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REVIEW

Medical Management of Pain in Chronic Pancreatitis

Vikesh K. Singh[1] · **Asbjørn M. Drewes**[2]

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Abstract The medical management of pain in chronic pancreatitis continues to pose significant challenges for clinicians caring for these patients. There are increasing data, suggesting that pain in chronic pancreatitis is largely due to peripheral and central sensitization that evolves, over time, as a result of nociceptive afferent associated with chronic inflammation and fibrosis of the pancreas. In many instances, patients rapidly progress to requiring opioid analgesics for the adequate treatment of pain despite the unequivocal risks associated with the long-term use of these drugs. Centrally acting drugs, such as gabapentinoids, appear to be effective means of treating pain due to their inhibition of neurotransmitters involved in central sensitization, but side effects limit their use. The present review explores the evidence for various non-pharmacologic and pharmacologic treatments for pain in chronic pancreatitis.

Keywords Chronic pancreatitis · Pain · Analgesics

General Considerations

The present review will focus on the medical management of abdominal pain in chronic pancreatitis (CP). Extrapancreatic morphologic findings such as pseudocysts, distal bile duct stricture, and duodenal stenosis can cause pain in CP, but since treatment involves endoscopy and/or surgery, these will not be covered in this review. Abdominal pain is the most common and difficult to manage symptom in CP. Both constant [1, 2] and severe [3, 4] abdominal pain have been shown to significantly reduce quality of life in CP. Since medical therapies for abdominal pain are limited, opioid analgesics have become the cornerstone of therapy for many patients but this is also suboptimal due to their risks and side effects.

There are several obstacles to developing and trialing new drugs for the treatment of pain in CP. The *first* is the lack of clear diagnostic criteria for noncalcific CP, also commonly referred to as mild, early or "minimal change" CP. Recent evidence-based guidelines from both the American Pancreatic Association [5] and United European Gastroenterology [6] continue to focus on radiologic and endoscopic studies of pancreatic morphology for diagnosing noncalcific CP. Limitations of the studies that form the basis for these guidelines include the use of histology as the "gold standard" for CP. Hence, asymptomatic pancreatic fibrosis is commonly seen with advanced age [7, 8], alcohol [9], smoking [10], chronic kidney disease [11], and diabetes [12]. Standard endoscopic ultrasound criteria have poor correlation with fibrosis in noncalcific CP and limit its use [13]. "Abnormal" side branches as per the Cambridge classification are problematic as they can be seen with aging [14], poorly correlate with histology [15], and are subject to high interobserver variability. Perhaps most importantly, morphologic findings in CP poorly correlate with pain, even when advanced changes such as calcifications, strictures and pseudocysts are present [16–18]. This results in an overdiagnosis of noncalcific CP in many patients who more likely have a functional

✉ Vikesh K. Singh
vsingh@jhmi.edu

[1] Pancreatitis Center, Division of Gastroenterology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[2] Mech-Sense, Centre for Pancreatic Diseases, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Mølleparkvej, 9000 Aalborg, Denmark

gastrointestinal disorder. There is now an international consensus effort to define CP by the pathophysiologic changes that occur from the early to late stages of the disease [19]. A critical feature of this definition is the recognition that acute recurrent pancreatitis is an early stage of CP. While few patients with a first episode of acute pancreatitis progress to CP, the majority of CP patients with late-stage findings have had a history of acute recurrent pancreatitis.

The *second* is the overall lack of understanding of the mechanisms of pain in CP and how these might be differentiated from the pain of other gastrointestinal diseases. The challenges surrounding pain in CP was the subject of a recent consensus meeting [20]. While ductal obstruction by stones and/or strictures was thought to be the basis for pain in CP for decades, recent studies suggest that neuropathic changes better correlate with pain in CP. Progressive inflammation and fibrosis of the pancreas lead to an increased density and hypertrophy of pancreatic nerves [21]. Pancreatic nociceptive signals are transmitted by the primary nociceptive afferent, whose cell body lies in the dorsal root ganglia and terminates in the dorsal horn of the spinal cord, into the central nervous system. Over time, ongoing nociceptive afferent barrage results in increased neural responsiveness or sensitization of the peripheral nerves and central nervous system. This is clinically manifested by allodynia and hyperalgesia of the pancreas, which can explain, for example, post-prandial pain, but may also spread to other organs and somatic tissue [22–24]. Evidence of this sensitization is also reflected by the referred pain that occurs at noninjured sites due to viscerosomatic convergence at the spinal cord and brain. This explains why patients with CP experience increased pain to abdominal palpation compared to normal patients and why therapies directed at the source of nociceptive input are not likely to be effective [25, 26]. Ongoing pain in CP also causes reorganization and structural changes in the areas of the brain that correspond to visceral pain processing [27–30] which may explain the cognitive decline seen on neuropsychological testing in CP patients [31].

The *third* is a lack of a multidimensional pain assessment tool for CP [32]. Many of the existing pain assessment tools have either been validated for use in other diseases or do not capture all of the important aspects of pain in CP. *Finally*, a placebo rate of 20% has been reported in systematic review of 7 randomized controlled trials of medical therapies for painful CP [33]. This is important to ensure that future placebo-controlled trials of medical therapies for pain are adequately powered.

Alcohol and Smoking Cessation

While most studies have evaluated the impact of alcohol and smoking cessation on disease progression in CP, the role of cessation on pain has not been as rigorously evaluated. A review of 7 studies of 456 patients with alcoholic CP found that there was either no or decreased pain in 74 and 38% of patients who stopped versus continued to drink alcohol, respectively, over a variable follow-up period ranging from <1 to >20 years [34]. Ongoing alcohol consumption may increase the frequency of painful episodes only in those CP patients with preserved exocrine function [35]. Another study evaluating 205 patients with nonobstructive CP, followed for at least 10 years, found that ongoing drinking and smoking predicted the annual number of pain relapses in the multivariable analysis [36]. Smoking cessation can be difficult to achieve in CP. A recent study evaluating the impact of a smoking cessation program, incorporating counseling, achieved rates of 0 versus 19% at 18 months in 27 CP and 200 control patients, respectively, over 18 months [37].

Dietary Modification and Delivery

While patients with CP are commonly counseled to avoid high fat diets, data supporting this recommendation are conflicting due to study design, small numbers of patients, focus on alcoholic CP with variable alcohol consumption in control patients, and importantly, the problems associated with dietary assessment and recall [38–42].

After a pilot study of 2 CP patients showed that a low-fat elemental diet can reduce pain [43], two additional studies have shown a similar benefit. One study evaluated a low-fat elemental diet in 596 CP patients and showed a mean decrease in their pain from 52.9 to 32.9 mm on the VAS score ($p < 0.001$) over 12 weeks [44]. Another evaluated 17 patients, primarily with nonalcoholic early-stage CP, over 8 weeks and reported a complete and partial pain relief in 59% (10/17) and 29% (5/17), respectively [45]. The latter study found no pain relief in remaining two patients with advanced CP manifested by calcifications and atrophy and suggested that the greatest impact of an elemental diet on pain is likely in early-stage CP. Since elemental diets have been shown to reduce pancreatic enzyme secretion by 50% independent of CCK levels [46], it is possible that the pain benefit of an elemental diet in early-stage CP is due to relatively preserved pancreatic exocrine function that is diminished in late-stage CP where central mechanisms are more likely to

drive pain [47]. Based on the premise that medium chain triglycerides (MCT) reduce CCK levels, a pilot study showed a mean improvement of 61.8% in pain scores in 8 CP patients over 10 weeks on a low-fat diet (<20 g per day) and at least 3 cans of a mixture of MCT and hydrolyzed proteins [48]. In addition to the type of feeding, the site of administration also influences pancreatic secretion as increasing reductions in trypsin secretion are seen with distal jejunal compared to gastric feeding tubes [49]. It should be stressed, however, that these studies were only observational without control groups and the data should be interpreted carefully. The placement of nasojejunal tubes in CP patients has been shown to not only result in an improvement in nutritional parameters but also in pain, with 76–79% of patients demonstrating a response [50, 51]. It is not clear whether the pain benefit seen is due to a reduction in pancreatic secretion or bypass of the stomach, particularly since delayed gastric emptying is seen in nearly half of early CP [52] as well as CP patients who have undergone total pancreatectomy [53]. Since enteral nutrition is not practical over the long term, this approach is typically utilized to help patients wean off opioid analgesics and improve their nutritional status prior to surgery.

Pancreatic Enzyme Supplements

The postulated benefit of pancreatic enzyme supplements for the treatment of pain is related to the negative feedback inhibition of the pancreas through intraduodenal protease-mediated denaturation of CCK-releasing peptide which results in lower CCK levels and pancreatic stimulation. Prior studies have shown that high CCK levels are present in CP patients with pain [54]. Pancreatic enzymes are commonly used by clinicians for the treatment of pain in CP. A survey study of 110 providers found that nearly half would prescribe pancreatic enzymes for the relief of pain in a hypothetical opioid-naïve CP patient [55]. Another study evaluating 516 CP patients found that constant (OR 3.42) and intermittent (OR 1.98) pains were significant predictors of pancreatic enzyme use but not of provider perceived efficacy in multivariable analyses [56]. However, a recent systematic review and meta-analysis of 5 trials evaluating the use of pancreatic enzymes for the treatment of CP pain found no difference in mean daily pain scores when compared to placebo [57]. If enzymes are utilized, non-coated formulations may be more effective as they are prone to exert their effects in the proximal duodenum where CCK-releasing peptide is localized.

Antioxidants

Micronutrient deficiency is common in CP and can lead to oxidative stress [58]. The resulting free radicals can cause pancreatic injury and inflammation. Several randomized controlled trials have evaluated antioxidant therapy as a means of treating pain in CP. Despite significant heterogeneity across trials, there have been 4 systematic reviews with meta-analysis which have concluded that there is no significant difference with antioxidant therapy compared to placebo for pain relief in CP [59–62]. Interestingly, two of these studies did find significant pain relief in the subgroup of patients treated with antioxidant preparations that contained methionine [59, 60]. A Cochrane review of 12 trials with 585 patients found a mild reduction in pain on the VAS after 1–6 months of therapy with antioxidants compared to placebo [63]. While mild adverse events occurred in 16% of patients, these were sufficient to lead to a discontinuation of therapy. A recent prospective study evaluated medical therapy consisting of a well-balanced diet, methionine containing antioxidant cocktail and pancreatic enzymes in 288 consecutive patients with painful CP with step up to endoscopic and/or surgery if needed [64]. At 1 year, significant pain relief was achieved in 52.1% with medical therapy. These results are at odds with a follow-up study from a prior trial in the UK in which 30 patients were treated with antioxidants for a median of 4 years and no differences were found in the proportion of patients with and without pain [65]. There were several differences in these two studies including patient demographics, etiology and stage of CP, use of concurrent endoscopy and/or surgery as well as antioxidant preparations. Therefore, no firm conclusions can be drawn for the use of antioxidants but they may be effective in selected patients.

Nonopioid and Opioid Analgesics

The "three-step ladder" of the World Health Organization for the treatment of cancer pain has been widely adopted as the paradigm for the treatment of not only cancer but also other conditions associated with chronic pain [66]. However, there are clear limitations of using the ladder for the treatment of neuropathic pain [67].

The first step of the ladder advocates for the use of nonopioid analgesics and adjuvants with escalation toward higher potency opioids with persisting or increasing pain. Paracetamol or acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are common first-step agents. It should be highlighted that neither drug has been evaluated in CP. Paracetamol is generally safe but does not typically result in satisfactory pain relief. One potential

reason is the lower paracetamol plasma concentrations in CP patients due to either a motility disorder resulting in bacterial overgrowth with resulting malabsorption and/or induction of hepatic cytochrome P450 enzymes by alcohol and/or smoking [68]. Through their inhibition of cyclooxygenase (COX) isozymes and prostanoid synthesis, NSAIDs exert their anti-inflammatory, analgesic, and antipyretic effects. While NSAIDs have been shown to be effective for treating the pain of musculoskeletal disorders [69], they are considered to be less effective for treating visceral pain due to their gastrointestinal and cardiovascular toxicity. A recent review suggests using the lowest dose of NSAID for the shortest possible time and avoiding long-acting formulations, those with highest gastrointestinal toxicity, concomitant use of drugs that may increase risk of gastrointestinal bleeding (e.g., selective serotonin reuptake inhibitors (SSRIs) and coumarins), eradicating H. pylori in those with history of peptic ulcer disease and using proton pump inhibitor for those at risk of gastrointestinal toxicity [70].

Opioid analgesics are additive therapies for persistent or increasing pain on the second and third steps of the WHO ladder. There are a few important principles that should be considered before initiating opioid therapy. The first is that opioids should not be used as first-line therapy in patients with chronic nonmalignant pain syndromes. While comparative data between the use of opioids versus nonopioid analgesics for the long-term treatment of chronic nonmalignant pain are lacking, it is clear that long-term use of opioid analgesics in this context has not been shown to be effective [71] and is associated with the risk of misuse, addiction and overdose as well as several gastrointestinal side effects, including opioid induced bowel dysfunction [72, 73]. This was a "choosing wisely" recommendation of the American Society of Anesthesiologists—Pain Medicine in January 2014 [74] and followed by the CDC guidelines in 2016 [75] which advocate for the use of nonopioid therapies for chronic pain; discussion of risks/benefits as well as monitoring for harm; use of short-acting opioids at the lowest possible dose and for the shortest time; and avoidance of concurrent benzodiazepine use. The second is that data supporting the use of opioids for chronic neuropathic pain are lacking. There was a single randomized controlled trial of a high versus low dose oral μ-opioid receptor (OR) agonist (levorphanol) in 81 patients with neuropathic pain disorders over 8 weeks that found a higher analgesic effect in the high dose arm but at the expense of increased side effects [76]. While CP is not a classic neuropathic pain disorder, where pain arises due to nerve damage without tissue injury, the transmission of nociception and development of sensitization are similar to both. The third is that the rationale use of opioids and their side effects requires understanding their complex pharmacology [77] and the growing recognition of the importance of opioid pharmacogenetics [78, 79].

While the overall number of outpatient visits for chronic abdominal pain declined from 14.8 to 12.2 million in the USA, the prevalence of visits associated with an opioid prescription increased from 5.9 to 12.2% between 1997 and 2008 [80]. It is now known that initial prescription for opioids [81] and being under the care of a high intensity opioid prescriber [82] are directly associated with long-term use. Few studies document the epidemiology of opioid analgesic use specifically in CP. An older Danish study found that 0.2% of 480,000 patients were prescribed opioids over a 1-month period with pancreatitis being the second most common chronic nonmalignant for opioid use at 7% after back pain at 29% [83]. A more recent study of 210 patients with chronic noncancer pain from Taiwan included 44 CP patients (21%) who used a mean daily morphine equivalent dose of 189.2 mg with a standard deviation of 184.7 mg [84]. Daily mean opioid doses in this range have been shown to significantly increase the risk of hospitalization in CP [85].

A few studies have evaluated opioids for the treatment of pain in CP. One small trial randomized 25 patients to morphine and tramadol, a weak μ-OR agonist that also inhibits serotonin and norepinephrine reuptake resulting in reduced pain transmission at the spinal cord. At day 4, 67 versus 20% of the patients randomized to tramadol and morphine, respectively, reported excellent analgesia ($p < 0.001$) with less impact on gut transit time with tramadol [86]. The daily mean dose of 840 mg of tramadol was higher than is approved for use in clinical practice in the USA (daily maximum dose of 400 mg). Nonetheless, the safety profile and the weak OR agonist activity of tramadol make it a preferred first-line opioid for the treatment of pain in CP. Most clinically available opioids primarily exert their effect on the μ-OR which mediates euphoria and addiction. However, there are experimental data, suggesting that κ-OR agonists may better treat gastrointestinal pain [87]. While oxycodone interacts at all ORs, it also has strong activity at the κ-OR [88]. A blinded crossover study of 10 CP patients found that 15 mg of oxycodone better attenuated experimentally induced pain than 30 mg of morphine [89]. An earlier pilot trial of 6 patients with CP found that a peripherally selective κ-OR agonist (AD 10-0101) significantly reduced pain compared to placebo [90]. With regard to stronger opioids, there was a crossover trial of 18 patients with CP that showed no difference in pain control of quality of life between sustained release morphine and transdermal fentanyl but that the later was associated with skin site reactions in 44% of patients [91].

There will never be a biomarker for pain as it is a subjective response but biomarkers that assess nociceptive

activity will help tailor the use of opioids in individual patients. A recent prospective study from 5 European countries evaluated quantitative sensory testing, electroencephalography and an assessment of pain catastrophizing prior to the initiation of opioid therapy for chronic pain in 59 patients and found that pain reduction could be predicted by features on neurosensory and psychologic testing [92]. The findings of this study will require validation in larger number of patients and in those with chronic visceral pain syndromes such as CP.

Centrally Acting Drugs

Since opioids are not effective for treating pain in CP patients with evidence of central sensitization, there have been increasing efforts at using centrally acting drugs for analgesia. The preponderance of studies that have evaluated centrally acting drugs in gastroenterology has focused on functional gastrointestinal disorders [93–97]. However, the antinociceptive effects of centrally acting drugs readily extend to chronic visceral pain syndromes such as CP since the signal transduction, conduction and relay of nociceptive impulses from the abdominal viscera to the spinal cord and brain with eventual sensitization are similar.

The best studied centrally acting drug in CP is the anticonvulsant, pregabalin, an alpha-2-delta ligand that inhibits the release of neurotransmitters from pre-synaptic nerves. There were two trials for the treatment of experimental pain that showed a significant increase in the thresholds to painful stimulation on neurosensory testing in CP patients who received pregabalin compared to placebo [98, 99]. A randomized trial of 64 patients, 34 to escalating doses of pregabalin (maximum daily dose of 600 mg) and 30 to placebo, showed reductions in the mean daily pain score of 36 versus 24% over 3 weeks, respectively ($p = 0.02$) [100]. A follow-up study of these trial participants demonstrated that the responders to pregabalin had greater evidence of central sensitization on their pre-drug neurosensory testing compared to nonresponders, suggesting that neurosensory testing could be used to select which patients to treat with pregabalin [101]. There is evidence of variation in serum pregabalin levels as another potential explanation for the variable efficacy of pregabalin for the treatment of pain in CP, similar to that of paracetamol [102].

There is a randomized trial currently being conducted in the Netherlands to examine early surgery versus step up management consisting of medical and endoscopic therapy for the management of pain in large duct CP. The medical management arm includes, in addition to opioid and nonopioid analgesics, the use of centrally acting medications, in particular, pregabalin to a maximum of 600 mg per day, gabapentin to a maximum of 2400 mg per day, and amitriptyline to a maximum of 100 mg per day [103]. This trial is the first to examine a combination of centrally acting agents for the management of pain in CP. A recently published trial compared a combination of antioxidants and pregabalin ($n = 42$) to placebo ($n = 45$) in patients with calcific CP after complete endoscopic ductal stone clearance and found significant improvements in pain among the patients in the antioxidant–pregabalin arm at 2 months [104]. This trial suggests that the combined treatment of obstruction, oxidative stress and central sensitization may have greater impact on pain relief in an idiopathic CP patient population than a single treatment alone.

S-ketamine is a *N*-methyl-D-aspartate (NMDA) receptor antagonist that reduces central sensitization and was shown to significantly reduce experimental pain in a blinded crossover trial of 9 patients with CP [105]. There is an ongoing trial evaluating *S*-ketamine versus placebo for the treatment of pain in CP [106].

Summary

Progress in treating pain in chronic pancreatitis will require better diagnostic techniques for early disease, a recognition that pain is largely driven by central mechanisms and not structural changes of the pancreas, and validated pain assessment tools utilized in well-designed clinical trials. Alcohol and smoking cessation are important behavioral modifications that can impact pain. Low-fat elemental diets and nasojejunal enteral feeding may reduce pain in chronic pancreatitis. Pancreatic enzymes and antioxidant preparations do not, at present, have sufficient evidence supporting their general use as treatments for pain. Despite the limitations of the WHO pain ladder, it continues to guide the use of nonopioid and opioid analgesics in patients with chronic pain. The initial use of paracetamol or acetaminophen with escalation to pregabalin and/or tramadol followed by oxycodone or other strong opioids is reasonable steps on the ladder of managing pain in chronic pancreatitis. Over time, it is likely that studies of additional centrally acting drugs, other than pregabalin, will be used to support their use over opioids. Development and use of biomarkers of nociceptive activation will be important for tailoring medical therapies for pain in individual patients with chronic pancreatitis.

Key Findings/Future Unmet Needs/Implications

- While pain in chronic pancreatitis is multifactorial, there is increasing recognition of the importance of peripheral and central sensitization, as manifested by

allodynia, hyperalgesia and deficient descending inhibition, as a key mechanism of pain.
- Alcohol and smoking cessation, low-fat elemental diets and use of nasojejunal feeding tubes for enteral nutrition are all associated with pain relief in chronic pancreatitis, but controlled studies are needed.
- Opioid analgesics are commonly used to treat pain in chronic pancreatitis, but the long-term risks and complications of these drugs as well as their overall lack of efficacy in treating central sensitization should temper enthusiasm for their use.
- More trials of the various classes of centrally acting drugs for treating pain in chronic pancreatitis are needed.
- Biomarkers of nociceptive activation (e.g., quantitative neurosensory testing) need to be further studied as means of selecting patients for non-pharmacologic and pharmacologic therapies for pain in chronic pancreatitis.

Compliance with ethical standards

Conflict of interest None.

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