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Precision Medicine Treatment for Painful Chronic Pancreatitis

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Abstract

Purpose of Review Traditional pain management of painful chronic pancreatitis (CP) follows a trial-and-error approach, often leading to long-term opioids and ineffective interventions. A precision medicine approach, tailoring treatment based on pain mechanisms, may allow a more targeted and rational use of interventions for painful CP. This review provides clinical pearls on how to diagnose each pain mechanism and presents a framework for mechanism-based management of CP.

Recent Findings Pain from CP can be caused by nociceptive, neuropathic, and/or nociplastic mechanisms. These pain mechanisms are not mutually exclusive and can co-exist within the same individual. The mechanisms leading to pain on an individual patient can be determined using a combination of medical history, survey instruments, abdominal imaging, response to different therapies, quantitative sensory testing, neuroimaging, and complex genetics. Treatments should be tailored to the underlying pain mechanism: (A) analgesics, lifestyle modification, endoscopic procedures, and surgery for nociceptive pain; (B) gabapentinoids and celiac plexus block for neuropathic pain; and (C) non-pharmacologic interventions (e.g. exercise, cognitive behavioral therapy, yoga), antidepressants (e.g. duloxetine, amitriptyline), acupuncture and neuromodulation approaches for nociplastic pain.

Summary A mechanism-based management of painful CP is feasible. However, there is a need to further refine the tools to diagnose pain mechanisms at the bedside and to develop more effective interventions for painful CP.

Keywords Chronic Pancreatitis · Pain · Nociplastic · Neuropathic · Precision Medicine · Opioid

Introduction

Chronic pancreatitis (CP) is a progressive and irreversible fibro-inflammatory disorder of the pancreas characterized by abdominal pain, exocrine insufficiency, and diabetes [1]. Abdominal pain is experienced by 80–90% of patients with CP and has a profound negative effect on quality of life [2, 3]. Current guidelines recommend treating pain using a trial-and-error approach adopted from other pain conditions [4–6]. Most patients fail achieving sufficient analgesia with non-opioid analgesics, resulting in ~75% of patients with CP being prescribed opioids, ~60% undergoing endoscopic interventions, and ~30% having a pancreatic surgery [7–10]. Despite these and other treatments, half of the patients with CP continue experiencing significant pain even a decade after disease onset [10]. A major reason for treatment failure is that pain in the context of CP is complex and caused by at least three different mechanisms that often overlap with one another: nociceptive, neuropathic, and nociplastic pain. Use of a precision-medicine treatment approach in which patients receive therapies based on their pain mechanisms could improve pain management in CP and has the potential to avoid unnecessary treatments. Herein, we will discuss the mechanisms implicated in pain of CP, provide tools to aid in the assessment of pain at the bedside, and present a framework to tailor treatments for each type of pain mechanism.

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Mechanisms of Pain in Chronic Pancreatitis

The International Association for the Study of Pain (IASP) classifies pain into 3 mechanisms: nociceptive, neuropathic, and nociplastic (Fig. 1). These pain mechanisms are not mutually exclusive and can co-exist within the same individual. Alternative pain mechanisms not included in these 3 categories may exist, however, we will focus on the categories currently recognized by the IASP.

Nociceptive Pain Nociceptive pain results from damage to non-nervous tissue with subsequent activation of nociceptors. Examples in CP include pain from pancreatic inflammation in acute pancreatitis, pancreatic duct (PD) hypertension due to a stone and/or stricture, or mechanical luminal obstruction by a pseudocyst. This type of pain is often well-localized and may respond better to peripherally-directed therapies such as non-steroidal anti-inflammatory drugs (NSAIDs), ductal decompression, or pseudocyst drainage.

Neuropathic Pain Neuropathic pain arises from injury or insult to peripheral or central nerves responsible for processing sensory information from the body. Representative conditions causing neuropathic pain include diabetic or nutritional neuropathy, which may be present in patients with CP. It's been recognized that CP can induce damage of perineural sheaths in the intrapancreatic nerves and increased neural density and hypertrophy, leading to hyperexcitability of afferent neurons and neuropathic pain [11]. Treatment often involves gabapentinoids or nerve blocks.

Nociplastic Pain This form of pain is caused by different central nervous system (CNS) pathways that lead to either augmented pain signals, diminished pain inhibition, or both [12, 13]. Nociplastic pain is a new term synonymous of older terms such as centralized pain or central sensitization [14]. Classic conditions driven by nociplastic pain are fibromyalgia and irritable bowel syndrome [15]. Accumulating evidence suggests that a subset of patients with CP have nociplastic pain [16–20]. This is characterized by widespread pain, CNS-driven symptoms (e.g. fatigue, memory problems, sleep difficulty, and/or mood disturbances), lack of response to peripherally-directed therapies alone, and preferential response to centrally-directed therapies (e.g. exercise, mindfulness, duloxetine) [21–23]. Opioids are particularly ineffective or may even worsen nociplastic pain through opioid-induced hyperalgesia [24].

Identifying the specific mechanisms causing pain in individual patients could allow a more targeted and rational use of interventions that act specifically on those mechanisms.

Fig. 1 Mechanisms of pain in CP. (NSAIDs: non-steroidal anti-inflammatory drugs; ERCP: endoscopic retrograde cholangiopancreatography; PD: pancreatic duct. Created in https://BioRender.com)

Effective treatments of nociplastic pain differ from those for nociceptive pain, as it primarily relies on non-pharmacologic therapies. The diagnosis of nociplastic pain does not in any way imply that nociceptive or neuropathic mechanisms of pain do not exist or do not require treatment [15]. These mechanisms often co-exist in the same patient and all need treatment. While there is not a single diagnostic tool that can specifically determine the pain mechanism implicated in a patient, in the following sections we will provide clinical pearls and a framework that can help clinicians toward a more structured approach to mechanism-based pain management of CP (Table 1).

Current Status of Pain Management in CP

Bedside Pain Assessment

Pain from CP has been classically reported as a dull epigastric pain that radiates to the back and worsens after meals. However, pain can be distributed anywhere in the abdomen and can sometimes be a clue for non-pancreatic origin of pain [25]. Pain severity assessments using a numeric rating or visual analogue scale are commonly done in clinical practice and fluctuate over time [26]. The severity of pain can be helpful, as higher intensity is correlated with anxiety, depression, sleep disturbance, physical disability, and impaired quality of life [27]. When stratifying pain patterns as constant or intermittent pain, several studies have shown that constant pain is associated with higher opioid use, increased resource utilization, lower quality of life, and self-reported features of nociplastic pain [18, 27–29]. A novel disease specific pain assessment tool (Comprehensive Pain Assessment Tool Short Form [COMPAT-SF]) that incorporate some of these and other dimensions (pain severity, pattern, provoking factors, spreading, and qualitative descriptors) has been developed and validated for painful CP [30, 31]. While these tools are helpful to monitor and understand the patient's pain experience, these provide limited information on the mechanisms of pain. Similar to other chronic pain conditions, physical examination is mostly useful to screen for serious concomitant pathologies (e.g. perforation, peritonitis, gastric outlet obstruction) and performs poorly to explain the mechanism of pain.

Abdominal Imaging

Cross-sectional images (computed tomography [CT] and/or magnetic resonance imaging [MRI]) are often used to assess

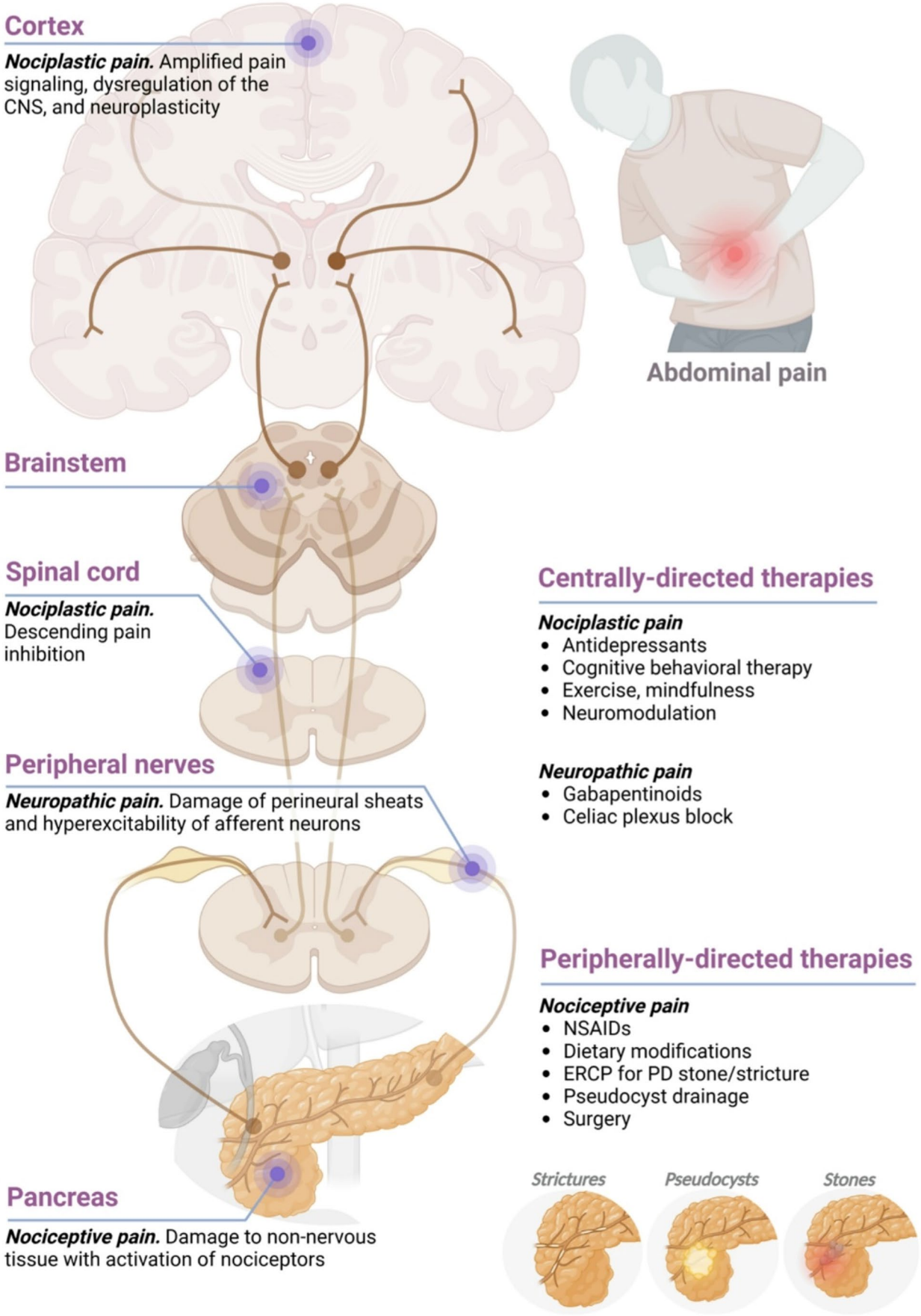
Cortex
Nociplastic pain. Amplified pain signaling, dysregulation of the CNS, and neuroplasticity
Abdominal pain
Brainstem
Spinal cord
Nociplastic pain. Descending pain inhibition
Peripheral nerves
Neuropathic pain. Damage of perineural sheats and hyperexcitability of afferent neurons
Pancreas
Nociceptive pain. Damage to non-nervous tissue with activation of nociceptors
Centrally-directed therapies
Nociplastic pain
Antidepressants
Cognitive behavioral therapy
Exercise, mindfulness
Neuromodulation
Neuropathic pain
Gabapentinoids
Celiac plexus block
Peripherally-directed therapies
Nociceptive pain
NSAIDs
Dietary modifications
ERCP for PD stone/stricture
Pseudocyst drainage
Surgery
Strictures
Pseudocysts
Stones

Table 1 Mechanistic-based approach for the treatment of painful CP

	Nociceptive	Neuropathic	Nociplastic
Mechanism	- Caused by direct tissue damage and activation of nociceptors due to pancreatic inflammation, ductal hypertension, or local complications.	- Nerve injury due to perineural sheath damage, neural hypertrophy, or increased neural density.	- Central sensitization with amplified pain signaling and/or loss of descending inhibitory pain control. - Either from long-term nociceptive/neuropathic input (bottom-up) or primary CNS dysfunction (top-down).
Phenotype	- Well-localized, deep, and dull pain in the epigastric region, radiating to the back. - Often episodic and related to meals. - Cross sectional images demonstrating PD stone/stricture, pseudocysts, inflammatory mass, biliary obstruction, duodenal stricture, or non-pancreatic etiology. - QST without hyperalgesia or abnormalities in pain processing.	- Pain is burning, tingling, electric-shock-like, or as a cold sensation. - It can follow dermatomal distribution and may present with allodynia or hyperalgesia. - Can be spontaneous or triggered by touch/movement. - QST with segmental hyperalgesia	- Widespread and constant pain, often shifting in intensity and location. - Accompanied by CNS-related symptoms like fatigue, sleep disturbance, mood issues, and cognitive dysfunction. - Poor response to conventional analgesics or pancreatic interventions. - QST with widespread hyperalgesia, facilitated temporal summation, and impaired conditioned pain modulation
Treatment	- **Non-pharmacologic**: Alcohol and smoking cessation, dietary modifications (low-fat diet, pancreatic rest). - **Pharmacologic**: NSAIDs, acetaminophen, short-term opioids, pancreatic enzyme replacement, antioxidants. - **Procedures**: ERCP, ESWL, surgical drainage/resection, TPIAT.	- **Pharmacologic**: Gabapentinoids (pregabalin, gabapentin). - **Procedures**: Celiac plexus block	- **Non-pharmacologic**: Exercise (walking, yoga, tai chi), sleep optimization, cognitive behavioral therapy, mindfulness. - **Pharmacologic**: Serotonin-norepinephrine reuptake inhibitors (duloxetine, milnacipran), tricyclic antidepressants (amitriptyline). - **Procedures**: Acupuncture, neuromodulation (spinal cord stimulation, transcranial magnetic stimulation).

PD: pancreatic duct; QST: quantitative sensory testing; NSAID: non-steroidal anti-inflammatory drugs; ERCP: endoscopic retrograde cholangiopancreatography; ESWL: extracorporeal shock wave lithotripsy; TPIAT: total pancreatectomy with islet auto-transplantation; CNS: central nervous system

for PD obstruction, local complications, and non-pancreatic etiology. When large duct obstruction by stones and/or strictures is noticed in cross-sectional images, it is often believed that the pain is due to ductal hypertension. This is the basis to offer endoscopic or surgical decompressive interventions as standard of care in patients with large-duct disease and pain refractory to analgesic therapy [4–6]. Similarly, cross-sectional images may identify local complications such as biliary strictures, pseudocysts, inflammatory mass, or gastric outlet obstruction, which are other recognized causes for nociceptive pain in CP that can be corrected with endoscopic, radiologic, and/or surgical procedures.

Medical Treatment

Patients with CP and their healthcare providers often assume that all their pain is nociceptive in nature. Medical management of pain in CP starts with non-opioid analgesics (e.g. acetaminophen, NSAIDs) [4]. Opioids are reserved for patients who don't improve with other methods, but up to 75% of patients with CP are prescribed opioids at least once and 44% are regular opioid users [10, 32]. In the United States, this has positioned CP as the gastrointestinal condition with the highest rates of opioid prescriptions in the outpatient setting, above chronic liver disease and Crohn's disease [33]. While the efficacy of opioids has not been compared to non-opioid analgesics in CP, opioids have shown to be ineffective in other chronic non-cancer pain conditions [34]. Not only are opioids often ineffective, but they also carry a risk for toxicity, overdose, dependence, and can further exacerbate CP-related pain. Given the limited efficacy of conventional analgesics, adjuvant therapies such as gabapentinoids (e.g. pregabalin, gabapentin) and/or antidepressants (e.g. duloxetine, nortriptyline, amitriptyline) are used with variable success and toxicity [5, 32].

Ductal Decompressive Procedures

Pancreatic stones are often treated with endoscopic retrograde cholangiopancreatography (ERCP) and sometimes

requires extracorporeal shock wave lithotripsy (ESWL) [35]. Clinical trials have focused in comparing endoscopic vs. surgical drainage procedures for patients with CP and PD obstruction, showing that surgery provides superior pain relief and is more cost-effective [36–38]. These interventions assume that pain in patients with CP and large-duct disease is nociceptive in nature. However, emerging data supports that even in patients with PD obstruction or other local complications, pain may be beyond nociceptive input alone. First, imaging findings such as ductal obstruction, inflammation, or pseudocyst, do not correlate with symptoms in patients with CP [17, 39]. For instance, there are patients with PD stones and/or ductal stricture who have no abdominal pain and patients with a single calcification who have severe abdominal pain. Second, in randomized controlled trials (RCTs) of patients with large-duct disease who undergo either endoscopic or surgical decompression for abdominal pain, ~40–60% of patients lack any pain relief at variable long-term follow-up periods [36, 37, 40]. If pain was purely nociceptive, a higher analgesic response would be expected with these interventions. Third, a recently published RCT showed that ESWL and ERCP provided pain relief comparable to sham at 24 weeks from the intervention, although pain relief at 12 weeks was superior with ductal decompression [41]. All this supports that alternative pain mechanisms should be considered before assuming that the pain is nociceptive in nature and automatically proceeding with ductal decompressive procedures, particularly given the high risk of complications associated with ERCP and pancreatic surgery. Knowing if the pain is only nociceptive in patients with ductal obstruction may allow providers to more confidently maximize medical, endoscopic, and surgical options. In contrast, if nociplastic pain was also present, this is an additional element to be treated in addition or in lieu of peripheral pathways.

Nociplastic Pain in CP

There are no validated diagnostic criteria specifically for nociplastic pain. Key phenotypic features include spatial distribution of pain and comorbid CNS symptoms. Other chronic pain conditions such as cirrhosis, autoimmune rheumatologic disorders, multiple sclerosis, and osteoarthritis, lead to nociplastic pain in variable prevalence [13, 42–44]. Because the term 'nociplastic pain' is relatively new, there are no prevalence estimates of nociplastic pain in CP [13].

Mechanisms

The pathophysiology of nociplastic pain includes amplification of ascending pain information and/or loss of descending inhibitory pain controls. Different pathways can be disrupted at the level of the spinal cord, brainstem, subcortical structures and/or neocortex and lead to the same process, reflecting the complexity and heterogeneity of nociplastic pain. There are two subsets of nociplastic pain: top-down and bottom-up. In bottom-up nociplastic pain, repeated nociceptive and/or neuropathic stimulation leads to augmented pain processing through ascending pathways to the CNS. Pain mediated by bottom-up pathways may respond to peripherally-directed treatments at least initially [45]. If the peripheral stimulus persists, synaptic connections may grow and reorganize in the CNS leading to neuroplasticity. In top-down nociplastic pain, augmented pain processing originates from the CNS independently from nociceptive or neuropathic input [45]. This pain mechanism is likely associated with a primary brain disorder, emerges early in life with sleep or memory problems, and has familial/genetic contribution [46]. In CP, nociplastic pain is likely caused by bottom-up mechanisms due to repeated nociceptive stimulation. However, top-down nociplastic pain likely plays a role in CP given the life experiences with substance use and genetic alterations in the nervous-system development, growth, and connectivity in these patients [47].

Phenotype

Nociplastic pain is often constant and is widely distributed across the body [13, 45]. The pain is typically described as dull, deep and aching with variation in location and intensity over time, and worsening or easing in response to multiple nonspecific factors. Approximately 60% of patients with painful CP experience constant pain, though this pattern may vary over time [27–29]. When using quantitative sensory testing (QST) in patients with painful CP, ~25% of patients have widespread hyperalgesia, which refers to increased pain sensitivity across multiple areas of the body [19]. These are the patients with higher pain intensity, higher rates of constant pain, lower quality of life, and limited physical functioning [19].

Other CNS-related symptoms such as fatigue, sleep, memory, concentration, and mood problems, are also inherent to nociplastic pain and are prevalent in CP. In a recent systematic review of 9 studies, the pooled prevalence of depression was 36% [48]. Anxiety is also common, reported in ~25–45% of patients with CP [49, 50]. Both depression and anxiety often overlap in the same patient [50]. Patients with psychiatric comorbidities have higher rates of pain severity, pain interference, and suicide [50, 51]. Using single nucleotide polymorphisms, an increased genetic susceptibility for depression, anxiety, and post-traumatic stress disorder has been observed in patients with CP and severe/constant pain [47, 52, 53]. Other CNS-related symptoms

have been less studied. Cross-sectional studies have shown that in patients with CP, 36% have fatigue, 50–70% have sleep disorders, and 41% have cognitive impairment [54–56]. These CNS-related symptoms are interconnected, with pain exacerbating these issues, which in turn further amplify pain perception. Recognizing these symptoms as key treatment targets is essential in managing CP-related pain.

Other characteristics described in patients with nociplastic pain include unresponsiveness to conventional analgesics or procedures intended to relieve pain, presence of numerous comorbid illnesses, personal history of chronic pain in different anatomical locations, family history of chronic pain, and hypersensitivities or numerous 'allergies' [45].

Sensory Abnormalities

Quantitative sensory testing (QST) uses standardized stimulations (e.g. thermal, mechanical, electrical, chemical or ischemic) of somatic and visceral tissue to explore subjective pain intensity response. Patients with nociplastic pain display increased sensitivity to painful (referred to as hyperalgesia) and normally non-painful (referred to as allodynia) somatic stimulation [19, 57]. Hyperalgesia in nociplastic pain is characteristically multisite and occurs both in symptomatic and asymptomatic remote body sites [58]. Other nociplastic features identified through QST include facilitated temporal summation of pain (increasing pain in response to repeated stimuli of equal intensity) and impaired conditioned pain modulation (a painful test stimulus is evaluated in the absence and in the presence of a second painful conditioning stimulus applied to a remote region of the body, with lack of reduction of pain during the presentation of the conditioning stimulus). Patients with nociplastic pain may also have multisensory sensitivity, with sensory amplification of sounds, smells, and light [59].

A bedside protocol for pancreatic QST evaluation has been developed and validated to assess pain mechanisms in CP [60]. Based on this protocol, three distinct patient groups have been identified: patients without hyperalgesia, segmental hyperalgesia, and widespread hyperalgesia [57]. Among these subgroups, patients with widespread hyperalgesia report higher pain intensity, persistent pain, and significantly reduced quality of life [19]. QST has also been studied in a pilot study as a predictor of analgesic response to endoscopic and surgical therapy in CP, with patients with widespread hyperalgesia having the lowest response to these therapies [61]. Even though QST can be helpful, there is substantial inter-participant and intra-participant heterogeneity in QST outcomes, and some individuals with nociplastic pain demonstrate normal to near-normal sensory processing [45, 62]. For these reasons, QST alone should not be used for the diagnosis or classification of nociplastic pain.

Brain Abnormalities

In patients with nociplastic pain, functional brain imaging studies show abnormal brain connectivity between brain regions. Pain widespreadness is associated with increased functional connectivity between regions of the default mode, salience and sensorimotor networks [63]. There are also abnormal responses in the descending pain modulatory system, which modulates activity in the spinal dorsal horn. These changes lead to a net disinhibition manifested by a decreased threshold for peripheral nociceptive firing [15]. In patients with CP, it has been demonstrated that there is abnormal cerebral processing, with a posterior shift of the operculo-insular source and an anterior shift of the cingulate source [64]. Structural brain changes have also been observed in CP, with MRI studies showing reduced cortical thickness in the precentral and superior temporal gyri [65].

Treatment

The treatment of nociplastic pain relies on non-pharmacological interventions, which should focus first on poor sleep and physical inactivity [66]. Either walking or water-based exercise programs can be helpful to stay active [21]. Other movement-based therapies such as yoga, tai chi and Qi Gong, have also been shown to be effective in nociplastic pain [15]. Specifically in CP, yoga demonstrated improvement of quality of life in 1 RCT of 60 patients with CP [67]. For sleep problems, a range of interventions including general sleep hygiene instructions readily available on websites, cognitive behavioral therapy (CBT) for insomnia, or low doses of tricyclics (e.g., cyclobenzaprine, amitriptyline), have shown promising results in pain [68]. Although beneficial in patients with chronic pain, these interventions have not yet been studied in CP. Self-management programs using CBT offers strategies and support to make behavioral changes consistent with improved health. A number of CBT programs have demonstrated to be effective in improving pain and function in a variety of chronic pain conditions [69]. A web-based CBT program for chronic pain was recently adapted for CP and tested in a pilot RCT of 30 patients with CP [70]. This program showed to be feasible, acceptable by patients with CP, and showed preliminary efficacy in reducing pain with the support of a professional coach [70]. An ongoing multicenter RCT in the US is enrolling patients to confirm the efficacy of this approach in CP (IMPACT-2 trial, NCT06386224).

Acupuncture is another non-pharmacologic intervention that has shown to be effective treating nociplastic pain [66]. The role of acupuncture in CP has been evaluated in 2 prior studies with conflicting results. The first study was conducted 3 decades ago in 23 patients with painful CP

and showed that both electroacupuncture (5 sessions over two weeks) and transcutaneous electrical nerve stimulation (TENS, daily stimulation over 3 weeks) failed to provide significant pain relief compared to sham [71]. In contrast, a more recent study of 15 patients with painful CP, one session of traditional acupuncture led to more pain relief compared with sham stimulation [72]. However, the effect was short-lived, and after 1-week follow-up, there was no difference in clinical pain scores between groups.

Neuromodulation with electrical impulses or chemical agents to specific nerve via non-invasive, minimally invasive, or surgical approaches, has also been investigated for nociplastic pain with variable results [73]. In CP, a recent systematic review of 22 studies using neuromodulation techniques (7 RCTs, 14 case series, and 1 survey), showed that repetitive transcranial magnetic stimulation (2 crossover clinical trials) and spinal cord stimulation (6 case series) had promising analgesic effects [74–76]. However, a recent RCT comparing spinal cord stimulation with sham, showed lack of significant pain relief with this intervention [77]. Further studies evaluating these approaches are awaited.

The pharmacologic therapies with the best evidence to treat nociplastic pain are duloxetine and milnacipran (both selective serotonin and norepinephrine reuptake inhibitors, SNRIs) [23]. Tricyclic antidepressants such as amitriptyline and nortriptyline have been used successfully for irritable bowel syndrome, another type of nociplastic pain [78]. None of these therapies have been formally assessed in patients with CP but are recommended by consensus guidelines when other therapies fail even in the absence of psychiatric comorbidities [5]. Other psychotropic medications are often needed when psychiatric comorbidities are present and may also help with nociplastic pain.

Neuropathic Pain in CP

Diagnosis

The diagnosis of neuropathic pain in CP is based on history and physical examination. The pain is characterized by abnormal sensations such as tingling, numbness, burning, cold, or electric shock. This type of pain typically follows the trajectory of peripheral nerves in a dermatomal distribution. Sometimes the pain is described as sharp, stabbing, or lancinating, which is difficult to differentiate from other types of pain. On physical examination, patients with neuropathic pain can be found to have allodynia and/or hyperalgesia. Different screening tools are available to help identifying neuropathic pain, including painDETECT, Neuropathic Pain Questionnaire, and PROMIS Pain Quality Short Forms [79, 80]. Using the latter instrument, pain was classified as neuropathic in 37% of a prospectively enrolled cohort of 391 patients with CP and abdominal pain [20]. However, among the patients with neuropathic pain, 87% also had nociceptive pain and only 13% had neuropathic pain alone. There is no confirmatory test for neuropathic pain in CP. QST can be helpful, with neuropathic pain displaying segmental hyperalgesia [81]. Serum biomarkers appear promising, as shown in a study that found that higher serum levels of glycoprotein 130 (GP130), a coreceptor for interleukin 6, was associated with neuropathic pain [82].

Treatment

First line therapy of neuropathic pain includes using gabapentin or pregabalin [83]. Of these, only pregabalin has been studied in CP [84]. In one RCT of 64 patients with CP and chronic pain that were randomized to either escalating doses of pregabalin (150–600 mg per day) or placebo, pregabalin was superior in reducing opioid use and pain severity at 3 weeks [84]. Pregabalin was overall well tolerated, with mild side effects like dizziness and drowsiness. In a mechanistic study of a subgroup of patients from this trial, QST findings of segmental hyperalgesia of the pancreatic viscerotome was associated with higher pregabalin efficacy, which indicates that QST could help selecting patients that respond best to this therapy [81]. In 2 other RCTs comparing the combination of pregabalin with antioxidants vs. placebo, the combination therapy reduced pain scores and number of painful days [85, 86].

Celiac plexus block (CPB) can be considered as an alternative therapy for neuropathic pain. This is recommended by guidelines for pain management in CP when other treatments have failed [4, 35]. However, two prior meta-analyses have suggested an efficacy of only ~50% with CPB [87, 88]. A multicenter RCT is being conducted to assess the analgesic efficacy of CPB as compared to sham in patients with painful CP (NCT06178315) [89].

Nociceptive Pain in CP

Phenotype

Nociceptive pain is well-localized, reproducible, and proportional to the injury. If pain is from acute pancreatitis, serum pancreatic enzymes may be elevated. Abdominal cross-sectional images can reveal a pain source (e.g. PD stone, acute pancreatitis, pseudocyst, inflammatory mass). However, diagnosing the pain mechanism with images alone is challenging, as multiple overlapping mechanisms may contribute to pain. Analgesic relief to traditional NSAIDs or

acetaminophen can serve as a clue to the nociceptive nature of pain. Especially with small duct CP, the diagnosis of nociceptive pain is often one of exclusion, made after ruling out nociplastic and neuropathic pain mechanisms.

Treatment

In the absence of ductal obstruction or other local complication, pain management is based in the use of NSAIDs and acetaminophen. In patients with acute nociceptive pain, a short course of opioids can be effective [90]. Cessation of alcohol and tobacco can potentially reduce abdominal pain from CP [91, 92]. Pancreatic secretion can be decreased with pancreatic enzyme replacement therapy, which can be effective in reducing pain in some patients [93, 94]. Pancreatic stimulation can also be decreased with diet modification (e.g. low fat diet) or cessation of food intake with temporal use of nasojejunal feedings or parenteral nutrition [95, 96]. Combined antioxidants (selenium, beta-carotene, vitamin C, vitamin E, and methionine), showed to provide pain relief without serious adverse events in a meta-analysis of 9 RCTS [97]. A subset of patients with CP may have small intestinal bacterial overgrowth, gastroparesis, constipation, or musculoskeletal pain, who would benefit of targeted therapies for these conditions [98, 99].

In patients with large duct disease, the standard of care is still ductal decompression. The choice between surgical or endoscopic drainage remains a subject of debate, with current data supporting the use of early surgical drainage for short and long-term pain relief [35–38, 100]. However, surgery is not suitable for all patients and often patients or providers prefer less invasive approaches before surgery. Total pancreatectomy and islet auto-transplantation (TP-IAT) can provide pain relief and better quality of life to selected patients with CP and nociceptive pain who do not improve by other methods [101]. Table 2 summarizes all the therapies evaluated in RCTs for patients with CP and that reported pain outcomes.

Conclusion

Pain management in CP remains a significant challenge due to the interplay of nociceptive, neuropathic and nociplastic pain. Recognizing between the different pain mechanisms implicated in each patient's pain experience, has the potential to more rationally assign the correct therapies. Patients with predominant nociceptive pain benefit from peripherally-directed interventions, while those with nociplastic pain require a multimodal approach integrating non-pharmacologic and centrally-directed therapies. Future research should focus on refining patient phenotyping tools and developing personalized treatment algorithms to optimize outcomes. A shift towards precision medicine, integrating novel diagnostic techniques with tailored interventions, holds promise for improving the pain experience and quality of life of patients with CP.

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  This study highlights the heterogeneity of pain mechanisms in CP, emphasizing the importance of using survey methods and patient reported outcomes to differentiate pain mechanisms in CP at the bedside.

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  This study portrays the role of pancreatic QST to classify pain mechanisms in CP and how these findings are independent of psychiatric comorbidities. It emphasizes the importance on developing more precise tools that can guide on personalized treatment decisions based on the individual's pain mechanism(s) present.

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  This study compared ESWL +ERCP vs. sham in patients with CP and ductal obstruction. Results showed modest short-term pain relief at 12 weeks but no long-term benefits at 24 weeks, highlighting that alternative pain mechanisms may be present in patients with ductal obstruction that need to be

Table 2 Published RCTs evaluating therapies for patients with CP and that reported pain outcomes

Intervention	Comparison	Studies	Results	Targeted pain mechanism	Conclusion
Combined ESWL and ERCP	Sham	1 RCT (n = 106) [41]	In patients with PD stone, ESWL + ERCP provided more pain relief at 12 weeks, but no difference at 24 weeks	Nociceptive	Beneficial at 12 weeks but not sustained at 24 weeks
Pancreatic surgery	ERCP	3 RCTs (n = 199) [24, 37, 40]	In patients with obstructed PD, surgery was superior to ERCP in improving pain relief, complete pain relief, and quality of life. Similar mortality, adverse events, or hospital stay	Nociceptive	Beneficial, but lack comparisons with sham
PERT	Placebo	1 RCT (n = 54) [94]	More pain relief with PERT, though not statistically significant	Nociceptive	Unclear benefit
Anti-oxidants	Placebo	8 RCTs (n = 478) [102–109]	Three RCTs reported moderate pain relief with antioxidants [102–104], while five studies found no benefits [105–109]	Nociceptive	Possibly beneficial
Camostat (protease inhibitor)	Placebo	1 RCT (n = 264) [110]	No significant difference in pain relief or change in quality of life	Nociceptive	Not beneficial
Pregabalin [84–86]	Placebo	3 RCTs (n = 241) [84–86]	One RCT found pregabalin had more pain relief and reduced opioid use at 3 weeks [84]. Two RCTs showed pregabalin and antioxidants reduced pain up to 6 months, analgesic use, or admissions [85, 86]	Neuropathic	Beneficial
Yoga	Usual care	1 RCT (n = 60) [67]	Improved quality of life, with improved bodily pain domain with yoga	Nociplastic	Possibly beneficial
Cannabinoids (single dose)	Placebo	1 RCT (n = 24) [111]	No significant differences in pain relief	Nociplastic	Not beneficial
Web-based CBT	Usual care	1 RCT (n = 30) [70]	This pilot trial showed significant reduction in pain interference and intensity after three months of CBT	Nociplastic	Possibly beneficial
Acupuncture (single session)	Sham	1 RCT (n = 15) [72]	Acupuncture provided immediate pain relief, but the effect was not durable at 1-7 days	Nociplastic	Possibly beneficial, but short-lasting effect
TENS or electroacupuncture	Sham	1 RCT (n = 23) [71]	Neither TENS or electroacupuncture showed analgesic benefits	Nociplastic	Not beneficial
rTMS	Sham	2 RCTs (n = 22) [75, 76]	Significant pain relief with low-frequency stimulation, with effects lasting 3 weeks	Nociplastic	Possibly beneficial
tDCS and tPCS	Sham	1 RCT (n = 6) [112]	No significant pain relief	Nociplastic	Not beneficial
Non-invasive VNS	Sham	2 RCTs (n = 42) [113, 114]	No significant pain relief	Nociplastic	Not beneficial
SCS	Sham	1 RCT (n = 16) [77]	No significant pain relief	Nociplastic	Not beneficial

ESWL: extracorporeal shock wave lithotripsy; ERCP: endoscopic retrograde cholangiopancreatography; RCT: randomized clinical trials, PD: pancreatic duct; PERT: pancreatic enzyme replacement therapy; CBT: cognitive behavioral therapy; TENS: transcutaneous electrical nerve stimulation; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; tPCS: transcranial pulsed current stimulation; VNS: vagal nerve stimulation; SCS: spinal cord stimulation

addressed prior to deciding on ductal decompressive interventions.

- van Veldhuisen CL, Kempeneers MA, de Rijk FEM, Bouwense SA, Bruno MJ, Fockens P, et al. Long-Term Outcomes of Early Surgery vs Endoscopy First in Chronic Pancreatitis: Follow-Up Analysis of the ESCAPE Randomized Clinical Trial. JAMA Surg. 2025;160(2):126–33. https://doi.org/10.1001/jamasurg.2024.5182.

  This study highlights the long-term benefits of early surgery over an endoscopy in painful CP with dilated PD. Early surgery led to lower pain scores, higher patient satisfaction, and reduced need for reinterventions.

- Sheth SG, Machicado JD, Chalhoub JM, Forsmark C, Zyromski N, Thosani NC, et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the management of chronic pancreatitis: summary and recommendations. Gastrointestinal Endoscopy. 2024;100(4):584–94. https://doi.org/10.1016/j.gie.2024.05.016.

This guideline from the ASGE provides evidence-based recommendations on endoscopic management of CP, addressing pain relief, PD obstructions, and complications.

- Andrade MF, Fabris-Moraes W, Pacheco-Barrios K, Fregni F. Effect of Neurostimulation on Chronic Pancreatic Pain: A Systematic Review. Neuromodulation. 2024;27(8):1255–65. https://doi.org/10.1016/j.neurom.2024.08.003.

  This systematic review highlights the potential of neurostimulation in reducing CP-related pain and opioid use, with promising effects observed for repetitive transcranical magnetic stimulation and spinal cord stimulation.

- Kaplan CM, Kelleher E, Irani A, Schrepf A, Clauw DJ, Harte SE. Deciphering nociplastic pain: clinical features, risk factors and potential mechanisms. Nat Rev Neurol. 2024;20(6):347–63. https://doi.org/10.1038/s41582-024-00966-8.

  This review explains the meaning of nociplastic pain, highlighting its key symptoms, risk factors, and mechanisms while providing valuable insights into diagnosis and treatment.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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