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Medical Treatment of Pain in Chronic Pancreatitis

Guidelines for Clinical Practice

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Introduction

The most common symptom in chronic pancreatitis (CP) is abdominal pain, which is present in about 70% of the patients. Both pain intensity and the frequency of pain attacks have been shown to reduce quality of life in patients with CP. The typical description of the pain is a constant dull ache in the epigastrium with referral to the back (including referred muscle hyperalgesia). The pain often increases with food intake, but it can manifest in a variety of ways, ranging from limited intermittent pain to constant, intense, and severe pain [1]. Previously it was believed that pancreatic pain would "burn out" as the disease process evolved [2], but today the burnout theory is obsolete as evidence against it has been provided in large retrospective studies [3,4,**5**]. Thus, a "wait-and-see" approach is not advisable and early and effective management will likely decrease the suffering and at least theoretically lead to less chronification of the pain. It is known from other chronic pain conditions that the longer the pain persists and the stronger it is, the more effect pain has on central sensitization processes and the more difficult it is to treat [6].

Unfortunately, management of pancreatic pain remains a therapeutic challenge and, in comparison with somatic pain, management regimens for visceral pain are only sparsely documented [7]. However, the variability in the phenotypic presentation of different pain syndromes is found to be greater between patients than between different pain syndromes [8]. Together with clinical experience, this justifies the use of evidence gained from the management of patients with other pain syndromes in CP. Consequently, the approach used in the treatment of somatic pain is typically used as a framework for visceral pain management, with analgesic use based on the World Health Organization (WHO) ladder [9,10]. On the other hand, although visceral, somatic, neuropathic, and inflammatory chronic pain conditions share common mechanistic features, visceral and somatic pain have several important differences that should be considered when initiating analgesic treatment [6]. Hence, visceral pain is more diffuse and difficult to localize and this can lead to inadequate differential diagnosis. Visceral pain is also accompanied by symptoms arising from the autonomic and enteric nervous systems that may need specific management [11]. Chronic visceral pain induces peripheral and central sensitization more frequently than somatic pain conditions and this can be a therapeutic challenge [12]. Finally, when drug absorption and metabolism are considered, the gut and liver are of major importance, but these are often malfunctioning in CP and also the main targets of side effects and this adds to the complexity of pain management. Although pain management in CP may be more difficult than in other painful conditions, it can frequently be treated satisfactorily. Treatment should always be multimodal and multidisciplinary, but medical treatment is the cornerstone in pain management of CP and other treatment modalities can seldom stand alone without the support of analgesics. In the following sections the medical treatment is described with focus on practical guidance for management.

Pathogenesis of Pain

It was a previously common belief that increased pressure in the tissue and/or ductal system could explain pain in most patients [13]. However, newer studies have not shown a direct relation between the micro- or macro-structural findings in CP (as characterized by different imaging modalities) and pain characteristics [14,15]. An alternative explanation, based on more than a decade's research, has

Clinical Pancreatology for Practising Gastroenterologists and Surgeons, Second Edition. Edited by J. Enrique Domínguez-Muñoz.

indicated that pain in many cases has a neuropathic component, with evidence of peripheral neural sensitization and nerve destruction following inflammation and fibrosis [16,17]. Experimental and human studies have provided evidence for pancreatic neuropathy and neuroplasticity at both the peripheral (pancreatic gland) and central level of the sensory system, which to a high degree resembles what is seen in neuropathic pain disorders. Consequently, pregabalin, a drug that has shown its effectiveness in neuropathic pain, has also been shown to be effective in patients with painful CP in a randomized placebo-controlled trial [18]. However, pain due to the complications of the disease and to the adverse effects of treatment is also frequent and must not be overlooked as an additional source of pain, as this is often easier to treat than "genuine" pancreatic pain. Table 36.1 shows the different pain mechanisms that may come into play in CP (for details see Poulsen et al. [19]).

As a new dimension, the characterization of pain mechanisms underlying painful CP can theoretically facilitate individualized treatment that targets the involved mechanism and thereby enables personalized pharmacological treatment, improves patient outcomes, and reduces unwanted side effects. Currently, the most promising method is by assessing the pain profile using quantitative sensory testing and by evaluating treatment response. This concept has been described in comprehensive reviews and for more detail the reader is referred to Kuhlmann et al. [20].

Table 36.1 Main reasons for pain in chronic pancreatitis.

Primary pancreatic pain
Ductal and tissue hypertension
Active inflammation
Parenchymal ischemia
Neuropathic pain
Secondary pain
Local complications
Pseudocysts
Adenocarcinoma
Remote complications
Small bowel strictures
Gastroparesis
Obstruction of bile duct and duodenum
Peptic ulcer
Small intestinal bacterial overgrowth
Mesenteric ischemia
Pancreatogenic diabetic and related visceral neuropathy
Iatrogenic pain
Surgical and/or endoscopic complications
Adverse effect of medication (e.g. opioid-induced constipation and hyperalgesia)

Medical Pain Management

Risk Factors

Although not analgesics, risk factors involved in the deterioration of the disease should be avoided. Abstinence from alcohol and smoking should therefore be strongly advised in patients with CP. High alcohol intake is a risk factor for acute and chronic pancreatitis [21], and abstinence from alcohol is associated with reduction in frequency of recurrence of pancreatitis [22,23]. However, prospective studies evaluating the effects of cessation of alcohol on chronic pain are lacking. Pharmacological and supportive therapies are often needed to ensure that patients refrain from alcohol intake (for review see Drewes et al. [7]). Recent data show that alcohol use is associated with inflammatory complications, whereas smoking is associated with fibrosis and pancreatic insufficiency, and hence the toxic risk factors may be independent [24]. Several studies have shown that smoking tobacco, particularly cigarettes, increases the risk for developing both acute [25,26] and chronic [27,28] pancreatitis and this relative risk is dose-dependent. More than 80% of patients with alcoholic CP are smokers and smoking potentiates alcohol toxicity in dose-dependent way [28]. However, no studies have evaluated the effect of smoking cessation on pain in patients with CP, but considering the health risks of smoking, including acceleration of disease progression, abstinence is still advisable. As for alcohol dependence, pharmacological and non-pharmacological treatment is often necessary and has been outlined in detail in Drewes et al. [7].

Enzymes and Antioxidants

It is also recommended that pancreatic enzyme therapy with or without antioxidants should be used to manage pain in patients with CP. In a review of six trials [29], pain relief using pancreatic enzymes as uncoated tablets was noted in two trials [30,31] and no benefit was noted in four trials that used acid-protected capsule forms of enzymes [32–35]. The reason could be that pancreatic enzymes were not released in the duodenum in the acid-protected form. However, previous studies were limited by heterogeneity with regard to patient population and enzyme preparations. It is recommended that enzyme therapy be tested for pain relief, preferably using an uncoated preparation in adequate dosage of four to eight tablets per day. Whether or not antioxidants may be helpful in pain

treatment is also up for discussion. Oxidative stress as a mechanism of inflammation in CP has been demonstrated [36–40]. Meta-analyses of randomized controlled trials have shown beneficial effect of antioxidants in patients with CP [41–43], and a combination of pregabalin and antioxidants also resulted in benefit in those who had recurrence of pain after surgical and/or endoscopic therapy [44]. However, most studies were performed in Asia, and a randomized controlled European study did not show benefit in patients with predominantly alcohol-related CP [45]. Therefore the current recommendation is that antioxidants can be used, even though the evidence is limited [7].

Analgesics

Standard guidelines for analgesic therapy follow the principles of the WHO pain ladder. This principle was originally launched for cancer pain treatment, and is based on drugs with increasing analgesic potency (levels I–III) until pain relief is obtained (Figure 36.1). In the first step, non-opioid drugs such as paracetamol (acetominophen) or nonsteroidal anti-inflammatory drugs (NSAIDs) should be used. If this medication is insufficient, weak opioids such as codeine or tramadol are added at the second step. In the third step, weak opioids are replaced by strong opioids. At each stage of the ladder, it is possible to administer adjuvant medication such as tricyclic antidepressants or anticonvulsants. Side effects are simultaneously monitored and handled [46]. However, the value of such a systematic approach has been questioned, and often step II analgesics are not used. A recent study [47] also showed that in cancer pain it is better and safer to start with level III opioids and titrate slowly until adequate pain relief is achieved.

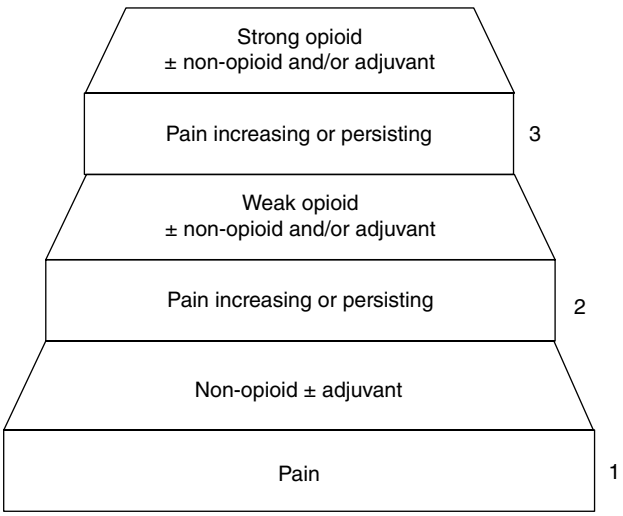

Figure 36.1 Modified version of the WHO analgesic pain ladder. For details see text.

Although not studied in CP, this approach may be valid in some patients with severe pain. Of note, analgesic treatment can seldom stand alone, and in modern pain management the ladder is only used a guide to oral medications where treatment also includes invasive management and supportive care and nursing (multimodal analgesia). Finally, it should not be forgotten that the individual experiences and manifestations of pain are influenced by a complex series of interactions involving sensory, pathophysiological, affective, sociocultural, behavioral, and cognitive elements [48]. Hence, pharmacological treatment remains an essential component of pain management and a key component is finding the balance between effective treatment and acceptable side effects. Practical guidelines are shown in Table 36.2, and in the following sections the medications most used in pain management are described:

Simple Analgesics

Non-opioid analgesics are used as the first step and paracetamol is the preferred level I medication due to its limited side effects. It must be used with caution in patients with concomitant liver impairment or in severe malnutrition as often seen in CP (see also following section), but otherwise there are no major restrictions. NSAIDs are very effective in selected patients, especially when inflammatory pain is suspected. Because of the increased prevalence of peptic ulcer in CP (for mechanisms see Poulsen et al. [19]), NSAIDs should only be used for short-term treatment and always together with proton pump inhibitors [49]. Cyclooxygenase-2 selective drugs can also be used in patients at high risk for gastrointestinal complications as long as there is no renal or cardiovascular disease. In clinical practice, step I analgesics are often insufficient to alleviate pain as monotherapy in CP, but are often necessary when more potent analgesics are added.

Adjuvant Analgesics

Adjuvant analgesics are a heterogeneous group of analgesics initially developed for indications other than pain and include antidepressants, anticonvulsants, and anxiolytics. Although their effects are mainly documented in neuropathic pain conditions [50], adjuvant analgesics have been widely used in the clinic to treat all forms of pain. The most frequently used anticonvulsive agents are the gabapentinoids (gabapentin, pregabalin). These drugs have proven effective in neuropathic pain conditions, but are also used for other types of pain. Pregabalin is also effective in visceral pain, and in patients with CP it was found to produce moderate pain relief with relatively limited side effects [18]. Moreover, a reduction in opioid dose in the short term may be seen, although longer-term studies are needed [51]. Recently, it has been proposed that gabapentinoids possess a potential for misuse. It is

Table 36.2 Recommended oral analgesics for pain management in chronic pancreatitis.

Drug class	Examples[a]	Comments
Non-opioid analgesics	Paracetamol 1 g ×4	Used for milder pain. NSAIDs should normally be avoided but can be used in selected patients together with proton pump inhibitors. Metamizole may also be considered
Weak opioids	Tramadol CR 50–200 mg ×2	Codeine and tramadol potentiate the effect of non-opioid analgesics. Both are prodrugs, metabolized to active opioids
Strong opioids	Oxycodone CR starting at 15 mg ×2	There is potentially a risk for addiction and major side effects. Few patients may develop opioid-induced hyperalgesia and the medication should be used carefully and preferably only episodically, but no other drugs can alleviate strong pain
Anticonvulsants	Pregabalin titrated from 75 mg to 300 mg twice daily	Has proven effective in patients with pain due to CP, but the therapeutic gain is often limited due to the side effects, although these often vanish during treatment
Tricyclic antidepressants	Amitriptyline 10–50 mg at night-time	Side effects often limit their use. Several classes exist and have different effect in the individual patient, but effect first appears after several weeks of treatment
SSRIs	Citalopram titrated up to 40 mg at night-time	This class is not an effective analgesic, but can be used in case of comorbid anxiety and depression
SNRIs	Duloxetine titrated up to 120 mg at night-time	The effects of SNRIs are well documented in somatic pain disorders, especially when there is a neuropathic component, and clinical experience shows that they can also be used in patients with CP
Anxiolytics	Diazepam 5 mg ×3	May dampen anxiety, but have limited, if any, analgesic effect
Antipsychotics	Levomepromazine titrated up to 100 mg daily	May potentiate the analgesic effect in selected patients

[a] Examples reflect the authors' normal practice and can only be regarded as a suggestion for clinical management. For details, see text.
CR, controlled release; CP, chronic pancreatitis; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin/norepinephrine reuptake inhibitors.

hypothesized that both gabapentin and pregabalin may have effects on the dopaminergic "reward" system [52]. However, the magnitude of the abuse potential and the mechanism behind it are not fully understood [53]. Distinct pharmacokinetics involving the absolute bioavailability of these two drugs (gabapentin: dose-dependent bioavailability; pregabalin: remains the same irrespective of dose) [54] may explain why pregabalin is perceived as more "powerful" by drug misusers [55,56]. Prescribers should pay attention to signs of abuse, especially in patients with a history of substance abuse.

Antidepressive medications are also widely used and their positive effects are documented in pain management for somatic disorders. Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin/norepinephrine reuptake inhibitors (SNRIs) have shown useful properties in both neuropathic pain conditions and functional disorders. However, it is unclear if they all have direct analgesic effects or have indirect benefit by reducing anxiety and depression [57].

On the other hand, TCAs appear to have neuromodulatory properties that are unrelated to their psychotropic effects [58]. It is important to start at very low doses and titrate slowly over weeks as side effects such as cardiovascular events can be dose-limiting [59]. It should be noted that there are major differences in receptor properties and analgesic mechanisms between the different TCAs and therefore an individual approach is necessary. The same is the case for the SSRIs/SNRIs. Because of the sedative effects, a single dose at night-time may be preferable. Unfortunately, clinical experience indicates that the side-effect profile often makes them less suitable. Although supported in preclinical studies, it has been disputed whether the mechanisms of adjuvant analgesics differ from that of other analgesics such as opioids. Recently, we have used a human model where the neuronal activity along the neuraxis was following during treatment with venlafaxine (an SNRI) and oxycodone (a strong opioid). We were able to demonstrate that venlafaxine had a strong effect on the brainstem and descending inhibitory pathways that

dampened the activity of the spinal cord, whereas the effects of the opioid were mainly present in the limbic system and higher cortical structures [60]. Such data support clinical studies [61] and emphasize that combination therapies are effective in multidisciplinary pain management.

Opioids

Opioid analgesics are indispensable for the management of severe pain as no other alternatives exist [62], but in non-cancer pain therapy they should only be initiated when more simple strategies have failed following a reasonable trial period [63]. Opioids are highly effective and relatively safe analgesics and their appropriate use by competent clinicians is a crucial element in modern pain management. However, treatment is often complicated by severe adverse effects and may lead to addiction. Furthermore, some opioids such as codeine, tramadol and morphine are contraindicated or require prolonged dose intervals in patients with severe renal and hepatic insufficiency. Patients with chronic pain and opioid use disorders may benefit from partial opioid antagonists such as buprenorphine, though randomized controlled trials are not available [64]. Opioids should form part of a multifaceted strategy that includes all necessary adjuvant analgesics, non-drug interventions, psychological support, and rehabilitation. There are enormous variations in opioid use across the globe, and even within countries and neighboring regions, deviations are observed [65,66]. This is based partly on local traditions, partly on regulatory issues, and to some degree on "opiophobia." It is mandatory to understand the complexity of opioid treatment, or alternatively treat patients in close collaboration with dedicated pain specialists. Several recommendations exist such as the recent European position paper [63] and the reader is referred to such guidelines. Of note, all patients must be fully educated on the proposed therapeutic strategy and informed about the risks for addiction and side effects, especially opioid-induced bowel dysfunction, emesis, and effects on the central nervous system. In some cases, the pain increases despite increased dose and in such situations opioid-induced bowel dysfunction or opioid-induced hyperalgesia should be suspected as this may mimic the pain in CP (for details, see Drewes et al. [67] and Drossman and Szigethy [68]). Treatment may include increased use of laxatives, opioid antagonists with restricted effect on the gut, tapentadol, or in the case of hyperalgesia tapering of opioids [68,69].

Patients on long-term opioid therapy must be kept under close clinical surveillance and, if possible, opioids shall be restricted to intermittent use. Sustained-release medication may lead to constant and long-term treatment with a higher risk of dependency, and although not evidence based it may be restricted to selected cases. After one to two months of treatment, a dose reduction should be considered and discussed with the patients. For further information the reader is referred to the European position paper [63].

Codeine is a weak opioid in level II analgesia, but it is metabolized in the liver by cytochrome P450 (CYP)2D6, where about 10% is transformed to morphine. It is therefore associated with the same spectrum of opioid-related side effects as seen for stronger opioids. Because of individual expression of CYP2D6, about 10% of patients experience no effect with codeine, whereas 1% are ultra-rapid metabolizers and experience more than average effect. Tramadol possesses both weak opioid agonist activity and an effect on norepinephrine and serotonin uptake. Tramadol is in many places the preferred level II analgesic. However, it is a prodrug that is metabolized to more potent opioid analgesic metabolites, particularly *O*-desmethyltramadol. Effect and side effects are influenced by an individual's CYP genetics, with poor metabolizers experiencing low and ultra-metabolizers high *O*-desmethyltramadol. Level III analgesics comprise the group of strong opioids such as morphine. Most clinically available opioids have their activity at the μ-receptor, but preclinical and experimental studies suggest that activation of the κ-receptor (another opioid receptor activated by oxycodone for example) may also be important in visceral pain [70]. Buprenorphine is another drug with complex activation of several receptor types, and it may be beneficial in hyperalgesia and deep pain although more clinical studies are needed [71]. Transdermal administration of opioids is not recommended as first-line opioid therapy but should be reserved for patients having trouble with tablet ingestion, such as CP patients with postprandial pain. In an open label, randomized, crossover trial, transdermal fentanyl patches were compared with sustained-release morphine tablets. No significant differences were found for pain control or patients' preference or quality of life, while 44% of patients treated with fentanyl plaster reported side effects mainly as a rash at application site [72].

There is marked interindividual variability in responsiveness to different opioids, and in circumstances where an individual patient fails to achieve satisfactory pain control and/or they are troubled by unacceptable side effects, a trial of an alternative opioid is indicated. Opioid rotation may be difficult and for guidelines the reader is referred to Drewes et al. [65].

Alternative Treatments

Cannabinoids, ketamine, clonidine, benzodiazepines, antipsychotics, and steroids may be used in difficult cases (for details, see Portenoy [73]). Medical marijuana includes plant-derived cannabinoids such as tetrahydrocannabinol and cannabidiol, and synthetic cannabinoids such as nabilone and dronabinol. Tetrahydrocannabinol is the

most abundant cannabinoid and has psychotropic activity. For treatment of pain, cannabinoid derivatives are mostly prescribed in the palliative phase, where additional benefits include relief of nausea, stimulation of appetite, and better sleep. Although small series report modest pain relief, sound clinical evidence is lacking for relief of pain as well as other beneficial effects [74]. However, a recent epidemiological study indicated that cannabinoids may be useful in elderly patients [75]. In patients with CP, some studies have shown no or limited effects, and treatment is still based on an individual level [76,77]. Despite lack of evidence, "medical marijuana" is broadly used in palliative cancer care in some countries, either prescribed by GPs or self-prescribed.

Ketamine, an *N*-methyl-D-aspartate receptor antagonist, is used not only for anesthesia but also as a potent analgesic in acute and chronic pain. It has effects as an antihyperalgesic, reducing central sensitization and opioid-induced tolerance and hyperalgesia [78]. The mode of administration is still not standardized, and whereas some guidelines have recommended intravenous or subcutaneous use, randomized studies have also found effects of intranasal administration [79]. Although ketamine is an interesting remedy to revert or reduce central sensitization and its associated hyperalgesia, there are several limitations with the drug due to the side effects, which may be rather severe with long-term negative consequences.

Experimental and clinical evidence suggest a key role for nerve growth factor (NGF) in the generation and maintenance of a wide range of pain states. Consequently, drug discovery efforts have resulted in several humanized anti-NGF monoclonal antibodies that have entered clinical trials as potential analgesics [80]. NGF is upregulated in pain patients and is known to play a pivotal role in the process of peripheral sensitization. Therefore NGF antagonism may also be effective for pain relief in these patients [81]. Other drugs, such as clonidine (centrally acting α_2-adrenergic agonist), quetiapine (second-generation antipsychotic), and neurokinin-1 receptor (NK-1R) antagonists, have all demonstrated analgesic efficacy and may be used in selected patients [82].

The opioid antagonist naltrexone hydrochloride has, in low doses (4.5 mg), been suggested as beneficial in a range of inflammatory pain conditions such as Crohn's disease, multiple sclerosis, and fibromyalgia. Reports also describe therapeutic effects in pancreatic cancer [83]. It acts as a glial modulator, antagonizing Toll-like receptor 4, likely producing anti-inflammatory effects. Additionally, blockade of opioid receptors, resulting in compensatory release of endogenous opioids, contributes to analgesia and modulates the immune response [84]. However, more clinical trials are warranted before it can be recommended in patients with pain due to CP.

Personalized Treatment

In practice pain treatment is mainly guided by clinical evidence. Experimental pain methods may add to identification of the pain phenotype and can include neurophysiological and psychological testing whereby specific pain mechanisms and psychiatric comorbidity are detected and rational treatment initiated [7,85]. For example, in patients with pain due to CP, segmental hyperalgesia of the epigastric skin area (pancreatic viscerotome), detected by quantitative sensory testing, may serve as a clinical marker of central sensitization and predict the response to gabapentinoids [86]. Also, up to 40% of chronic pain patients are depressed and recognition of mood disorders may identify patients where adjuvant therapy with antidepressants is particular beneficial [7]. Over the past few decades, significant progress has been made in our understanding of the basic science of pain and the effect of analgesics. However, treatment should always be individualized, and the complexity of pain taken into consideration.

Pharmacological Considerations

It should be stressed that altered gastrointestinal physiology and function such as in CP can lead to alterations in the bioavailability of orally delivered analgesics (for details, see Olesen et al. [87]). Theoretically, a dysfunctional gastrointestinal tract may adversely impact drug release, for example if gastric pH, gastric emptying time, or lipase enzyme or bile secretion are altered. However, only a few studies undertaken in small populations have addressed the effects of the pharmacokinetics in CP. Given that most medications are absorbed in the small intestine, delayed gastric emptying, as occurs in opioid-treated patients or those with diabetes, will slow the time to peak concentration and delay the onset of action of medications [88]. In patients with CP, exocrine pancreatic insufficiency is associated with changes in gastrointestinal intraluminal pH resulting in fat malabsorption [87], which might affect drug release from lipid-based matrices. Finally, associated diabetes may cause dysmotility and small intestinal bacterial overgrowth [87,89,90], which can affect pH and thus drug release from water-swellable matrices as well as drug absorption. Multimorbidity is also frequent in CP and, for example, ischemic heart disease and renal or hepatic dysfunction may affect drug distribution, metabolism, and excretion. Because of multimorbidity, polypharmacy is also prevalent. In summary, CP can potentially affect the gut with consequences for the absorption of orally administered drugs [91], and if the response to analgesics is not as expected, other treatments such as transdermal

administration can be used where bioavailability is independent of disease in the gut [92].

Conclusion

Intense abdominal pain is the dominant feature of CP and is associated with poor quality of life. Basic studies of pancreatic nerves and experimental human pain research have provided evidence that pain processing is abnormal in these patients and in many cases resembles that seen in neuropathic pain disorders. In addition, adverse effects and complications of medical and interventional therapies may account for a substantial morbidity in many patients and should be considered an additional source of pain. Management should be individualized and, if possible, directed against the pain mechanism in the individual patient. Comorbidities and potential changes in absorption, distribution, and elimination of analgesics should also be taken into consideration, especially in treatment failures. Management should always be based on multimodal strategies where different specialties work together in concert, and although endoscopic and surgical treatments may be effective in selected patients [93], pharmacological treatment is still the mainstay of pain management in CP.

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