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Pain Management in Chronic Pancreatitis

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Introduction

Abdominal pain is the most common symptom in chronic pancreatitis (CP), and it remains a clinical challenge. Pain affects about 90% of patients along the course of the disease and can present in various forms [1,2]. The classical description of pancreatic pain is a constant, dull, epigastric pain that radiates to the back and is worsened by intake of high-fat foods [3]. Intensity can present in forms ranging from a barely noticeable sensation to immense, continuous pain. Some patients experience episodes of severe abdominal pain, whereas others experience a daily aching pain that may be exacerbated by acute flares [3]. Pain pattern has traditionally been looked at as either type A pain (intermittent pain with pain-free intervals in-between) or type B pain (constant pain with or without exacerbations) as described by Ammann et al. [4], but recent research concluded that several shifts between pain patterns can occur during the course of the disease [5]. Regardless of the type of presentation, pancreatic pain highly affects quality of life and is a risk factor for hospitalizations [6,7]. In an examination of 540 American CP patients in the NAPS2 (North American Pancreatitis Study 2) cohort, most patients reported at least one hospitalization in the last year, 25% were on disability benefits, and there was no association between the duration of the disease and pain severity [1].

Pathophysiology

Pain in CP is poorly understood, and the underlying mechanisms are still debated. However, generally, it is agreed that pancreatic pain has elements of nociceptive pain, obstructive factors, and neuropathic/neuroplastic pain [3,8].

Nociception is the process whereby the sensory nervous system encodes noxious stimulations. It involves the activation of specific neural processes leading to an action potential that forwards the signal through the dorsal horn of the spinal cord and through ascending pathways to the limbic, thalamic, and cortical regions of the brain. Nociception can lead to the perception of pain, but as outlined below, pain is a subjective experience including affective and cognitive components, together with suffering and changes in behavior.

It is hypothesized that ductal and mechanical alterations can cause pain, especially ductal obstructions and local inflammatory masses. However, radiological findings are not correlated with pain severity [3,9], and postoperative long-term pain relief is dependent on many other factors [10].

The perception of pain is generally induced by tissue injury, but the neural structures can become sensitized over time. Sensitization will induce a greater neural response to noxious stimulations and increase the sensation of pain, leading to hyperalgesia. Sensitization can occur both peripherally in the primary nociceptors and centrally at the spinal level or higher levels, including the brain [11].

In CP, continuous inflammation can cause the pancreatic nerve fibers to convey signals to the brain, which is perceived as pain. The inflammation will cause the pancreatic tissue to break down, and the nerves can then be exposed to toxins and chemicals, leading to nerve hypertrophy, an increase in density, and an increased number of nerve endings [12]. These findings correlate with pain intensity and support the theory of neuropathic pain [13]. In such cases, spontaneous firing from the damaged

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nerves and central sensitization, and lack of normal inhibition can amplify the pain.

Pancreatic nociception seems to be affected significantly in CP, where increased excitability is linked to an upregulation of several molecules, including the vanilloid receptor TRPV1, calcitonin gene-related peptide (CGRP), nerve growth factor (NGF), and the protease-activated receptor 2 (PAR-2) [8]. This upregulation is believed to drive neural sensitization, starting peripherally and progressing centrally.

Pain in CP can also be secondary, related to complications of CP and treatment [14]. For example, CP patients are at increased risk of developing peptic ulcers and bacterial overgrowth in the small intestines. Furthermore, the analgesic treatment, especially opioid treatment, may result in severe side effects that can increase pain, including constipation and opioid-induced hyperalgesia. All of these complications need to be addressed appropriately to reduce pain.

Pancreatic pain does, however, comprise more than just nociception and pain intensity. Cognitive dimensions of pain include how the patient perceives him/herself in pain and predispositions for coping with pain, including temper and personality traits. Affective dimensions include depression and anxiety, which affect pain processing and the perception of pain. Finally, behavioral dimensions, such as grimacing, crying, and limping, can induce empathy in relatives and secondarily increase pain behavior. However, this negative spiral can ultimately also increase pain perception [15].

This multifactorial nature needs to be taken into account when managing pain in CP. However, patients differ with respect to pathophysiology, genetic and social factors, etc., and treatment should be tailored to the individual rather than a one-size-fits-all approach [16].

Pain Assessment

The clinician should always start with a thorough pain assessment to guide treatment. Pain intensity, pain pattern, factors that provoke or worsen pain can be important when determining which mechanisms are involved in the development of pain. In addition, this information can be used when evaluating whether the pain is nociceptive or neuropathic. Evaluation should include questions on pain intensity and characteristic features, pain interference on physical and emotional functioning, and quality of life assessment [17]. For details, the reader is referred to a recent guideline paper in pain assessment of CP [14]. Unfortunately, pain assessment tools developed specifically for CP have proven to be either dominated by unidimensionality, lack of validity and reliability testing, or poor coverage [18]. For example, the Izbicki pain score developed for CP has been used in several studies, although it has never been formally validated [19,20]. Other pain questionnaires such as the Brief Pain Inventory have also been used extensively in CP and it is validated for nonmalignant pain; however, it lacks focus on features characteristic of pancreatic pain [21]. As a result, the COMprehensive Pain Assessment Tool (COMPAT) has been developed to include all core dimensions of pain and aspects specific to CP [22]. In addition, a short-form was recently developed to increase the clinical usability, comprising five pain dimensions to characterize pancreatic pain, including pain severity, pain pattern, factors provoking pain, qualitative pain assessment, and spreading pain. It has been validated and tested to be reliable in three centers in Denmark, New Zealand, and the United States [23].

As many pain assessment questionnaires do not include quality of life assessment, they can be accompanied by questionnaires such as, for example, the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire for quality of life assessment [24].

Besides pain assessment tools, quantitative sensory testing (QST) has been examined as a diagnostic test for assessing somatosensory function in CP. QST is a method for determining how patients respond to painful stimulations. For example, a QST technique called the Pancreatic QST (P-QST) protocol uses bedside pressure testing, repetitive stimulations, and conditioned pain modulation testing to evaluate the nociceptive responses indirectly [25]. Studies using P-QST have phenotyped patients based on pain patterns and correlate increasing widespread hypersensitivity with pain intensity, pain interference, and quality of life [26]. In addition, neurophysiological examinations, including P-QST, can be used to guide treatment according to the presence of segmental hyperalgesia and deficient descending pain inhibition [27]. However, these methods are only available in the most advanced laboratories and are still considered research tools.

Noninterventional Pain Treatment

Pain management should start with optimizing lifestyle factors. Alcohol consumption is a significant risk factor for the development of acute-in-chronic pancreatitis. It has also been linked to the occurrence of severe pain [9]. Likewise, smoking is related to pancreatic pain as there is an increased risk of pain with an increasing number of daily cigarettes [9]. Therefore, abstinence from alcohol and smoking is an important part of hindering the progression of chronic pain and acute flares into chronic pain. It can be supported

with medications for alcohol dependence, such as naltrexone, nicotine substitution, cognitive therapy, or mindfulness-based therapy [27]. However, even in abstinence from alcohol and smoking, the pain often persists.

Pain treatment should be managed in an interdisciplinary fashion, starting with an open discussion on treatment goals. An alignment of expectations is important, as some patients might expect complete resolution of pain, which is seldom achievable. A psychological evaluation is also essential, as comorbid depression and anxiety can worsen the sensation of pain as pain, anxiety, and depression are neuroanatomically and neurochemically linked [28]. Cognitive therapy can also be used to improve both affective mood disorders and improve pain-coping [29].

Neuromodulation has also been used successfully in treating pancreatic pain by modulating brain plasticity where mechanisms such as hyperpolarization, activation of endogenous opioids, and descending inhibition may also play a role [27,30]. It can suppress activity or promote the facilitation of the targeted area, but high-quality randomized controlled studies (RCT) are lacking. A small RCT showed that acupuncture was beneficial in CP, but the effect is short-lasting [31]. Pilot studies have shown an effect of transcranial magnetic stimulations and spinal cord stimulation, but studies have lacked a valid placebo arm and as such are subject to major bias [32].

Endoscopic and Surgical Pain Treatment

Endoscopic and surgical pain treatment is based on the rationale that pain originates from the pancreas's structural changes, such as main duct obstruction due to strictures or stones or inflammatory masses in the pancreas. Endoscopic treatment is used in the case of obstruction of the main pancreatic duct, where endoscopic retrograde cholangiopancreatography (ERCP) procedures can maintain drainage from the main pancreatic duct by pancreatic papillotomy, by extraction of pancreatic stones, or temporary stent placement [33]. However, the "plumbing theory" where ductal obstruction is the main cause of pancreatic pain is still debated. Although studies on endoscopic treatments have shown significant improvement in pain intensity in most patients, the studies are biased by several factors, including patient selection, short follow-up period, poor pain assessment methodology, and especially lack of sham control [32]. To circumvent these biases, an ongoing RCT (SCHOKE trial) randomizes patients to either active or sham extracorporeal shock-wave lithotripsy and endoscopic treatment, and currently, 50 patients are enrolled [34].

In randomized studies, surgery has proven to be superior to endoscopic treatment [20]. Surgical procedures include resection, either partial or total pancreatectomy, surgical drainage, and combinations. The argument for surgical treatment is that eliminating the source of the nociceptive pain could result in decreased firing from primary afferents and lead to decreased pain [32]. Total pancreatectomy with islet cell transplantation has gained increasing popularity but carries the risk of neuropathic pain development. Furthermore, metabolic consequences can be severe, and technical challenges remain an obstacle [11]. As studies with sham interventions are not possible with pancreatic surgery, controlled studies where patients are followed strictly for several years after surgery are needed, which may identify the role of surgery in CP [32]. However, most series have shown that a significant proportion of the patients still suffer from pain, and therefore pharmacological management is still needed.

The rationale for surgery is also applied when using neuroablative procedures to treat pain. This argument is supported by the fact that local treatments such as neural blocks can alleviate pain in peripheral nerve injury [35]. However, although neural blocks can initially affect pain intensity, studies show that they do not reduce the risk of developing allodynia or hyperalgesia [36], and nerve destruction may, in the long run, worsen neuropathy, and hence pain [30].

Pharmacological Pain Management

Simple analgesics are recommended as the first line of treatment in painful CP, especially paracetamol/acetaminophen. Nonsteroidal anti-inflammatory drugs (NSAID) can be used in selected cases but are of limited value due to gastrointestinal toxicity and CP patients' predisposition for peptic ulcers [27].

Second to simple analgesics is adjuvant therapy consisting mainly of anticonvulsants, antidepressants, and anxiolytics. In the anticonvulsive drug group, only pregabalin has been evaluated in RCT in CP and proven to provide moderate pain relief [37,38]. It has also been shown that pregabalin has inhibitory effects on central sensitization by reducing spreading hyperalgesia [39]. In addition, randomized controlled studies have shown that segmental hyperalgesia is predictive of the analgesic effect of pregabalin in CP [40]. Pregabalin is licensed for neuropathic pain and fibromyalgia but has also been used in other painful conditions with good results [41].

Antidepressants have never been examined as analgesic treatment in CP patients. However, as the noradrenergic system plays an important role in endogenous pain

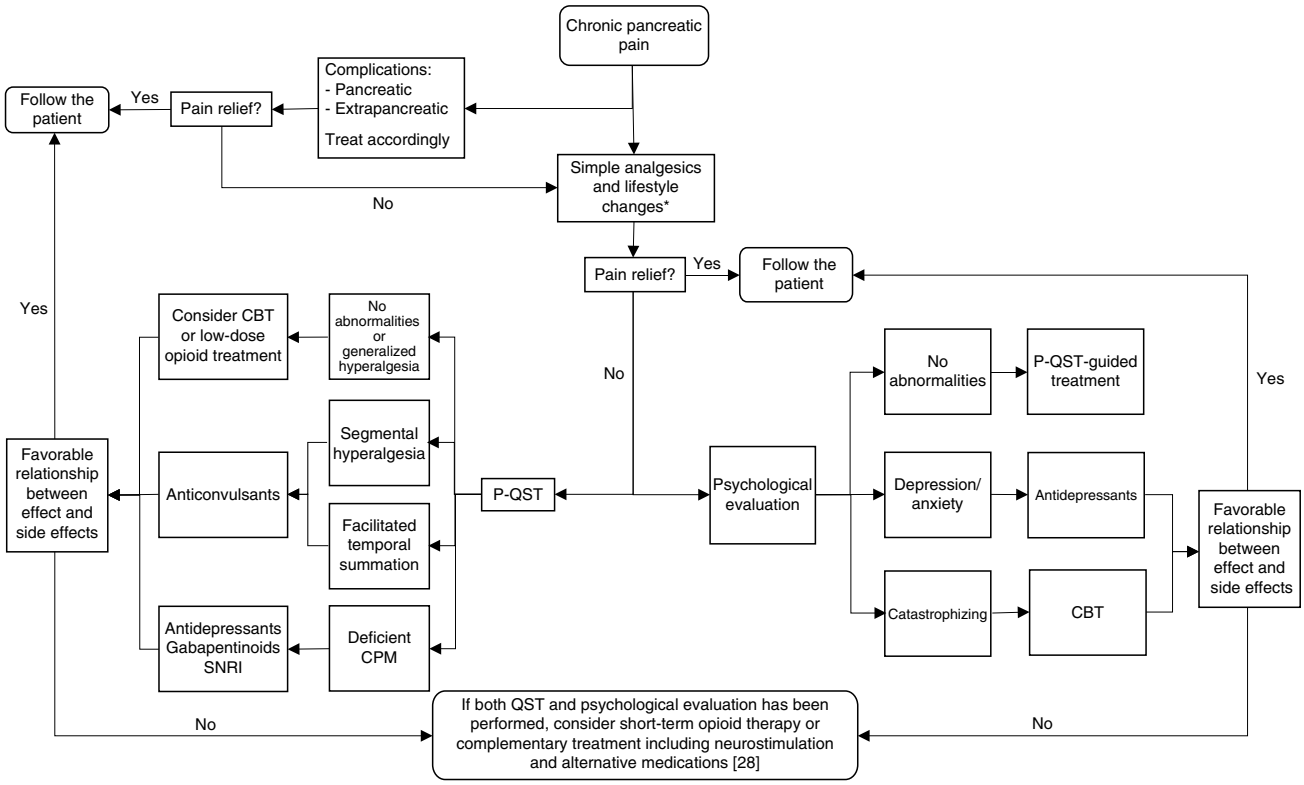

Figure 59.1 An example of a mechanism-based treatment algorithm. Simple analgesics include NSAID and paracetamol/acetaminophen; complementary treatments include acupuncture, vagal nerve stimulations, etc. P-QST*: quantitative sensory testing; CBT: cognitive behavioral therapy; CPM: conditioned pain modulation; SNRI: serotonin and norepinephrine reuptake inhibitors. *Optimize nutrition and add antioxidants in selected cases, cessation of alcohol and tobacco use.

modulation and antidepressants have proven effective in neuropathic pain [42], the effects may be transferable. It can also be questioned whether RCT in CP patients are needed for all analgesics. Although these patients have many specific features, there is evidence that treatment is likely to be based on the level of the individual rather than at the level of the disease [43]. Hence, data from studies in other pain patients can likely be extrapolated to CP. For example, Arendt-Nielsen and colleagues have shown that the function of the endogenous pain modulatory system predicts the analgesic effect of duloxetine in diabetic neuropathy, and other types of tricyclic antidepressants have been shown to improve the ability to modulate pain [44]. In addition, antidepressants can also be used to treat comorbid depression and anxiety, as the involvement of norepinephrine and serotonin in these diseases can affect pain processing and increase pain sensation.

Although pain management with simple analgesics and adjuvants is preferable, many patients need opioids to dampen their pain. It is necessary to closely monitor patients on opioid treatment, as adverse effects are common and include symptoms such as constipation, nausea, and opioid-induced hyperalgesia, which significantly affect the quality of life; for details, see [45,46]. Furthermore, it is estimated that only about 25% of CP patients benefit from opioid treatment, and it is necessary to evaluate treatment effects often [27]. Tramadol possesses a weak opioid agonist activity and affects the serotonin- and norepinephrine uptake [47], thereby having a dual-action effect. It is shown to be superior in South African CP patients and has fewer gastrointestinal side effects [48]. However, the results have not been validated in other ethnicities.

In general, the problem with analgesics is not the efficacy but the side effects. It is outside the scope of this chapter to describe the balance between effects and side effects and how to balance between them to the benefit of the patients, but the reader is referred to [49].

In Figure 59.1, a proposal for noninvasive treatment of pain in CP is shown.

Conclusion

Pain management remains a challenging and frustrating part of caring for patients with CP, as many issues remain unsolved.

Treatment has to be tailored to the individual, and successful pain management begins with good communication, where it is important to agree upon treatment goals early in the process. The analgesic strategy is multimodal and may include invasive treatments, medical treatments, and adjuvant treatments, bearing in mind that pain in CP is a combination of nociceptive and neuropathic/neuroplastic pain.

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