SMART Systems Review

Quantitative Sensory Testing in Gastrointestinal Pain: Precision Phenotyping for Personalized Treatment

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Abstract: Visceral pain is one of the most common and challenging symptoms encountered in gastroenterology due to its heterogeneity in clinical presentation, etiology, and underlying mechanisms. These features also make it difficult to treat. Quantitative Sensory Testing (QST) offers a unique approach that can help identify sensory patterns that shed light on underlying mechanistic features of patients' visceral pain experience by probing static and dynamic pain processing (e.g. pain thresholds/tolerance, temporal summation, and conditioned pain modulation) using somatic and visceral stimuli. Though largely utilized in research and laboratory settings to date, this technique carries promise in identifying not only relevant subgroups of patients, such as those with segmental versus widespread hyperalgesia or those with impaired endogenous descending inhibition, but also potential treatment targets that could facilitate a more personalized and successful approach to the treatment of visceral pain in the future. Notably, in chronic pancreatitis, QST can help link sensory phenotypes to clinical pain burden and may predict who will respond to specific analgesics or anticipate the success of invasive therapies, thereby allowing for a more targeted approach to care. In this review, we focus on the specific QST modalities most commonly applied across the gastrointestinal pain disorders, including pressure algometry, thermal, chemical and electrical testing, mechanical distension (e.g., barostat-based paradigms), and multimodal stimulation, and discuss the rationale for these approaches, summarize key insights gained from studies to date, and highlight potential future treatment targets.

Key words: Quantitative Sensory Testing (QST), Visceral Pain, Gastrointestinal Pain, Chronic Pancreatitis, Functional Dyspepsia, Irritable Bowel Syndrome, Inflammatory Bowel Disease

Outline:

Abbreviations used in this paper: QST, quantitative sensory testing; GI, gastrointestinal; DFNS, German Research Network on Neuropathic Pain; TS, temporal summation; CPM, conditioned pain modulation; CP, chronic pancreatitis; TPIAT, total pancreatectomy with auto-islet transplant; P-QST, pancreatic quantitative sensory testing; DGBI, Disorder of Gut and Brain Interaction; IBS, irritable bowel syndrome; FD, functional dyspepsia; IBS-C, irritable bowel syndrome, constipation predominant; NCCP, non-cardiac chest pain; IBD, inflammatory bowel disease; UC, ulcerative colitis; MRI, magnetic resonance imaging; SAT, Sensory Adaptation Training

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1. Introduction

Visceral pain is one of the most common and challenging symptoms encountered in gastroenterology, owing to its marked heterogeneity in etiology, clinical presentation, and underlying mechanisms. Chronic visceral pain is strongly associated with impaired quality of life and imposes a substantial financial and socioeconomic burden on patients and healthcare systems.[1] As clinical practice increasingly shifts from symptom-based diagnostic and therapeutic strategies toward a pathophysiology-based framework, there is a growing need for mechanistic classifications that support precision-medicine approaches in gastrointestinal (GI) disorders.[2]

Given the profound heterogeneity in sensory profiles among patients with GI pain, quantitative sensory testing (QST) offers a valuable approach for identifying mechanistically relevant subgroups.[3,4] Contemporary QST methodology was constructed on earlier psychophysical sensory testing paradigms, and was rigorously standardized and validated through the nationwide multicenter trials of the German Research Network on Neuropathic Pain (DFNS).[5] Importantly, while the DFNS protocol was originally developed and validated for somatic neuropathic pain disorders, with extensive normative data derived from cutaneous sensory testing, researchers have since adapted these core principles to the unique challenges of visceral pain, including pancreatic disorders, where they have been used to characterize altered nociceptive processing.

QST is a method that can evaluate patterns of sensory loss and gain through the testing of both cutaneous and deep tissue sensitivity to reveal evidence of abnormal nociception or pain signal processing.[6] As a non-invasive translational tool, QST enables consistent characterization of sensory abnormalities across functional and inflammatory GI conditions, providing insights into pain-processing pathways and facilitating sensory phenotyping relevant to individualized treatment strategies.[7,8] As such, QST offers a rare opportunity to characterize GI neurosensory phenomena both within and across the spectrum of GI diseases. While this technique has been widely applied in GI pain, there remains much to explore and discover. In this review, we focus on the specific QST modalities most commonly applied across GI disorders that cause visceral pain, as well as interpretation of results to date, and future applications for use in the treatment of GI pain.

2. QST Methodologies

QST has been applied in many environments including laboratory-based experimental pain evaluation (requiring specialized equipment and highly standardized stimulus delivery) and bedside or clinic-based streamlined evaluations (in attempts to optimize feasibility and dissemination).[9] Previously published QST protocols in disorders of GI pain involve multiple testing modalities and stimuli that include both static and dynamic measures that probe a range of nerve fiber subtypes, afferent pathways, and central pain-processing mechanisms. (Table 1).[7]

A key neurophysiologic concept underpinning QST in GI pain is viscerosomatic convergence, in which visceral afferents synapse on spinal dorsal horn neurons that also receive somatic input from the same spinal segment. With ongoing visceral nociceptive drive, these shared spinal circuits can become sensitized, leading to receptive field expansion and secondary hyperalgesia in segmentally related somatic areas. This framework provides the rationale for dermatomally guided somatic testing—probing referred pain areas—as a practical, indirect measure of altered visceral nociceptive processing and central sensitization, and can help distinguish patterns of localized versus widespread hyperalgesia across GI pain disorders.[4,10]

The common aim of these measures is to reveal evidence of altered pain processing or perception such as hyperalgesia, hypoesthesia, allodynia, or hyperpathia. Measures are both static, assessing pain threshold (the lowest stimulus intensity perceived as painful) and pain tolerance (the maximum tolerable stimulus), and dynamic, including temporal summation (TS) and conditioned pain modulation (CPM). TS reflects increased pain responses to repeated noxious stimulation, indicating sensitization through a 'wind-up' type of phenomenon, while CPM reflects the (potentially impaired) integrity of descending inhibitory pathways by assessing how a second noxious stimulus modulates the perception of an initial one.[11]

3. QST in Pancreatic Disorders

QST has been widely used to describe sensory abnormalities and characterize pain phenotypes in the disease process of chronic pancreatitis (CP), a disease with no cure in which up to 80% of patients experience visceral pain that is challenging to treat.[12] Although much of this pain may stem from inflammation of the pancreatic gland, obstruction of the pancreatic duct, peripancreatic or pancreatic nerve damage or nerve inflammation, there remain factors that are more difficult to identify and treat, including central sensitization. Central sensitization refers to an activity-dependent increase in the excitability and synaptic efficacy of neurons within the central nervous system, such that normal or previously subthreshold inputs begin to generate amplified pain responses.[10] Repeated or persistent nociceptive input can lead to sustained amplification of pain signaling, lowered pain thresholds, and allow pain to persist even when peripheral drivers are reduced or removed. QST has been used as a proxy test for identification of characteristics of supraspinal central sensitization in CP, a phenomenon of neuropathic and neuroplastic remod-

eling thought to result from persistent pain stimuli.[13-19] Multiple studies have shown that relief from pancreatic duct obstruction alone (a common target for treatment of CP pain performed via endoscopic or surgical approach), unfortunately does not relieve or resolve pain in a durable fashion for many CP patients, leaving them with an incomplete explanation for their symptoms.[20-22] Even in patients who have undergone a complete removal of their

Table 1. Categories of Sensitivity Testing Used in Quantitative Sensory Testing for Gastrointestinal Pain

Stimulus Modality	Mechanism	Types of GI disease in which this testing has been utilized
Mechanical Distension Balloon/Barostat	Intraluminal balloon inflation stretches gut walls and activates mechanoreceptors, thresholds for discomfort/pain are measured. Barostat methods assess gut tone, compliance, and sensitivity during distension.[31,83]	IBS (visceral hypersensitivity to rectal/colonic distension)[46-49] FD (gastric sensitivity)[56] IBD (rectal sensitivity and rectal compliance)[63-65] Esophagus, non-cardiac chest pain (esophagus hypersensitivity)[60]
Pressure Algometry	Application of pressure to somatic regions (dermatomes or muscles) sharing spinal segments with visceral organs, to detect secondary hyperalgesia. Measures pressure-pain detection and tolerance thresholds.[31,83]	Chronic pancreatitis (segmental or central sensitization)[34]
Thermal Stimulation (Heat/Cold)	Temperature-controlled stimuli (e.g. hot or cold water perfused intraluminally via a balloon) activate thermosensitive visceral afferents. Pain threshold and tolerance to intraluminal heat/cold are recorded.[31,83]	IBS (rectal hypersensitivity to thermal stimuli)[84] IBS (rectal sensitivity to cold water stimuli)[85]
Electrical Stimulation	Intraluminal or transmucosal electrical current activate visceral afferent fibers directly and assess central or spinal processing of visceral sensations.[31,83,86]	IBS (altered spinal transmission of nociceptive signals)[87] Chronic Pancreatitis (skin electrical stimuli over the pancreatic dermatome to measure electric pain detection thresholds)[30]
Chemical Stimulation	Chemical irritants are delivered to visceral sites to activate chemosensory pathways.[31,83]	Non-cardiac chest pain (esophagus acid provocation or acid perfusion test)[59,88] IBS (capsaicin rectal stimulation)[89]
Multimodal stimulation	A multimodal technique of visceral sensory assessment integrating electrical, mechanical and thermal stimulation into the same device.[31,83]	GI disorders involve esophagus, rectum and rectosigmoid[62,90]
Dynamic paradigms	Temporal summation (TS; wind-up): Increased pain ratings across repeated identical noxious stimuli delivered at a fixed intensity/frequency, reflecting facilitated central pain processing/central sensitization.[11]	Esophagus (electrical stimuli showed perceptual wind-up and is enhanced after acid induced central sensitization)[79] Chronic pancreatitis (repetitive pin-prick stimuli assess TS)[32]
	Conditioned pain modulation (CPM; 'pain inhibits pain'): Assesses endogenous descending inhibitory control by measuring the change in perceived intensity of a test stimulus during/after a spatially remote conditioning stimulus.[11]	Chronic pancreatitis (cold pressor/ice-water hand immersion is applied to engaging descending inhibitory pathways, and changes in pressure pain detection/tolerance are compared before and after the conditioning stimulus to quantify CPM)[32] IBS (heat pain combined with noxious cold-water immersion, little to no inhibition of heat pain observed in IBS patients)[91]

pancreas via total pancreatectomy with auto-islet transplant (TPIAT), a substantial proportion of adults continue to experience ongoing pain and/or opioid requirements.[23,24] In an adult cohort undergoing TPIAT, opioid independence was achieved in only 46%, and 83% developed a new characteristic abdominal pain.[25] QST is meant to address the possibility that central sensitization may account for a portion of this persistent, difficult-to-manage pain.[26]

Experimental QST protocols performed in a research setting have previously demonstrated correlation of central sensitization with severe CP[14,27], and identified central sensitization as a predictor of poor surgical outcome after treatment with thoracoscopic splanchnic denervation in CP.[28,29] The presence of sensitization at the pancreatic viscerotome (corresponding to T10 or the 10th thoracic dermatome and as detected by electrical tetanic stimulation) has predicted a positive therapeutic response to pregabalin.[30] Early QST investigations were limited by protocols requiring particular experimental settings and extensive training. Direct visceral stimulation approaches—commonly used in esophageal and rectal QST studies—are not easily translated to the pancreas.[31] As a result, most early pancreatic QST work has relied on indirect somatic stimulation paradigms performed in controlled experimental settings, which has constrained broader participation and dissemination.

More recently, a clinically-feasible pancreas-specific QST protocol designed for bedside use, pancreatic QST (P-QST), has been developed through the work of a collaborative research consortium.[32] P-QST preserves the core mechanistic constructs (segmental vs widespread sensitization and impaired descending inhibition) while omitting technically demanding components such as electrical stimulation and emphasizing standardized, noninvasive measures suitable for clinical implementation. This protocol has been widely disseminated through 15 major pancreas research centers in multiple continents, and has the potential for adoption into routine clinical practice.[3,33]

P-QST evaluates both static and dynamic components of CP pain. Aspects of this testing protocol include the use of pressure testing (via digital algometer) of the T10 dermatome as a pancreatic viscerotome proxy. This site is chosen because pancreatic visceral afferents and somatic afferents from the T10 segment converge on shared spinal dorsal horn circuitry (Figure 1). Pancreatic nociceptive input can therefore produce segmentally distributed secondary hyperalgesia in the corresponding T10 dermatome, making T10 pressure sensitivity a practical somatic surrogate for pancreas-linked sensitization. The P-QST protocol uses comparison of pressure pain detection and tolerance between pancreatic versus non-pancreatic (control) dermatomes to evaluate systemic changes in sensory processing suggestive of hyperalgesia. The protocol also uses non-invasive pin-prick testing to evaluate for abnormal TS. Hand immersion in ice-water for two minutes serves as a noxious stimulus to activate the central descending inhibition pathway, and subsequent comparison of pressure algometer testing before and after the stimulus allows for detection of appropriate elevation in the pain detection threshold following pathway activation (CPM paradigm).

Since its establishment, the P-QST protocol has succeeded in specifying precisely pain profiles among patients with painful CP. In particular, patients with widespread hyperalgesia report significantly higher pain intensity and rates of constant pain, as well as decreased quality of life and physical functioning compared to those with either pancreatic segmental hyperalgesia or no hyperalgesia.[34] There is significant overlap in the contribution of hyperalgesia, pancreatic ductal obstruction, and psychiatric comorbidity in the population of patients with painful CP.[26] In those CP patients who do have resolution of their pain with treatment, hyperalgesia may persist but there is significantly less psychiatric comorbidity present than in their counterparts who have never had pain (and who experience neither hyperalgesia or psychiatric distress) and their counterparts who have ongoing pain (and significant psychiatric comorbidity).[35] P-QST has also shown in a preliminary study the ability to predict response to treatment in patients with widespread hyperalgesia.[36] An appropriately-powered observational clinical trial is ongoing to assess the ability of P-QST to predict response to relief of ductal obstruction in painful chronic pancreatitis.[37]

Use of P-QST in other diseases of the pancreas – both acute pancreatitis and pancreatic cancer – has been rare but carries potential promise. A cross-sectional study utilizing P-QST in patients with pancreatic cancer has revealed that there is abnormal central pain processing in pancreatic cancer patients, with 19% each having widespread and segmental hyperalgesia.[38] A single small study looking at multiple QST somatosensory parameters in patients with AP (n = 23), CP (n = 20), autoimmune pancreatitis (n = 10), and pancreatic cancer (n = 17), slight differences in profiles across disease states were found, but importantly found that patients with AP compared to CP have evidence of blunt pressure hyperalgesia and more profound somatosensory losses.[39] Notably, the CP cohort in this study largely represented early-stage disease with low opioid use, which may account for the limited hyperalgesia observed and the apparent differences from prior QST studies in more advanced painful CP, where segmental and/or widespread hypersensitivity is more consistently reported.

P-QST shows promise in helping to understand mechanisms underlying pancreatic pain in multiple pancreatic disease processes. In other painful conditions, QST has been used to guide treatment decisions by identifying patients with central sensitization, and guiding therapy

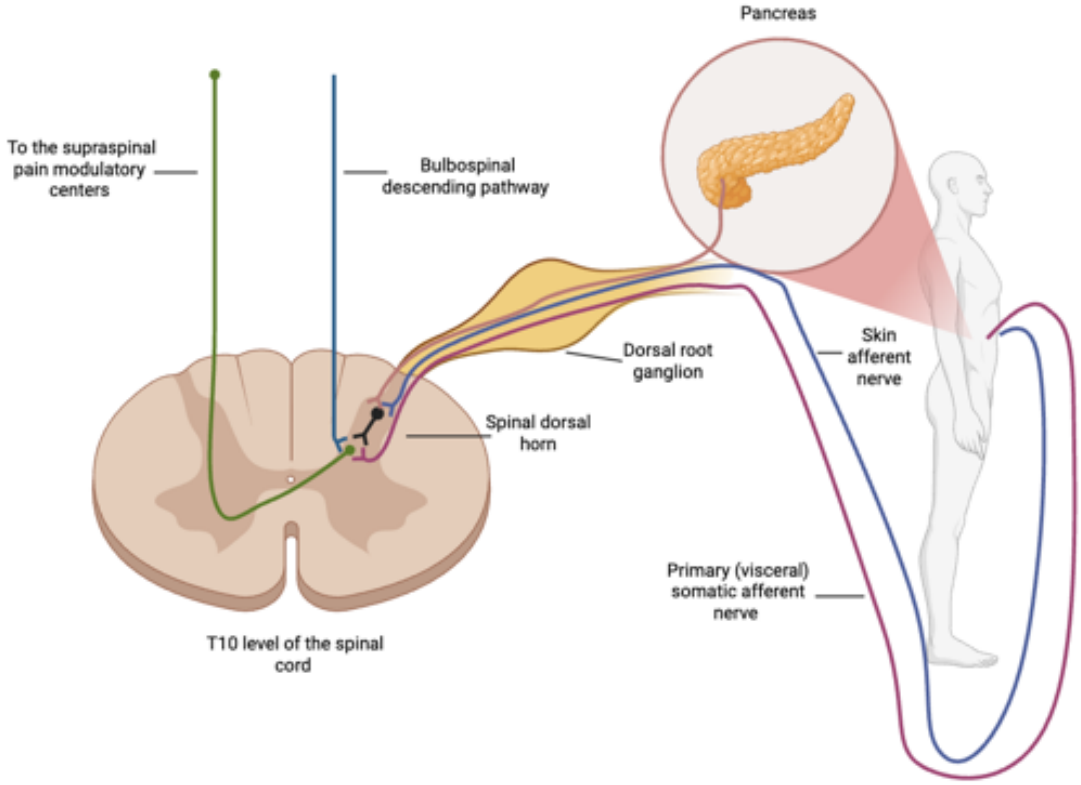

Figure 1.

This figure represents an illustration of the endogenous neural circuitry that is central to the technique of Pancreatic Quantitative Sensory Testing (P-QST). By extension, this is also a demonstration of potential points of pathophysiology evaluated by this method. The T10 level of the spinal cord is of central import as this is the level from which innervation of the pancreas occurs. Convergence between pancreatic afferent and skin afferent nerves in the T10 dermatome (the latter in the skin of the upper abdomen and back) allows for detection of sensitization of the nerves in the pancreatic viscerotome. The nerves at this level may be sensitized by persistent afferent pain signals beginning at the pancreas in the setting of pancreatic inflammation or underlying pancreatic pathology. This sensitization may result in the lowering of the pain threshold to pressure testing of the skin and deep tissue. Not pictured here are extra-pancreatic dermatomes also tested: spreading of the sensitization along the neuroaxis may then result in lowering of pain thresholds in other dermatomes such as L4 (also assessed in P-QST). The bulbospinal pathway in patients with normal processing can effectively gate visceral pain signals and inhibit the pain pathway; this may be altered in the setting of neuropathic or neuroplastic changes. Pain experienced by the patient may result from a combination of nociceptive processing and the activation of other brain centers that manage affective, cognitive, and evaluative information. The pain experience may be dominated over time by one or more of these factors as pain chronification takes place.

according to likelihood of response.[40-42] The hope is that QST (and specifically P-QST) may offer this opportunity for pancreatic disease and be successfully used as both a predictor of treatment outcome and potentially a method to track response for future treatment trials.

4. QST in Disorders of Brain-Gut Interactions and Luminal GI Disorders

Disorders of gut–brain interaction (DGBI) comprise a group of gastrointestinal conditions in which the most frequently encountered diagnoses include irritable bowel syndrome (IBS) and functional dyspepsia (FD).[43] Visceral hypersensitivity and alterations in central nervous system processing are key mechanisms underlying their pathophysiology.[44,45] Given the breadth of this literature, the studies highlighted below represent selected examples of how QST has been applied to elucidate pain mechanisms across DGBI and other luminal GI disorders. QST (using multiple testing modalities) has provided important insights into the mechanisms contributing to pain experience in these conditions.

Rectal barostat testing has previously been used to assess symptoms associated with rectal compliance in patients with IBS.[46] For example, in a Rome II cohort of 109 IBS patients and 29 healthy controls, 39% of IBS patients had lowered discomfort and/or pain thresholds, and 61% met criteria for “altered rectal perception” when combining thresholds, unpleasantness ratings, and viscerosomatic referral area; this subgroup also reported greater symptom severity (notably pain and bloating) and the association was not simply explained by anxiety/depression in

multivariable analyses.[47] Increased sensitivity to controlled rectal distension has also been consistently reported across multiple investigations, reinforcing visceral hypersensitivity as a central feature of IBS pathophysiology.[48,49]

Patients with functional gastrointestinal disorders have also demonstrated altered somatic pain processing. In a different Rome II-based cohort study (33 patients with functional GI disorders including 24 IBS, 8 FD, 1 functional chest pain vs. 33 healthy controls), a standardized cold-water hand immersion test showed earlier somatic pain perception in patients and reduced pain tolerance, with ~33% of patients falling below the lower limit of the control range.[50] In another study[51], female diarrhea-predominant IBS participants (n=27) and healthy controls (n=25) underwent somatic sensitivity test at the forearm and calf using a contact thermode, while central pain modulation was assessed through counterirritation paradigms involving sustained cold stimulus applied to the hand and electric shocks delivered to the ankle. Individuals with IBS exhibited lower pain thresholds to both rectal and calf stimuli, as well as increased heat-induced pain at the calf and forearm. Importantly, cold-induced pain inhibited shock-induced pain in healthy controls but failed to do so in patients with IBS, indicating impaired endogenous pain inhibitory mechanisms. These findings support the presence of widespread hypersensitivity and altered pain inhibition processes in IBS, a pattern further corroborated by other studies reporting increased sensitivity to heat stimuli, impaired CPM, and lower pressure pain detection threshold at distal body sites.[49,52,53] Further evidence for altered central pain modulation in IBS comes from studies employing CPM paradigms. Two systematic reviews with meta-analyses have shown that CPM responses are significantly reduced in IBS compared with healthy controls, supporting the role of central sensitization in symptom generation.[54,55]

In patients with FD, both mechanical and chemical hypersensitivity have been well documented. Balloon distension and chemical infusion studies demonstrate heightened sensitivity of the stomach to mechanical stretch and chemical stimuli.[56] QST paradigms that activate TRPV1 (e.g., gastric pain modeling via oral capsaicin capsule titration) have demonstrated visceral/upper-GI chemosensory hypersensitivity in FD. In a randomized, double-blind, nocebo-controlled, cross-over design, patients with FD reached the pain endpoint at lower doses and reported greater symptom intensity than healthy controls, supporting enhanced chemosensory responsiveness.[57] Similarly, intraduodenal long-chain triglyceride infusion induces disproportionately greater fullness/nausea/bloating in FD and can augment symptom responses to gastric distension, consistent with nutrient-specific chemosensory hypersensitivity.[58]

The esophagus has been one of the most extensively studied areas for visceral QST paradigms. Sarkar et al conducted distal esophageal acid infusion studies in 19 healthy volunteers and 7 patients with non-cardiac chest pain (NCCP), and found NCCP patients demonstrated lower baseline pain thresholds and developed more pronounced and prolonged hypersensitivity after short acid exposure, suggesting the role of central sensitization.[59] Balloon distension studies further confirmed that a substantial subset of NCCP patients exhibit esophageal hypersensitivity independent of overt mucosal injury.[60] Olesen et al. designed a randomized, double-blind, placebo-controlled crossover model to induce reproducible esophageal hyperalgesia in healthy volunteers using combined acid (0.1 M HCl) and capsaicin perfusion. Fifteen participants underwent multimodal sensory testing (heat, mechanical distension, electrical stimulation) before and after chemical sensitization. All volunteers developed persistent sensitization (for at least 60 minutes) in at least one modality, with reduced heat and electrical pain thresholds and expansion of referred pain areas, consistent with both peripheral TRPV1-mediated sensitization and centrally mediated hyperalgesia, as inferred from expansion of referred pain areas.[61] Drewes et al. developed a multimodal esophageal QST model in 11 healthy volunteers integrating electrical stimulation, impedance planimetry-based mechanical distension and controlled cold/heat stimulation via intra-bag water recirculation. Across modalities, subjects showed clear stimulus–response relationships, reported both local and viscerosomatic referred pain, and the referred pain area expanded with increasing stimulus intensity. Repeated electrical bursts lowered detection thresholds, consistent with TS-like central facilitation.[62]

QST has also been applied in patients with inflammatory bowel disease (IBD). In ulcerative colitis (UC), altered rectal sensitivity[63,64] and reduced compliance[65] during balloon distension have been associated with hallmark symptoms of active disease, such as urgency and frequent defecation. Studies using controlled rectal distension (with impedance planimetry) have demonstrated hypersensitivity in active ulcerative colitis despite preserved rectal compliance and stiffness.[66] Notably, pharmacologic smooth muscle relaxation abolished this hypersensitivity, indicating that increased rectal smooth muscle tone rather than intrinsic wall stiffness contributes substantially to sensory abnormalities. These data highlight the value of controlled biomechanical QST paradigms that directly characterize wall deformation when interpreting visceral hypersensitivity. Notably, UC patients in remission who report IBS-like symptoms exhibit greater rectal sensitivity than those in remission without such symptoms, suggesting persistent sensory abnormalities beyond mucosal inflammation.[67] Incorporating QST into IBD phenotyping may help identify patients with IBS-like features and guide the use of

neuromodulators or centrally acting analgesics alongside standard anti-inflammatory therapy.

5. Advanced Technologies and Multimodal Phenotyping

Functional neuroimaging studies have provided complementary evidence for altered central pain processing in visceral pain disorders. A quantitative meta-analysis demonstrated that although both IBS patients and controls show activation in brain regions involved in visceral afferent processing (i.e. the thalamus, insula, and anterior midcingulate cortex), IBS patients more consistently recruit areas linked to emotional arousal (pregenual anterior cingulate cortex, amygdala) as well as a midbrain cluster implicated in endogenous pain modulation.[68] Other neuroimaging studies have similarly shown heightened activation of the insular cortex, prefrontal cortex[69], and anterior cingulate cortex[70] during rectal distension in IBS, further supporting central amplification of visceral signals. These imaging findings enrich the interpretation of QST by providing concrete neural correlates of altered sensory processing. Importantly, convergent evidence for central reorganization has also been demonstrated in pancreatic pain, particularly in painful CP. Structural magnetic resonance imaging (MRI) studies show reduced cortical thickness in key pain-processing regions (including the insula, secondary somatosensory cortex, prefrontal/frontal cortices, and midcingulate cortex) with regional thinning correlating with clinical pain intensity.[71] Diffusion tensor imaging studies indicate microstructural alterations across gray matter within the amygdala, cingulate cortex, insula, prefrontal cortex, and in white matter within the insula and prefrontal cortex, with additional alterations in the secondary sensory cortex. Microstructural metrics correlate with pain scores and vary by pain pattern.[72] More recently, resting-state functional MRI work has extended this framework by demonstrating altered intrinsic network coupling in CP (hyperconnectivity within default mode and salience networks and reduced anticorrelation between them), with default mode connectivity associated with anterior cingulate glutamatergic measures, highlighting a link between network-level dysfunction and central neurochemistry in CP pain.[73]

Building on these insights, precision medicine is increasingly recognized as an important future direction for management of GI pain of multiple etiologies.[74] Visceral hypersensitivity may serve as both a biological and clinical marker, and IBS QST findings are now being interpreted alongside cytokine profiles, microbiome signatures, and mucosal biopsy data to generate more detailed patient phenotypes.[4,75] A similar precision framework is emerging in painful CP, where P-QST phenotyping is being integrated with key clinical and treatment covariates (such as baseline pain burden, intervention type, and measures of technical ductal clearance) and neuroinflammatory biomarker profiles to build models that predict pain outcomes after invasive ductal decompression and may help refine patient selection for invasive therapy.[37]

Recent work has also incorporated QST into randomized controlled trial designs, including studies using machine-learning–based models to predict individual responses to self-management interventions before treatment begins.[76] Beyond traditional applications, emerging work highlights how computational modeling and artificial intelligence may substantially enhance the clinical utility of QST by individualizing reference values, identifying patient-specific protocols, integrating QST with immersive virtual-reality-based pain therapies and informing artificial intelligence-assisted treatment recommendations.[77] Integrating QST into the clinical assessment of GI pain offers insight into central versus peripheral mechanisms and pain modulatory capacity, thereby supporting individualized and mechanism-based therapeutic strategies.[78]

6. Limitations and Challenges

QST has several major limitations that should be acknowledged. There is a subjective component to patients' responses to sensory stimuli (i.e. reporting a certain threshold or sensation). The stimuli are standardized, which offers a relative comparison between the individual and appropriate reference population. However, QST relies on phasic, time-limited experimental stimuli, which can be hard to extrapolate to more complex clinical pain or to fully reflect the "real-world" pain experience, where multiple afferent inputs, inflammation, tissue pressure or ischemia, and central sensitization may occur simultaneously and fluctuate with time. To improve ecological validity, some paradigms incorporate multimodal stimulation models (for example, assessing TS using repetitive pinprick stimuli and engaging CPM using cold pressor/cold-water immersion paradigms in CP)[32] and/or chemical sensitization models (for example, multimodal esophageal protocols in which repeated electrical stimulation demonstrates perceptual wind-up and can be enhanced following acid perfusion–induced sensitization) that may better approximate clinically relevant symptom provocation, though they still do not capture the full complexity of chronic visceral pain.[79] Beyond these, an important aspect of QST is that testers themselves must be rigorously trained in order to administer the stimuli in a standardized fashion, and equipment/protocols must be calibrated and applied consistently to minimize inter-rater and site-to-site variability.[80] In addition, QST does not account for other factors that may influence the pain experience including anxiety, depression, or other psychiatric comorbidities.

7. Conclusions

QST is a promising methodology for advancing the exploration of GI pain. Despite its limitations, QST has the potential to offer phenotyping strategies for multiple GI diseases that cause visceral pain, to both characterize pain and offer insight into personalized treatment options based on those characteristics for optimization of outcomes. To emphasize this translational goal, we provide a concise summary (Table 2) linking common QST-defined sensory phenotypes with potential mechanism-based therapeutic approaches and supporting evidence. In addition, emerging therapies targeting specific sensory mechanisms, including sodium channel–directed approaches for peripheral hyperexcitability or "irritable nociceptor"–type phenotypes, may represent an important future direction.[81] Although current support for these approaches is derived largely from non-GI pain literature rather than GI-specific QST-guided studies, growing interest in selective sodium channel modulators, such as NaV1.8-targeted therapies[82], highlights the broader potential of phenotype-informed treatment development in visceral pain disorders. Such strategies of phenotyping will be crucial to any future ability to provide an individualized prediction of treatment response to planned interventions in multiple disease entities.

Table 2. QST-defined Sensory Phenotypes and Potential Mechanism-Based Therapeutic Approaches in Gastrointestinal Pain

QST-defined phenotype	Gastrointestinal disease context	Potential targeted therapy	Proposed mechanism for efficacy
Segmental pancreatic hyperalgesia	Chronic pancreatitis[30]	Pregabalin	Reduces neuronal excitability via α2δ Ca^{2+} channel modulation, may be most effective when segmental sensitization is present.
Widespread hyperalgesia	Chronic pancreatitis[92]	Pregabalin	Reduces neuronal excitability via α2δ Ca^{2+} channel modulation, may attenuate central hyperexcitability and spreading hyperalgesia
Impaired descending inhibition	Chronic pancreatitis[93,94]	Ketamine	NMDA-receptor antagonism may interrupt central sensitization, potentially improve pain modulation, and reduce amplified pain processing
Rectal visceral hypersensitivity	IBS/DGBI[95]	Pregabalin	Reduces neuronal excitability via α2δ Ca^{2+} channel modulation, may reduce excitatory neurotransmitter release and rectal hyperalgesia in hypersensitive IBS patients.
Rectal visceral hypersensitivity	IBS/DGBI[96]	Ketotifen	Mast cell–related mechanisms may contribute to peripheral sensitization, and ketotifen may secondarily dampen visceral hyperalgesia
Rectal visceral hypersensitivity	IBS-C/DGBI[97]	SAT	Repeated barostat-guided distension may promote sensory adaptation and improve rectal hypersensitivity.
Esophageal hypersensitivity	Esophageal hypersensitivity model (in healthy volunteers)[98]	Citalopram	May reduce mechanical and chemical esophageal hypersensitivity, likely through serotonergic modulation of pain processing.
Secondary esophageal hyperalgesia	Acid-sensitization model (in healthy volunteers)[99]	Pregabalin	May attenuate the development of acid-induced secondary esophageal hypersensitivity, likely via reduction of centrally mediated sensitization.
Gastric sensorimotor dysfunction	Functional dyspepsia[100]	Buspirone	Enhances proximal gastric relaxation and accommodation, which may improve postprandial distress symptoms.

IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome, constipation predominant; DGBI, disorder of gut and brain interaction; SAT, sensory adaptation training

References

1. Ford AC, Vanner S, Kashyap PC, Nasser Y. Chronic Visceral Pain: New peripheral mechanistic insights and resulting treatments. *Gastroenterology.* 2024;166(6):976-94.
2. Edwards RR, Schreiber KL, Dworkin RH, et al. Optimizing and accelerating the development of precision pain treatments for chronic pain: IMMPACT review and recommendations. *J Pain.* 2023;24(2):204-25.
3. Kuhlmann L, Olesen SS, Gronlund D, et al. Patient and disease characteristics associate with sensory testing results in chronic pancreatitis. *Clin J Pain.* 2019;35(9):786-93.
4. Zhou Q, Verne GN. New insights into visceral hypersensitivity--clinical implications in IBS. *Nat Rev Gastroenterol Hepatol.* 2011;8(6):349-55.
5. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain.* 2006;123(3):231-43.
6. Mücke M, Cuhls H, Radbruch L, et al. Quantitative sensory testing (QST). English version. *Schmerz.* 2021;35(Suppl 3):153-60.
7. Cruz-Almeida Y, Fillingim RB. Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Med.* 2014;15(1):61-72.
8. Kuhlmann L, Olesen SS, Drewes AM. Assessment of visceral pain with special reference to chronic pancreatitis. *Front Pain Res (Lausanne).* 2022;3:1067103.
9. van Driel MEC, Huygen FJPM, Rijsdijk M. Quantitative sensory testing: a practical guide and clinical applications. *BJA Educ.* 2024;24(9):326-34.
10. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* 2011;152(3 Suppl):S2-15.
11. Owens MA, Thomas PA, Crowe C, Goodin BR, Overstreet DS. Quantitative sensory testing for pain: What exactly are we measuring? *Curr Opin Psychol.* 2025;62:101988.
12. Singh VK, Yadav D, Garg PK. Diagnosis and management of chronic pancreatitis: A Review. *JAMA.* 2019;322(24):2422-34.
13. Bouwense SA, Buscher HC, van Goor H, Wilder-Smith OH. Has central sensitization become independent of nociceptive input in chronic pancreatitis patients who fail thoracoscopic splanchnicectomy? *Reg Anesth Pain Med.* 2011;36(6):531-6.
14. Bouwense SA, Olesen SS, Drewes AM, Frokjaer JB, van Goor H, Wilder-Smith OH. Is altered central pain processing related to disease stage in chronic pancreatitis patients with pain? An exploratory study. *PLoS One.* 2013;8(2):e55460.
15. Olesen SS, Frokjaer JB, Lelic D, Valeriani M, Drewes AM. Pain-associated adaptive cortical reorganisation in chronic pancreatitis. *Pancreatology.* 2010;10(6):742-51.
16. Olesen SS, Brock C, Krarup AL, et al. Descending inhibitory pain modulation is impaired in patients with chronic pancreatitis. *Clin Gastroenterol Hepatol.* 2010;8(8):724-30.
17. Xu GY, Winston JH, Shenoy M, Yin H, Pasricha PJ. Enhanced excitability and suppression of A-type K+ current of pancreas-specific afferent neurons in a rat model of chronic pancreatitis. *Am J Physiol Gastrointest Liver Physiol.* 2006;291(3):G424-31.
18. Zhu Y, Mehta K, Li C, et al. Systemic administration of anti-NGF increases A-type potassium currents and decreases pancreatic nociceptor excitability in a rat model of chronic pancreatitis. *Am J Physiol Gastrointest Liver Physiol.* 2012;302(1):G176-81.
19. Dimcevski G, Sami SA, Funch-Jensen P, et al. Pain in chronic pancreatitis: the role of reorganization in the central nervous system. *Gastroenterology.* 2007;132(4):1546-56.
20. Cahen DL, Gouma DJ, Laramee P, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. *Gastroenterology.* 2011;141(5):1690-5.
21. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N Engl J Med.* 2007;356(7):676-84.
22. Issa Y, Kempeneers MA, Bruno MJ, et al. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: The ESCAPE randomized clinical trial. *JAMA.* 2020;323(3):237-47.
23. Bellin MD, Beilman GJ, Sutherland DE, et al. How durable is total pancreatectomy and intraportal islet cell transplantation for treatment of chronic pancreatitis? *J Am Coll Surg.* 2019;228(4):329-39.
24. Sutherland DE, Radosevich DM, Bellin MD, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *Journal of the American College of Surgeons.* 2012;214(4):409-24.
25. Moran RA, Klapheke R, John GK, et al. Prevalence and predictors of pain and opioid analgesic use following total pancreatectomy with islet autotransplantation for pancreatitis. *Pancreatology.* 2017;17(5):732-7.
26. Olesen SS, Phillips AE, Faghih M, et al. Overlap and cumulative effects of pancreatic duct obstruction, abnormal pain processing and psychological distress on patient-reported outcomes in chronic pancreatitis. *Gut.* 2022;71(12):2518-25.
27. Buscher HC, van Goor H, Sweep CG, Lenders JW, Wilder-Smith OH. Increased sympathetic activity in chronic pancreatitis patients is associated with hyperalgesia. *J Pain Palliat Care Pharmacother.* 2010;24(4):362-6.
28. Bouwense SA, Ahmed Ali U, ten Broek RP, et al. Altered central pain processing after pancreatic surgery for chronic pancreatitis. *Br J Surg.* 2013;100(13):1797-804.

29. Buscher HC, van Goor H, Wilder-Smith OH. Effect of thoracoscopic splanchnic denervation on pain processing in chronic pancreatitis patients. *Eur J Pain.* 2007;11(4):437-43.
30. Olesen SS, Graversen C, Bouwense SA, van Goor H, Wilder-Smith OH, Drewes AM. Quantitative sensory testing predicts pregabalin efficacy in painful chronic pancreatitis. *PLoS One.* 2013;8(3):e57963.
31. Andresen V. Visceral sensitivity testing. *Best Pract Res Clin Gastroenterol.* 2009;23(3):313-24.
32. Phillips AE, Faghih M, Kuhlmann L, et al. A clinically feasible method for the assessment and characterization of pain in patients with chronic pancreatitis. *Pancreatology.* 2020;20(1):25-34.
33. Phillips AE, Faghih M, Singh VK, et al. Rationale for and development of the pancreatic quantitative sensory testing consortium to study pain in chronic pancreatitis. *Pancreas.* 2021;50(9):1298-304.
34. Faghih M, Phillips AE, Kuhlmann L, et al. Pancreatic QST differentiates chronic pancreatitis patients into distinct pain phenotypes independent of psychiatric comorbidities. *Clin Gastroenterol Hepatol.* 2022;20(1):153-61.e152.
35. Phillips AE, Bick BL, Faghih M, et al. Pain sensitivity and psychiatric comorbidities in chronic pancreatitis patients with and without pain: past experience matters. *Gastro Hep Adv.* 2022;1(5):796-802.
36. Phillips AE, Faghih M, Singh VK, et al. Widespread hyperalgesia by pancreatic quantitative sensory testing is associated with reduced pain response in chronic pancreatitis. *Pancreas.* 2023;52(4):e257-8.
37. Phillips AE, Afghani E, Akshintala VS, et al. Pancreatic quantitative sensory testing to predict treatment response of endoscopic therapy or surgery for painful chronic pancreatitis with pancreatic duct obstruction: study protocol for an observational clinical trial. *BMJ Open.* 2024;14(3):e081505.
38. Faghih M, Damm M, Bandhauer C, et al. Pancreatic adenocarcinoma patients with pain have abnormal central pain processing. *Pancreatology.* 2025;25(3):426-32.
39. Goltl P, Merz P, Schneider A, Ebert MP, Hirth M, Magerl W. Somatosensory profiling to differentiate distinct painful diseases of the pancreas-a quantitative sensory testing case-control study. *Pain.* 2025;166(10):2322-31.
40. Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain.* 2015;156(1):55-61.
41. Wylde V, Palmer S, Learmonth ID, Dieppe P. The association between pre-operative pain sensitisation and chronic pain after knee replacement: an exploratory study. *Osteoarthritis Cartilage.* 2013;21(9):1253-56.
42. Lundblad H, Kreicbergs A, Jansson KA. Prediction of persistent pain after total knee replacement for osteoarthritis. *J Bone Joint Surg Br.* 2008;90(2):166-71.
43. Keefer L, Ko CW, Ford AC. AGA clinical practice update on management of chronic gastrointestinal pain in disorders of gut-brain interaction: expert review. *Clin Gastroenterol Hepatol.* 2021;19(12):2481-8.e2481.
44. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. *Lancet.* 2020;396(10263):1675-88.
45. Ford AC, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. Functional dyspepsia. *Lancet.* 2020;396(10263):1689-1702.
46. van der Veek PP, Van Rood YR, Masclee AA. Symptom severity but not psychopathology predicts visceral hypersensitivity in irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2008;6(3):321-8.
47. Posserud I, Syrous A, Lindström L, Tack J, Abrahamsson H, Simrén M. Altered rectal perception in irritable bowel syndrome is associated with symptom severity. *Gastroenterology.* 2007;133(4):1113-23.
48. Sabate JM, Veyrac M, Mion F, et al. Relationship between rectal sensitivity, symptoms intensity and quality of life in patients with irritable bowel syndrome. *Aliment Pharmacol Ther.* 2008;28(4):484-90.
49. Wilder-Smith CH, Robert-Yap J. Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. *World J Gastroenterol.* 2007;13(27):3699-704.
50. Bouin M, Meunier P, Riberdy-Poitras M, Poitras P. Pain hypersensitivity in patients with functional gastrointestinal disorders: a gastrointestinal-specific defect or a general systemic condition? *Dig Dis Sci.* 2001;46(11):2542-8.
51. Piché M, Arsenault M, Poitras P, Rainville P, Bouin M. Widespread hypersensitivity is related to altered pain inhibition processes in irritable bowel syndrome. *Pain.* 2010;148(1):49-58.
52. Stabell N, Stubhaug A, Flægstad T, Mayer E, Naliboff BD, Nielsen CS. Widespread hyperalgesia in adolescents with symptoms of irritable bowel syndrome: results from a large population-based study. *J Pain.* 2014;15(9):898-906.
53. Rodrigues AC, Nicholas Verne G, Schmidt S, Mauderli AP. Hypersensitivity to cutaneous thermal nociceptive stimuli in irritable bowel syndrome. *Pain.* 2005;115(1-2):5-11.
54. Albusoda A, Ruffle JK, Friis KA, et al. Systematic review with meta-analysis: conditioned pain modulation in patients with the irritable bowel syndrome. *Aliment Pharmacol Ther.* 2018;48(8):797-806.
55. Marcuzzi A, Chakiath RJ, Siddall PJ, et al. Conditioned Pain Modulation (CPM) is Reduced in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of

CPM and the Role of Psychological Factors. *J Clin Gastroenterol.* 2019;53(6):399-408.
56. Narendren A, Boddupalli S, Segal JP. British Society of Gastroenterology guidelines on the management of functional dyspepsia. *Frontline Gastroenterol.* 2024;15(1):70-73.
57. Li X, Cao Y, Wong RK, Ho KY, Wilder-Smith CH. Visceral and somatic sensory function in functional dyspepsia. *Neurogastroenterol Motil.* 2013;25(3):246-253, e165.
58. Feinle-Bisset C, Azpiroz F. Dietary lipids and functional gastrointestinal disorders. *Am J Gastroenterol.* 2013;108(5):737-47.
59. Sarkar S, Aziz Q, Woolf CJ, Hobson AR, Thompson DG. Contribution of central sensitisation to the development of non-cardiac chest pain. *Lancet.* 2000;356(9236):1154-9.
60. Nasr I, Attaluri A, Coss-Adame E, Rao SS. Diagnostic utility of the oesophageal balloon distension test in the evaluation of oesophageal chest pain. *Aliment Pharmacol Ther.* 2012;35(12):1474-81.
61. Olesen AE, Staahl C, Brock C, Arendt-Nielsen L, Drewes AM. Evoked human oesophageal hyperalgesia: a potential tool for analgesic evaluation? *Basic Clin Pharmacol Toxicol.* 2009;105(2):126-36.
62. Drewes AM, Schipper KP, Dimcevski G, et al. Multimodal assessment of pain in the esophagus: a new experimental model. *Am J Physiol Gastrointest Liver Physiol.* 2002;283(1):G95-103.
63. Rao SS, Read NW, Davison PA, Bannister JJ, Holdsworth CD. Anorectal sensitivity and responses to rectal distention in patients with ulcerative colitis. *Gastroenterology.* 1987;93(6):1270-5.
64. Chang L, Munakata J, Mayer EA, et al. Perceptual responses in patients with inflammatory and functional bowel disease. *Gut.* 2000;47(4):497-505.
65. Brochard C, Siproudhis L, Ropert A, Mallak A, Bretagne JF, Bouguen G. Anorectal dysfunction in patients with ulcerative colitis: impaired adaptation or enhanced perception? *Neurogastroenterol Motil.* 2015;27(7):1032-7.
66. Drewes AM, Frokjaer JB, Larsen E, Reddy H, Arendt-Nielsen L, Gregersen H. Pain and mechanical properties of the rectum in patients with active ulcerative colitis. *Inflamm Bowel Dis.* 2006;12(4):294-303.
67. Mavroudis G, Strid H, Jonefjäll B, Simrén M. Visceral hypersensitivity is together with psychological distress and female gender associated with severity of IBS-like symptoms in quiescent ulcerative colitis. *Neurogastroenterol Motil.* 2021;33(3):e13998.
68. Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. *Gastroenterology.* 2011;140(1):91-100.
69. Yuan YZ, Tao RJ, Xu B, et al. Functional brain imaging in irritable bowel syndrome with rectal balloon-distention by using fMRI. *World J Gastroenterol.* 2003;9(6):1356-60.
70. Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology.* 2000;118(5):842-8.
71. Frøkjær JB, Bouwense SA, Olesen SS, et al. Reduced cortical thickness of brain areas involved in pain processing in patients with chronic pancreatitis. *Clin Gastroenterol Hepatol.* 2012;10(4):434-8.e431.
72. Frøkjær JB, Olesen SS, Gram M, et al. Altered brain microstructure assessed by diffusion tensor imaging in patients with chronic pancreatitis. *Gut.* 2011;60(11):1554-62.
73. Muthulingam JA, Hansen TM, Drewes AM, Olesen SS, Frøkjær JB. Disrupted functional connectivity of default mode and salience networks in chronic pancreatitis patients. *Clin Neurophysiol.* 2020;131(5):1021-9.
74. Abber SR, Burton-Murray H. Evidence without evolution: a call for precision behavioural therapy in irritable bowel syndrome. *Lancet Gastroenterol Hepatol.* 2025;10(12):1055-7.
75. Whitehead WE, Palsson OS. Is rectal pain sensitivity a biological marker for irritable bowel syndrome: psychological influences on pain perception. *Gastroenterology.* 1998;115(5):1263-71.
76. Chen J, Li A, Wu W, et al. Machine learning to phenotype pain and predict response to pain interventions among young adults with irritable bowel syndrome. *medRxiv.* 2025.
77. Petersen KK, Hughes S, Vollert J. The use of quantitative sensory testing for personalized pain medicine in the age of AI. *Pain.* 2025;166(11S):S85-S90.
78. Weaver KR, Griffioen MA, Klinedinst NJ, et al. Quantitative Sensory Testing Across Chronic Pain Conditions and Use in Special Populations. *Front Pain Res (Lausanne).* 2021;2:779068.
79. Sarkar S, Woolf CJ, Hobson AR, Thompson DG, Aziz Q. Perceptual wind-up in the human oesophagus is enhanced by central sensitisation. *Gut.* 2006;55(7):920-5.
80. Geber C, Klein T, Azad S, et al. Test-retest and interobserver reliability of quantitative sensory testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS): a multi-centre study. *Pain.* 2011;152(3):548-56.
81. Demant DT, Lund K, Vollert J, et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain.* 2014;155(11):2263-73.
82. Bertoch T, D'Aunno D, McCoun J, et al. Suzetrigine, a Nonopioid Na V 1.8 inhibitor for treatment of moderate-to-severe acute pain: two phase 3 randomized clinical trials. *Anesthesiology.* 2025;142(6):1085-99.

83. Mulak A. Testing of visceral sensitivity. *J Physiol Pharmacol.* 2003;54 Suppl 4:55-72.
84. Li Y, Wang Y, Zuo X, et al. Visceral perception thresholds after rectal thermal and pressure stimuli in irritable bowel syndrome patients. *J Gastroenterol Hepatol.* 2004;19(2):187-91.
85. Zuo XL, Li YQ, Shi L, et al. Visceral hypersensitivity following cold water intake in subjects with irritable bowel syndrome. *J Gastroenterol.* 2006;41(4):311-7.
86. Rössel P, Arendt-Nielsen L, Niddam D, Chen AC, Drewes AM. Short latency cerebral response evoked by painful electrical stimulation applied to the human sigmoid colon and to the convergent referred somatic pain area. *Exp Brain Res.* 2003;151(1):115-22.
87. Coffin B, Bouhassira D, Sabaté JM, Barbe L, Jian R. Alteration of the spinal modulation of nociceptive processing in patients with irritable bowel syndrome. *Gut.* 2004;53(10):1465-70.
88. Jung B, Steinbach J, Beaumont C, Mittal RK. Lack of association between esophageal acid sensitivity detected by prolonged pH monitoring and Bernstein testing. *Am J Gastroenterol.* 2004;99(3):410-5.
89. van Wanrooij SJ, Wouters MM, Van Oudenhove L, et al. Sensitivity testing in irritable bowel syndrome with rectal capsaicin stimulations: role of TRPV1 upregulation and sensitization in visceral hypersensitivity? *Am J Gastroenterol.* 2014;109(1):99-109.
90. Brock C, Nissen TD, Gravesen FH, et al. Multimodal sensory testing of the rectum and rectosigmoid: development and reproducibility of a new method. *Neurogastroenterol Motil.* 2008;20(8):908-18.
91. King CD, Wong F, Currie T, Mauderli AP, Fillingim RB, Riley JL. Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. *Pain.* 2009;143(3):172-8.
92. Bouwense SA, Olesen SS, Drewes AM, Poley JW, van Goor H, Wilder-Smith OH. Effects of pregabalin on central sensitization in patients with chronic pancreatitis in a randomized, controlled trial. *PLoS One.* 2012;7(8):e42096.
93. Juel J, Olesen SS, Olesen AE, et al. Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial). *BMJ Open.* 2015;5(3):e007087.
94. Pickering G, Morel V, Voute M. Managing chronic pain: the ketamine option. *CNS Drugs.* 2026;40(1):19-41.
95. Houghton LA, Fell C, Whorwell PJ, Jones I, Sudworth DP, Gale JD. Effect of a second-generation alpha2delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. *Gut.* 2007;56(9):1218-25.
96. Klooker TK, Braak B, Koopman KE, et al. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut.* 2010;59(9):1213-21.
97. Rao SSC, Coss-Adame E, Yan Y, Erdogan A, Valestin J, Ayyala DN. Sensory adaptation training or escitalopram for IBS with constipation and rectal hypersensitivity: a randomized controlled trial. *Clin Transl Gastroenterol.* 2021;12(7):e00381.
98. Broekaert D, Fischler B, Sifrim D, Janssens J, Tack J. Influence of citalopram, a selective serotonin reuptake inhibitor, on oesophageal hypersensitivity: a double-blind, placebo-controlled study. *Aliment Pharmacol Ther.* 2006;23(3):365-70.
99. Chua YC, Ng KS, Sharma A, et al. Randomised clinical trial: pregabalin attenuates the development of acid-induced oesophageal hypersensitivity in healthy volunteers - a placebo-controlled study. *Aliment Pharmacol Ther.* 2012;35(3):319-26.
100. Tack J, Janssen P, Masaoka T, Farre R, Van Oudenhove L. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. *Clin Gastroenterol Hepatol.* 2012;10(11):1239-45.

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