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Painful Chronic Pancreatitis - New approaches for evaluation and management

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Abstract

Purpose of Review.—Management of abdominal pain in patients with chronic pancreatitis (CP) is often suboptimal. We review recent data on the epidemiology and new approaches for managing pain in CP.

Recent findings.—CP duration does not appear to affect the pain experience. Pain pattern in CP patients frequently changes, and is not related to traditional patient and disease-related factors. Psychologic comorbidities, i.e. anxiety and depression, are frequent in patients with CP, and are associated with more severe pain and pain interference. Adjunctive treatments, such as cognitive behavioral therapy, may positively influence pain management in CP. Total pancreatectomy with islet autotransplantation (TPIAT) is an increasingly adopted treatment option in painful CP. Ongoing multicenter studies will help define optimal candidates, predictors of successful pain remission and diabetes outcomes after TPIAT. Pancreatic Quantitative Sensory testing (P-QST), a promising technique to interrogate nociception and sensory response, holds promise to identify patients with central sensitization. Initial studies show feasibility to stratify patients into defined pain profiles, and future studies will explore if these can help in prognostication of pain therapy.

Summary.—Several lines of investigations currently under evaluation are likely to have a positive impact on the management of pain in CP.

Keywords

Pain; psychosocial factors; cognitive behavioral therapy; TPIAT; Quantitative Sensory Testing; chronic pancreatitis

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Introduction.

Abdominal pain is the most common symptom of patients with chronic pancreatitis (CP), and is associated with a high economic, personal, and societal burden. Currently, the general approach to managing abdominal pain hinges on pancreatic morphology on cross-sectional imaging. After exclusion of non-pancreatic causes and local complications, patients with features suggestive of obstructive disease, i.e. pancreatic ductal obstruction due to stones and/or strictures, are offered endoscopic and/or surgical therapies, while those with non-obstructive disease are managed medically[1, 2]. Select patients who fail medical, endoscopic and sometimes surgical therapies may undergo a total pancreatectomy with islet autotransplantation (TPIAT)[3]. However, pain management is often suboptimal leading to chronic opioid use and its associated side effects, increased health care utilization and poor quality of life.

This review discusses recent studies that address knowledge gaps in the evaluation and management of pain in adult patients with CP. Specifically, we focus on the natural course of pain, the promising role of psychosocial interventions, outcomes and research opportunities with TPIAT, and how to identify patients more likely to benefit from interventions. Investigators in the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) are participating and/or leading in several of these initiatives.

Epidemiology of pain in CP.

There is a high degree of variability in the presence, severity and temporal nature of the pain experience in patients with CP. Cross-sectionally, in the North American Pancreatitis Studies (NAPS2), 14% patients reported no pain, 69% severe, 55% constant pain, and as many as 62% were on opioid medications[4]. Corresponding data from the Dutch Pancreatitis Study Group CARE cohort noted no pain in 28% patients, intermittent in 20%, constant pain in 52%, and 39% were using opioid medications. Higher pain severity was more likely to be associated with constant pain[5]. In both studies, morphologic appearance of pancreas on cross-sectional imaging did not correlate with patient's pain experience[5, 6].

Two recent studies evaluated the natural course of pain in CP. In 279 NAPS2 patients enrolled from UPMC, the median duration of observation was 12.4 years[7]. Abdominal pain at any time was noted in 89.6% patients, and about two thirds had Type B pain (persistent pain and/or clusters of recurrent severe pain). Endoscopic and/or surgical treatment was needed in 63.8%, mostly for management of abdominal pain. Pain at any time was more common in patients who underwent an intervention (98.7% vs. 75.2% in medical management arm). Close to half (46.6%) were noted to have abdominal pain at the end of follow up, and this was more common among patients in the intervention arm (58.4% vs. 25.7%). Importantly, disease duration did not associate with pain at the end of follow-up, severe or constant pain[7].

In the aforementioned CARE study, 905 patients provided longitudinal data during a median follow-up of 47 months. In yearly questionnaires, patients reported their pain pattern, pain intensity (Izbicki pain questionnaire), nature of pain (neuropathic) and quality of life. As many as 61% patients reported a change in pattern of pain at least once, approximately

one-third changed pain pattern each year, and these were not associated with endoscopic or surgical interventions. On multivariable regression analyses, pain intensity, as expected, was associated with a change in pain pattern, and surgical intervention with change from pain to no pain.

The lack of association of pain with many of the patient and disease-related factors underscores the need to identify other determinants for pain experience, such as the role of psychosocial factors and psychologic comorbidities and address these as part of pain management. Strategies to identify which patients are likely to respond to interventions are also important. These concepts are elaborated below.

Psychosocial interventions in painful CP.

Pain is a distressing symptom and reduces health-related quality of life (HRQOL) across multiple domains of physical, psychological, and social functioning[8, 9]. Central to contemporary models of chronic pain are the interrelationships among physical, psychological, and social factors that influence pain and disability – commonly referred to as the biopsychosocial model of pain[10]. Psychosocial factors are complex, in part because they serve as vulnerability or risk factors for developing or maintaining pain and disability, but they also serve as consequences of experiencing chronic pain. There are a common set of psychosocial variables that have been identified as relevant and significant to the pain experience including beliefs, appraisals, mood, and behaviors, and are often targeted in psychosocial treatments (for a review see [11]). For example, maladaptive beliefs (e.g., fear of pain) and high levels of pain catastrophizing (e.g., thoughts of helplessness and ability to cope with pain) have been shown to amplify pain and disability[11].

Psychological comorbidities are also common among individuals with chronic pain. For example, in one recent study among patients with CP, 40% had clinically significant levels of anxiety and depressive symptoms, which were associated with higher pain severity and pain interference[12]. Substance use, in particular alcohol abuse and smoking, are the most commonly recognized causes for recurrent acute and CP[13], and are also associated with increased pain interference and burden in general chronic pain populations[14, 15]. Studies in individuals with CP have predominantly focused on effects of pain on HRQOL, e.g., [16]. However, there are many gaps in understanding of other psychosocial risk and protective factors (e.g., pain catastrophizing, fear of pain, coping, optimism, social support, resilience). Table 1 highlights psychosocial factors relevant to painful CP.

Psychological therapies, and the principles on which they are based, play an important role in chronic pain management. There are different approaches to psychological treatment for chronic pain, including behavioral, cognitive, cognitive-behavioral, and mindfulness-based therapies. Cognitive-behavioral therapies (CBT) are the most well-studied treatments across a broad range of pain conditions. These therapies aim to enhance patients' beliefs in their ability to cope with pain, to change negative thoughts and feelings, and to change behaviors that maintain or worsen pain, disability, distress and catastrophic thinking[17]. Evidence shows that CBT is widely accepted; multiple systematic reviews and meta-analyses of CBT interventions for chronic pain demonstrate beneficial effects on pain, disability, and mood [18]. CBT is relevant to the experience of painful CP, especially given the persisting

impacts on HRQOL. However, to date, there has been limited application of psychosocial treatments to painful CP. One pilot study has evaluated the feasibility of a telephone-based mindfulness therapy service[19], where patients listened to daily pre-recorded telephone messages aiming to increase purposeful focused awareness. This study found that patients were willing to use this service and that they had some preliminary improvements in HRQOL.

Recent guidelines encourage the use of psychosocial interventions as part of a multidisciplinary approach to CP pain management[20]. Given the persistence of pain and its impacts, psychosocial interventions such as CBT could be of significant benefit to patients with CP. Future work on psychosocial interventions in painful CP is critically needed, especially large definitive randomized trials to evaluate patient benefit for reducing pain and disability and improving HRQOL. Moreover, further work is needed to understand psychosocial risk and protective factors in individuals with CP across the lifespan that may inform the optimization of psychosocial treatments for painful CP.

TPIAT.

The choice for surgical approach in CP depends on patient characteristics, disease features, and pancreas morphology. One approach that has gained traction over the past decade is TPIAT. TPIAT may particularly be considered for hereditary pancreatitis, and in small duct disease where surgical drainage procedures are infeasible[3]. In TPIAT, the pancreas is entirely resected. The pancreas is then processed by enzymatic and mechanical digestion to release islets, which are infused into the portal vein of the recipient to mitigate the severity of post-surgical diabetes. Islet isolation requires a specialized laboratory facility; isolation procedures are adapted for individual TPIAT recipients to address differences in pancreatic architecture with variable fibrosis and differences in the islet-exocrine pancreas morphology between children and adults[21].

Data from patients undergoing TPIAT before 2009 show a 10-year actuarial survival of 72%, with BMI >30 kg/m2 at surgery conveying a 9-fold increased risk for death at 10 years[22]. In a meta-analysis of 1,200 TPIAT recipients, about 30% were insulin independent and 63% were off opioids at 1 year after surgery[23]. HRQOL (typically assessed by Short Form (SF)-36 or SF-12) is improved after surgery[24, 25]. High residual pain burden after surgery, observed in a subset of patients, is associated with multiple ERCPs, alcohol etiology, and prolonged opioid use before surgery[26–28], and poor diabetes outcomes with low islet mass at transplant, previous pancreatic surgeries, and more advanced disease (Table 2)[24, 26–30]. TPIAT appears to be effective in reducing medical costs long-term in children and adults[31–33]. However, many unanswered questions remain. TPIAT is offered at only a few centers and requires specialized infrastructure. Most of the current data come from single center studies with variable compliance with clinical follow up. Therefore, studies are needed to understand generalizability of patient selection, safety, short- and long-term outcomes across centers.

The NIH-funded multicenter Prospective Observational Study in TPIAT (POST) is following patients undergoing TPIAT at 13 centers in the U.S. to define which patient and disease factors predict successful pain remission and diabetes outcomes after TPIAT, in order

to better select and stratify patients for this surgery[34]. POST will also study cost-effectiveness of TPIAT and a variety of other secondary outcomes in a diverse and rigorously phenotyped cohort. While outcomes data are not yet available, preliminary published data provide a snapshot of the typical patients seen for TPIAT in the United States. In the first 230 participants enrolled, the mean patient age at TPIAT was 31 years, 55% had genetic risk factors for pancreatitis identified, and only 12% had diabetes before surgery[35].

Aside from the potential therapeutic benefit to the patient, TPIAT has provided unique opportunities for pancreatitis research. Pancreas tissue from human patients is not routinely accessible for study, due to the invasiveness of pancreas biopsy. Thus, when pancreata are processed for TPIAT, there is an opportunity to utilize biopsy samples and discarded exocrine pancreas tissue to understand the mechanisms underlying pancreatitis. Recent research suggests different immunopathology and genetic expression pathways in hereditary versus idiopathic versus alcohol-mediated disease[36, 37]. Tissue from patients with hereditary forms of pancreatitis was observed to have a CD3+ T-cell predominate inflammatory infiltrate as opposed to a CD68+ macrophage infiltrate in idiopathic disease[36]. Pancreas tissue from patients undergoing TPIAT has also provided valuable insights on the clinical diagnosis of pancreatitis. MRI/MRCP was better than EUS for diagnosing non-calcific pancreatitis based on pancreas biopsy specimens, and CT-determined atrophy alone did not appear to correlate with fibrosis in patients with recurrent acute and CP[38–40]. These examples highlight opportunities to advance clinical research aside clinical care in TPIAT through multidisciplinary and multi-institutional collaboration.

Quantitative Sensory Testing.

A recent well-designed randomized trial (ESCAPE) from the Dutch Pancreatitis Study Group compared surgery vs. endoscopy first approach in patients with painful CP[41]. Although the surgery first approach was found to be superior, it is notable that durable pain relief at 18 months (complete or partial pain relief) was only modest in the surgery first arm (58% vs. 40% in the endoscopy arm). In carefully selected patients, 10–20% continue to struggle with high pain burden at 1 to 15 years after TPIAT[22, 24]. The lack of pain response even after invasive interventions is thought to be at least partially due to supraspinal central sensitization, a phenomenon of neuropathic and neuroplastic remodeling resulting from persistent pain stimuli[42–46].

Quantitative Sensory Testing (QST) is an investigative technique of standardized stimulations and evoked patient responses that tests nociception and elucidates detailed patterns of sensory response. QST has been used in other painful conditions to guide treatment decisions by identifying patients with central sensitization [47–49]. Earlier experimental QST protocols demonstrated correlation of central sensitization with more severe CP[43, 50], and identified central sensitization as a predictor of poor surgical outcome after thoracoscopic splanchnic denervation in CP[51, 52]. Moreover, the presence of sensitization at the pancreatic viscerotome predicted therapeutic response to pregabalin[53]. A new, refined, clinically-feasible bedside pancreas-specific QST protocol

(P-QST) has been developed through a collaborative research consortium, and has the potential for adoption into routine clinical practice[54, 55].

P-QST evaluates both static and dynamic components of visceral pain in CP. It uses pressure testing (with a digital algometer) of the T10 dermatome as a proxy for the pancreatic viscerotome (made possible by spinal convergence of visceral and somatic nerves) and testing of pancreatic and non-pancreatic (control) dermatomes to evaluate for systemic changes in sensory processing suggestive of central sensitization. Non-invasive pin-prick testing evaluates for temporal summation to detect neuronal hypersensitivity. A conditioned pain modulation paradigm is used to determine whether the central descending inhibition pathway is intact; for this, hand immersion in ice-water for two minutes serves as a noxious stimulus to activate the pathway and comparison of pressure algometer testing before and after the stimulus allows for detection of appropriate elevation in the pain detection threshold following pathway activation (Table 3 provides details).

The initial study enrolled 122 non-disease controls to establish a nomogram for phenotyping patients with painful CP into mutually exclusive pain phenotypes, i.e. no abnormal sensitization, segmental sensitization (sensitization of the pancreatic viscerotome), and widespread hyperalgesia suggestive of central sensitization[54]. A cross-sectional study applied this nomogram in 141 patients with painful CP and identified 34 (24%) as having central sensitization[56].

Incorporation of P-QST into the existing treatment paradigm for painful CP has the potential to optimize treatment strategies. It is hypothesized that patients with central sensitization are less likely to respond to successful invasive therapy due to altered pain processing. Therefore, patients who have no abnormal sensitization or segmental sensitization would be more likely to benefit from invasive treatments. Since central sensitization is only one aspect of pain response and P-QST does not account for clinical, psychosocial, or other disease factors affecting the pain experience, it is likely that a model incorporating P-QST results with predictors of pain response will provide an individualized prediction of treatment response to planned interventions. Future research is expected to address these questions.

Approach of the CPDPC to address knowledge gaps.

CPDPC has established a prospective, longitudinal cohort of CP in adults (PROCEED)[57]. In addition to deep phenotyping, data are being collected at enrollment and during follow-up for a variety of pain-related variables (e.g., temporal nature and severity, neuropathic or nociceptive pain quality, medication use, quality of life, etc.) and outcomes. These data provide an opportunity to perform a number of secondary analyses to understand the evolution and determinants of pain in CP. The linked biorepository allows performance of translational studies to identify mechanisms of pain and predictors of treatment response. An example is to define cytokine signatures that associate with mechanistic pain profiles. Such information could lead to a better understanding of pain mechanisms and potential therapeutic targets. Opportunities exist for collaboration with the POST study for data, samples and tissue specimens for clinical and mechanistic studies.

PROCEED also serves as a platform to conduct clinical trials for promising treatments for pain. As an example, partnering with PROCEED clinical sites[57] we recently completed a pilot feasibility randomized controlled trial of an internet CBT program in 30 adults with painful CP (ClinicalTrials.gov Identifier: NCT03322644). Our findings demonstrated feasibility and acceptability of internet-delivered CBT for chronic pain. Patients randomized to Internet-CBT vs. control demonstrated moderate to large effects in reducing pain intensity and pain interference from baseline to 3-months. A larger more definitive study has been planned. Finally, in context of the current review, predicting outcomes of endoscopic and/or surgical treatment performed for pain in CP patients based on P-QST profile is an approved ancillary study of the CPDPC.

Conclusions.

Current approaches to evaluation and management of pain in CP have limitations. Research in the next few years is expected to develop better ways to assess patient's pain experience, incorporate adjunctive treatments in pain management, and test strategies to prognosticate response to invasive treatments. These advances will provide individualized treatment planning and improve outcomes of pain management in CP.

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Key points.

- The pattern of pain in patients with chronic pancreatitis is dynamic, changes over time, and not influenced by disease duration.
- There is a high prevalence of psychologic comorbidity in patients with chronic pancreatitis, and these are associated with pain severity and interference.
- Cognitive behavioral therapy as an adjunctive treatment has the potential to improve outcomes of pain management.
- Ongoing longitudinal study on TPIAT will inform optimal candidacy, predictors of pain response and diabetes outcomes.
- Pancreatic quantitative sensory testing is a promising bedside testing technique that may help identify patients likely to benefit from invasive treatments.

Table 1.

Psychosocial mechanisms and functional outcomes relevant to painful CP.

Construct	Description	Process
Emotional function	Mood/affect; anxiety; depression	Vulnerability factor and influenced by ongoing pain
Substance use	Alcohol use; smoking; opioid misuse behaviors	Vulnerability factor and influenced by ongoing pain
Sleep quality	Perception of sleep quality, difficulties with sleep onset and maintenance, insomnia symptoms	Vulnerability factor and influenced by ongoing pain
Physical function	Ability to perform physical tasks and vigorous activities	Influenced by ongoing pain
Pain-related interference with daily activities	Interference due to pain on activities of daily life including work, social life, and recreation	Influenced by ongoing pain
Beliefs and expectations	Pain threat, fear of pain, coping efficacy	Vulnerability factor and influenced by ongoing pain
Trauma and stress	History of adverse childhood events; sexual or physical trauma; military trauma	Vulnerability factor
Catastrophizing	Rumination, magnification, and helplessness about pain	Vulnerability factor and influenced by ongoing pain
Social support	Perception of and satisfaction with help received from others (e.g., emotional, tangible)	Protective factor
Self-efficacy	Confidence in coping with pain and performing activities while in pain	Protective factor

Table 2 :

Risk factors associated with poor pain or diabetes outcomes, adapted and updated from Abu-El-Haija et al, ref. #3.

Factors associated with residual pain and/or opioid use after TPIAT	Factors associated with insulin independence and/or islet graft failure
Alcohol etiology of pancreatitis	Low islet mass transplanted
High dose or prolonged (>5 yrs) pre-operative opioid use	Alcohol etiology of pancreatitis
Pancreas divisum	Previous pancreas drainage or resection surgery
High number of prior ERCP stents (≥3)	Pancreatic atrophy or calcifications
Older age	Prolonged duration pancreatitis (>5 years)
Prior Whipple surgery	Adolescent/Adult (vs. young child)
Obesity (BMI ≥30 kg/m2)	Smoking history
	Pre-diabetes before TPIAT

Table 3.

Pancreatic Quantitative Sensory Testing (P-QST): Concepts and measurements assessing aspects of central sensitization.

	Temporal Summation	Pain Pressure Detection Thresholds	Cold Pressor Test	Conditioned Pain Modulation
Concept	Measures 'wind-up' neuronal hypersensitivity: increase in pain response to repeated stimuli of similar intensity	Evaluation of local or widespread hypersensitivity	Activation of central descending inhibitory pathway	Pain tolerance following activation of descending inhibitory pathway
Testing Technique	**Repetitive pin-prick stimulation.** Single stimulation at each site followed by 10 stimulations repeated at 1 second interval. Pain ratings on a 0–10 scale are obtained verbally from patient after single stimulus and series	**Pressure Algometer used to apply pressure at pancreatic and non-pancreatic dermatomes.** Pressure is applied at steadily increasing rate. Patient states when they first detect pain (pain pressure detection threshold)	**Hand is immersed in ice-chilled water bucket** for total 120 seconds, or less if pain is intolerable.	**Maximum pressure tolerance** is assessed at 15 cms above patella in L4 dermatome before and after cold pressor test is performed. Pressure is applied at steadily increasing rate. Patient states when they reach maximum pressure tolerance (pain pressure tolerance threshold)
Interpretation of Measurement	Larger response after 10 stimuli compared to response after one stimulus suggests neuronal hypersensitivity	Measurement of absolute pressure thresholds as well as ratio of pancreatic to non-pancreatic dermatomes facilitates assessment of abnormal local or widespread sensitization	Total time of ice water immersion tolerance indicates relative activation of descending inhibition	Pain tolerance following activation of descending inhibitory pathway should increase if pathway is intact and processing pain signals normally