previously proposed the following approach to defining silent IBD[63]: an individual with IBD will be determined to have silent disease if they: a) exhibit moderate-to-severe IBD-associated inflammation of the bowel, based upon direct gross (e.g., surgical), endoscopic, histologic, radiologic (CT and MR enterography), serologic (e.g., C-reactive protein) and/or stool-based (e.g., fecal calprotectin) assessment(s), and b) are found to be in clinical remission based upon simultaneous, IBD-symptom assessment surveys (including the lack of perceived abdominal pain at the time of the objective assessments described above).

In those who do have an established diagnosis of silent IBD, the general approach previously proposed to monitor for silent disease activity is to have patients undergo one or more objective tests on a regular, scheduled basis to evaluate for bowel-related or systemic inflammatory activity (Figure 2b). The optimal surveillance interval for silent IBD has not been determined. Regardless of the testing interval relied upon. Regardless of the testing interval relied upon, this approach has the theoretical benefit that it is relatively intuitive, as it incorporates testing strategies that IBD providers are familiar with and use on a regular basis. However, it has some important drawbacks. The tests described above can be expensive and, in the case of certain endoscopies and imaging studies, challenging to get scheduled. Their efficacy in screening for silent disease is also dependent on the frequency and timing of their use, as well as the disease location. For example, if they are not employed quickly or frequently enough, significant inflammation can develop that may lead to serious complications, including strictures, fistulae and/or abscesses. On the other hand, if they are employed too frequently, costs associated with testing may be very high and patients may be exposed to unnecessary risk related to the procedures above. Additionally, if an individual has inflammation focused in the deep small bowel, certain testing modalities (e.g., stool-based fecal calprotectin and standard endoscopic procedures such as esophagogastroduodenoscopy (EGD) or ileocolonoscopy) are unlikely to be reliable indicators of current activity. Thus, depending on the strategy employed, opportunities for effectively intervening on inflammation and disease-related complications are either not guaranteed or become prohibitively expensive, onerous and even potentially risk for the patient involved. In this setting, it would clearly be advantageous for providers and patients to have access to tools that can help predict individual risk for developing silent IBD, and that may be used to better tailor screening and/or intervention strategies on the individual level.

Figure 2b. Simplified Scheme for Current Management of Hypoalgesic (Silent) Inflammatory Bowel Disease



There are currently no guidelines for managing silent IBD. Objective testing includes endoscopy, body imaging, and laboratory testing (including blood and stool tests assessing for inflammation in the gut).

3. How Voltage-gated Sodium Channels Can Help Better Manage Abdominal Pain Disorders in Inflammatory Bowel Disease

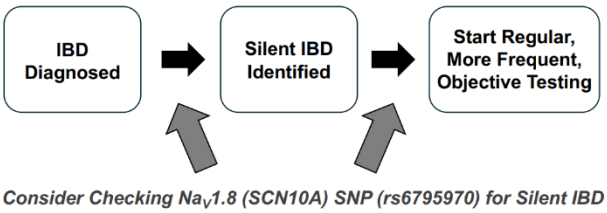
My approach to each case depends on whether or not an individual describes having abdominal pain. As indicated above, both the presence and absence of abdominal pain in IBD can present clinically significant challenges. In the

paragraphs below, I describe my general approach to each scenario, along with how our current knowledge relating to VGSCs can help to further optimize these approaches now.

For IBD patients who present with abdominal pain

In addition to taking the steps outlined above, it is now reasonable to consider additional or alternative interventions to address abdominal pain in IBD patients. For those individuals who describe persistent pain, particularly in the anorectal region, without evidence of persistent inflammation or other IBD-related complications (e.g., anorectal stricture, fistula, and/or abscesses), providers should prioritize non-toxic therapies (i.e., avoiding opioid and NSAID medications), and consider use of emerging $Na_V1.8$-targeting analgesic strategies (e.g., suzetrigine) (Figure 3a), ideally in coordination with a pain management specialist as these remain untested therapies in this setting. The latter point highlights the urgent need for further study of these agents in the context of digestive disorders, including IBD. As indicated above, it is also very important to obtain a careful history and physical examination, in part to accurately characterize the type of pain that patients are experiencing. In patients with long-standing, refractory anorectal pain that is not associated with active IBD-associated inflammation or complications, providers can explore genetic testing for $Na_V1.7$ (*SCN9A*) polymorphisms associated with PEPD. While this approach does not currently lead to novel pain management treatment(s), it could provide diagnostic resolution for what are frequently challenging and frustrating clinical situations. It is important to note, though, that these are relatively rare variants that require specialty genetic testing that is not necessarily easily available to most IBD providers.

Figure 3b. Using VGSCs to Help Manage Hypoalgesic (Silent) Inflammatory Bowel Disease



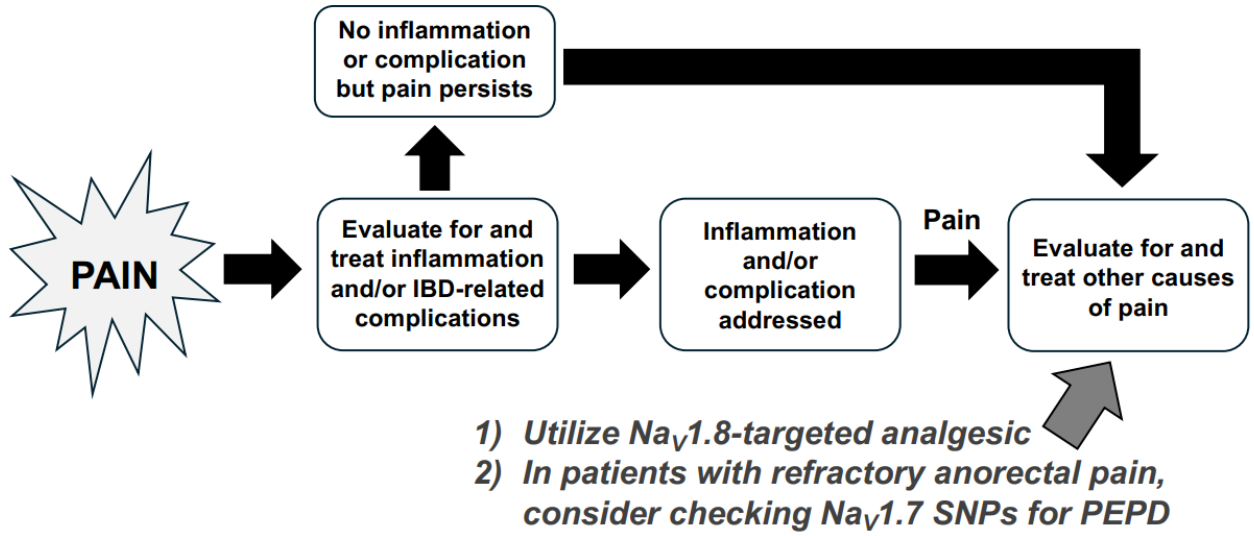
Early testing for the NaV1.8 (SCN10A) polymorphism, rs6795970, can help to stratify risk for silent IBD. Note: IBD = inflammatory bowel disease; SNP = single nucleotide polymorphism.

For IBD patients without abdominal pain (who may harbor silent disease)

As indicated above, there are currently no clear guidelines for how to most effectively evaluate for and manage silent IBD. Considering the increased likelihood these patients have for serious complications, due to their inability to sense active inflammation, it is critically important for IBD providers to find more effective means to stratify each patient's risk for this condition. This is particularly important to help determine when to effectively implement more aggressive surveillance strategies including the testing described above. In this setting, I think it would be reasonable to have patients undergo genetic testing to evaluate for homozygosity of the $Na_V1.8$ (*SCN10A*) polymorphism, rs6795970. (Figure 3b) This testing would ideally be undertaken as soon as the patient was diagnosed with IBD, or at least whenever the presence of silent IBD was realized or suspected.

Figure 3a. Using VGSCs To Help Manage Abdominal Pain in Inflammatory Bowel Disease

As in Figure 2a, simultaneous to these steps, providers are performing recurrent careful history and physicals, and employing a multi-disciplinary approach as appropriate. Note: DGBI = disorder of gut-brain interaction.



4. Future Directions

As indicated above, growing evidence suggests that VGSCs, particularly $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$, have significant potential to manage conditions associated with abdominal pain. However, more carefully crafted studies are necessary to better understand exactly how these channels influence abdominal pain, especially in humans. Additional studies, in larger and more carefully phenotyped patient populations, are needed to expand our understanding of the exact clinical impacts that the VGSC elements and VGSC-targeted therapies described above have in IBD, and other related disorders (including their effects on inflammatory status and other gastrointestinal functions that have a potential impact on abdominal pain perception, including motility). There is also a need for more careful characterization of the precise physiological impact of VGSC variants. To date, no biophysical (e.g., electrophysiological, etc.) studies of any of the VGSCs has been undertaken in human neurons or neuronal models. This is important, as there may be functional differences that standard animal or other proxy cellular models are not capable of accurately replicating.

We also need to harness our current knowledge about these channels to more effectively help our patients. For example, as outlined above, there are multiple polymorphisms related to several VGS genes that we know of already that have the potential to be used diagnostically. Most of them have not been formally categorized or, at the very least, made more easily accessible to medical providers to order. For the variants that have demonstrated promise in this regard (ex: homozygosity of rs6795970 in silent IBD), it would be useful to undertake prospective validation studies to determine whether screening for them in newly diagnosed IBD patients is impactful on clinical outcomes and healthcare costs. It is also essential to determine how these variants may work together to impact individual patient risk of pain-related disorders. In this context, it would be helpful to develop polygenic risk scores, or separate "polyomic" predictive models, to more precisely characterize each individual's aggregate risk for developing the conditions above.

Additionally, there are existing VGSC-targeted agents (e.g., suzetrigine) that need to be tested over longer periods of time (it is currently only FDA-approved for management of acute pain), as well as specifically in the setting of IBD in order to determine whether they safe and effective analgesic options in these settings. Similar studies should also be undertaken focusing on individuals suffering from other digestive disorders associated with alterations of abdominal pain perception, including DGBIs (e.g., IBS), chronic pancreatitis and gastroesophageal reflux disease to new a few. Finally, further research is required in order to develop additional medications that more selectively target VGSCs. If this research is done appropriately, we will be able to provide patients with more effective methods for screening and predicting abdominal pain disorders, while also having safer analgesic options to treat their pain.

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