

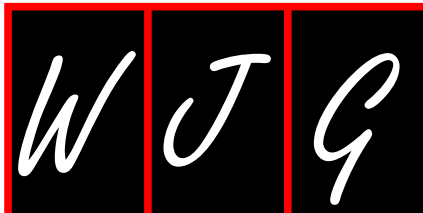
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Asbjørn Mohr Drewes, MD, PhD, DMSc, Professor, Series Editor

## Pharmacological pain management in chronic pancreatitis

Søren S Olesen, Jacob Juel, Carina Graversen, Yuri Kolesnikov, Oliver HG Wilder-Smith, Asbjørn M Drewes

Søren S Olesen, Jacob Juel, Asbjørn M Drewes, Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, 9000 Aalborg, Denmark

Carina Graversen, Mech-Sense, Department of Radiology, Aalborg University Hospital, 9000 Aalborg, Denmark

Carina Graversen, Department of Neurorehabilitation Engineering, Bernstein Center for Computational Neuroscience, University Medical Center Göttingen, Georg-August University, D-37077 Göttingen, Germany

Yuri Kolesnikov, Pain Service, Department of Oncology, East Tallinn Central Hospital, 19086 Tallinn, Estonia

Oliver HG Wilder-Smith, Pain and Nociception Neuroscience Research Group, Department of Anaesthesiology, Pain and Palliative Care, Radboud University Nijmegen Medical Centre, 6525 Nijmegen, The Netherlands

Oliver HG Wilder-Smith, Asbjørn M Drewes, Center for Sensory-Motor Interaction, Department of Health Science and Technology, Aalborg University, 9000 Aalborg, Denmark

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Correspondence to: Søren S Olesen, MD, PhD, Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Mølleparkvej 4, 9000 Aalborg, Denmark. [sso@mech-sense.com](mailto:sso@mech-sense.com)

Telephone: +45-9-9326243 Fax: +45-9-9326507

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### Abstract

Intense abdominal pain is a prominent feature of chronic pancreatitis and its treatment remains a major clinical challenge. 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 and chronic pain disorders. An important ultimate outcome of such aberrant pain processing is that once the disease has advanced and the pathophysiological processes are firmly established, the

generation of pain can become self-perpetuating and independent of the initial peripheral nociceptive drive. Consequently, the management of pain by traditional methods based on nociceptive deafferentation (*e.g.*, surgery and visceral nerve blockade) becomes difficult and often ineffective. This novel and improved understanding of pain aetiology requires a paradigm shift in pain management of chronic pancreatitis. Modern mechanism based pain treatments taking into account altered pain processing are likely to increasingly replace invasive therapies targeting the nociceptive source, which should be reserved for special and carefully selected cases. In this review, we offer an overview of the current available pharmacological options for pain management in chronic pancreatitis. In addition, future options for pain management are discussed with special emphasis on personalized pain medicine and multidisciplinary.

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**Key words:** Chronic pancreatitis; Pain; Treatment; Pharmacology; Analgesics; Adjuvant analgesics

**Core tip:** Pharmacological pain management in chronic pancreatitis is complicated and requires a multidisciplinary approach. Identification of risk factors associated with disease progression and evaluation of extra pancreatic causes of pain and complications is essential in all patients. Analgesics are typically titrated according to the World Health Organization ladder principle, but in some situations a top-down approach may be useful to control pain and avoid sensitization of central pain pathways. Adjuvant analgesics and combinations of drugs should be considered at an early stage. Non-encapsulated enzyme therapy, somatostatin-analogues and antioxidants can be considered as supplements to conventional analgesics in special situations.

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## INTRODUCTION

Chronic pancreatitis (CP) remains a major source of morbidity in the Northern Europe, with an annual incidence of approximately 10/100000 inhabitants<sup>[1]</sup>. It is a disease characterised by progressive destruction of the pancreatic gland and is typically characterised by severe abdominal pain. As the disease evolves, significant impairment of exocrine as well as endocrine functions also become evident<sup>[2,3]</sup>. The aetiological risk-factors associated with CP are multiple and involve both genetic and environmental factors. In the Northern Europe, excessive alcohol consumption is the leading cause of CP, although genetic susceptibility is also recognised as playing an increasing role<sup>[1,4]</sup>.

From the perspective of the patients (and their doctors) pain is the most significant symptom in CP, and most patients develop chronic pain during the course of their disease. The classic description of the pain is that of a constant, severe, dull ache in the mid-epigastrium, which often radiates to the back. It is typically worsened by high-fat foods, and pain attacks may last for days. However, just as the disease has different causes and morphological expressions, this classic pain pattern is not universal, and the location, character and quality of pain can be quite variable<sup>[2]</sup>. Furthermore, pain has been associated with malnutrition, narcotic addiction, physical and emotional disability, and major socioeconomic problems. Consequently, the clinical evaluation of pain is often blurred by addiction to alcohol and narcotic analgesics as well as by the personality disorders underlying these dependencies<sup>[3,5]</sup>. In view of this complex clinical presentation, it is not surprising that treatment of pain in patients with CP is challenging and often unsuccessful<sup>[6]</sup>.

The aim of this review is to summarise current available pharmacological therapies for pain in CP. In addition, future options for pain management are discussed with special emphasis on personalized pain medicine and multidisciplinary.

## OVERVIEW OF PAIN MECHANISMS IN CP

A detailed overview of the complex pain mechanisms underlying pain in CP is beyond the scope of this review and provided elsewhere in this issue of the journal. It is important to emphasise that none of the current acknowledged theories are mutually exclusive, and it is most likely that several pain mechanisms act in concert to cause pain in the individual patient.

Historically, the focus of pain treatment has been on

the pancreatic gland as a nociceptive source, based on the assumption that pain is generated by local pathology within or in close proximity to the pancreas. This mechanistic understanding of pain, has for many years, been the most widely accepted theory regarding the origin of pain in CP<sup>[7]</sup>. However, there is no direct relationship between the presence of pancreatic pathology such as duct dilation, pancreatic duct stones, pancreatic duct strictures, etc. and abdominal pain in CP pain patients<sup>[8-11]</sup>. Furthermore, the experimental evidence supporting this theory is sparse and findings have been conflicting<sup>[12]</sup>.

On the contrary, many current theories of the pathophysiology of CP postulate that in a high number of cases, repeated episodes of inflammation and pancreatic injury drive the process within the gland towards irreversible injury and are associated with damage to the pancreatic nerves<sup>[7,13,14]</sup>. Key in this theory is the recognition that the resulting ongoing and aggressive nociceptive input is likely associated with altered function of the pain processing system, particularly at the central level<sup>[15-18]</sup>. An important ultimate outcome of such aberrant pain processing is that once the disease has advanced and the pathophysiological processes are firmly established, the generation of pain can become self-perpetuating and independent of the initial peripheral nociceptive drive<sup>[19,20]</sup>. Consequently, the management of pain by traditional methods based on nociceptive deafferentation (*e.g.*, surgery and visceral nerve blockade) becomes difficult and ineffective<sup>[20]</sup>. This novel and improved understanding of pain aetiology requires a paradigm shift in pain management of CP. Hence, modern mechanism based pain treatments taking into account altered pain processing are likely to increasingly replace invasive therapies targeting the nociceptive source, which should be reserved for special and carefully selected cases.

## RISK-FACTOR MODIFICATION AND PROPHYLAXIS

The risk-factors associated with CP can be classified according to the MANNHEIM risk-factor classification system<sup>[4]</sup>. In this system, the multiple (M) risk factors underlying CP are categorised into six major subcategories of alcohol consumption (A), nicotine consumption (N), nutritional factors (N), hereditary factors (H), efferent pancreatic duct factors (E), immunological factors (I), and various rare miscellaneous and metabolic (M) factors. The rationale for modifying these risk-factors is to reduce recurrent injury to the pancreas. Hence, with repeated episodes of acute inflammation triggered by one or more risk factors, the inflammatory environment within the pancreas shifts towards chronic inflammation, with subsequent activation of pancreatic stellate cells, fibrinogenesis, and irreversible pancreatic damage<sup>[21]</sup>. Although not well established for all risk-factors (see below), it seems likely that prevention of recurrent pancreatitis attacks, clinical or sub-clinical, by risk-factor modification, will translate into a slowing of disease progression, less exo-

**Table 1 Recommended risk factor modifications in chronic pancreatitis according to the MANNHEIM criteria**

Risk factor	Treatment	Comments
Alcohol	Alcohol cessation	Decrease disease progression and may have beneficial effects on pain
Nicotine	Smoking cessation	Decrease disease progression and may have beneficial effects on pain
Nutritional	No specific recommendations	No prospective data
Hereditary	Endoscopic surveillance	Currently no formal evidence, a prospective trial has been initiated
	Pancreatectomy with autolog stem cell transplantation	Preferred strategy in some United States centers
Efferent duct	Endoscopy or surgical interventions	The benefit of intervention is controversial
Immunological	Steroid treatment	Treatment of autoimmune pancreatitis follows guidelines provided in <i>e.g.</i> , Ref. 32
Metabolic	Lipid lowering therapy, parathyroidectomy, <i>etc.</i>	Consider referral to an endocrinologist

**Table 2 Treatment of extrapancreatic causes of pain in chronic pancreatitis**

	Treatment	Comments
Peptic ulcer	Proton pump inhibitor +/- eradication of <i>H. pylori</i>	Avoid NSAIDs in CP Patients
Pseudocysts	Endoscopic drainage, transcutaneous drainage or surgical drainage	Preferred treatment dependant on pseudocyst localization and morphology
Duodenal obstruction	Endoscopic dilation or surgical therapy	Endoscopic dilation preferred as first line therapy
Bile duct obstruction	Covered metal stent or plastic stent	Controversial, one study found no relationship between bile duct obstruction and pain

NSAID: Nonsteroidal anti-inflammatory drugs; CP: Chronic pancreatitis; *H. pylori*: *Helicobacter pylori*.

crine and endocrine insufficiency and most importantly decreased abdominal pain. In Table 1 recommended risk factor modifications are summarized.

In patients with an alcoholic aetiology of CP, there is evidence to support that cessation of alcohol may have beneficial effects on disease progression and pain<sup>[22,23]</sup>. Furthermore, there is increasing evidence that tobacco use is also an important and independent risk factor for CP and that cigarette smoking accelerates progression of alcoholic CP<sup>[24,25]</sup>. Hence, tobacco cessation is highly recommended in these patients, although the association with pain relief has yet to be determined.

Data on the association between nutritional factors and CP are sparse. The consumption of a diet rich in fat and protein was associated with the development of CP in a case-control study<sup>[26]</sup>. However, retrospective descriptions of daily nutritional habits are difficult and such data may be subject to recall bias. Thus, it is difficult to provide a simple description of past daily nutrition in the majority of patients with CP and these findings needs to be confirmed in a prospective trial before specific recommendations can be made.

In patients with CP following gallstone pancreatitis, prevention of recurrent choledocholithiasis is crucial and reduces further damage to the pancreas<sup>[27]</sup>. In this situation cholecystectomy is recommended for patients suitable for surgery<sup>[28]</sup>. Also, patients with recurrent pancreatitis and efferent duct abnormalities such as pancreas divisum may benefit from endoscopic therapy or surgery to decrease the risk of recurrent pancreatitis and progression to CP<sup>[29]</sup>. However, data on this subject are limited and the optimal treatment of this specific entity is still a subject of controversy.

No specific treatment exists to modify the disease progression in hereditary CP. These patients have a sig-

nificantly increased risk of pancreatic cancer and surveillance or even total pancreatectomy with autologous islet-cell transplantation is recommended in some centers<sup>[30]</sup>. Patients with autoimmune pancreatitis comprise a special subset of patients with a potentially curable form of pancreatitis. Management of these patients is beyond the scope of this review and the reader is referred to reference<sup>[31]</sup>.

In CP due to metabolic abnormalities such as hypertriglyceridaemia, maintenance of triglycerides within the normal range would be expected to reduce the chance of repeated pancreatitis attacks and thus progression to CP<sup>[32]</sup>. Also, patients with hypercalcaemia induced pancreatitis due to hyperparathyroidism should be managed appropriately and - if necessary - referred to an endocrinologist.

## TREATMENT OF EXTRA-PANCREATIC CAUSES OF PAIN

In addition to risk factor modifications, extra-pancreatic causes of pain should be thoroughly investigated and treated (Table 2). Peptic ulcers are reported to have an increased prevalence in CP. This is possibly explained by changes in blood flow to the mucosa following attacks of acute pancreatitis as well as deterioration of pancreatic exocrine function resulting in a reduction of bicarbonate concentration and hence acidification of the milieu in the duodenal lumen. Also, increased gastric acid secretion and an increased prevalence of *Helicobacter pylori* in CP have been associated with the increased prevalence of peptic ulcers<sup>[33]</sup>. Another important source of pain in CP is pseudocysts, which should be investigated by an appropriate radiological work-up and treated accordingly<sup>[34]</sup>. Some patients may have pain as a consequence of obstruction of adjacent viscera (duodenum or common

**Table 3** Current available pharmacological treatments for pain in chronic pancreatitis

Pain mechanism	Treatment option(s)	Comments	Ref.
Raised levels of CCK	Pancreatic enzyme replacement therapy Somatostatin-analogues	Only non-enteric coated enzymes have proven effective Conflicting results, prolonged release formulations may be of value	[57-65] [67,68]
Pancreatic inflammation and oxidative stress	Antioxidants	Conflicting results, probably most valuable in tropical calcifying CP	[71,72]
Central sensitisation	Antidepressants (TCA, SSRI, SNRI) Gabapentinoids (Gabapentin/Pregabalin)	Expert opinion, no clinical data (Ref.) Modest effect on pain in a randomised placebo controlled trial (Pregabalin)	[2] [42]
Analgesics	Ketamine	Reverses hyperalgesia in an experimental pain study	[54]
	Tramadol <i>vs</i> morphine	No difference in pain relief in a randomised controlled trial, fewer side effects on tramadol treatment	[35]
	Fentanyl <i>vs</i> Morphine	No difference in pain relief in a randomised controlled trial	[41]
	Oxycodone <i>vs</i> Morphine ADL 10-0101:KOR agonist	Oxycodone superior to morphine on experimental pain measures KOR agonist superior to morphine on experimental and clinical pain measures. Limited number of patients ( $n = 6$ )	[39] [40]

CCK: Cholecystokinin; CP: Chronic pancreatitis; TCA: Tricyclic antidepressant; SSRI: Selective serotonin reuptake inhibitor; SNRI: Serotonin norepinephrine reuptake inhibitor; KOR: Kappa opioid receptor.

bile duct)<sup>[35]</sup>. However, the mechanisms underlying such “obstructive pain” remain unclear and in the case of bile duct obstruction there is evidence to the contrary<sup>[36]</sup>.

## ANALGESICS

The standard guideline for analgesic therapy in CP patients follows the principles of the “pain relief ladder” provided by the World Health Organization (WHO)<sup>[37]</sup>. This principle is based on the serial introduction of drugs with increasing analgesic potency, titrated until pain relief is obtained. However, in patients with a severe and debilitating pain pattern, a more aggressive approach using opioids combined with adjuvant analgesics as first line therapy (*i.e.*, a top-down approach), is useful to control pain and prevent sensitization of central pain pathways. An overview of the current available pharmacological therapies used to treat pain in CP is reported in Table 3.

Paracetamol is usually the preferred drug in level I analgesia due to its limited side effects. It has analgesic and antipyretic activity that work through central and peripheral non-opioid mechanisms, which have not yet been fully characterised<sup>[38]</sup>. Nonsteroidal anti-inflammatory drugs (NSAIDs) are particularly useful for treating musculoskeletal pain and are in general less favourable for visceral pain because of their toxicity to the GI tract<sup>[39]</sup>. Consequently, we recommend avoiding NSAIDs for painful CP.

Codeine is a weak opioid in level II analgesia, but is still associated with the same spectrum of opioid-related side effects seen for stronger opioids, *e.g.*, constipation, nausea, dyspepsia amongst other symptoms involved in opioid-induced bowel dysfunction<sup>[40]</sup>. Tramadol possesses both a weak opioid agonist activity along with an effect on noradrenaline and serotonin uptake in the spinal cord. It has been shown to be more potent than codeine and may be considered as a halfway house between level II and level III analgesics. Tramadol was also shown to be more efficacious than morphine in patients with CP, with fewer gastrointestinal side effects for the same level of

analgesia<sup>[41]</sup>.

Strong opioids, such as morphine, mainly exert their analgesic effects in the central nervous system, although it is now well known that opioid receptors are synthesised in the dorsal root ganglia and transported towards both central and peripheral nerve terminals<sup>[42]</sup>. Several opioid receptors exist, including the  $\mu$ -receptor,  $\delta$ -receptor and the  $\kappa$ -receptor<sup>[43]</sup>. Most clinically available opioids have their primary activity at the  $\mu$ -receptor and have been used widely to treat pain in CP patients<sup>[6]</sup>. However, animal studies have suggested that activation of the  $\kappa$ -receptor may be more efficacious for attenuation of gastrointestinal pain<sup>[44]</sup>. In keeping with these findings, oxycodone (an opioid targeting the  $\mu$ -,  $\delta$ - and  $\kappa$ -receptor) was shown to attenuate experimental visceral pain better than morphine in CP patients<sup>[45]</sup>. Also, in a pilot study including six CP patients with chronic abdominal pain, infusion of a peripherally restricted  $\kappa$ -receptor agonist (ADL 10-0101) - but not placebo - reduced clinical and experimental pain scores<sup>[46]</sup>. These findings were not replicated in patients with pain due to pancreatic cancer<sup>[47]</sup>, but this may relate to the confounders associated with clinical studies on opioids<sup>[48]</sup>. Taken together, these findings may suggest differentiated effects of opioids for pain management in CP patients. However, it must be emphasized that data from well-designed clinical studies with long-term follow-up are not yet available.

Opioids used in the outpatient clinic can be administered either orally (*i.e.*, tablets) or transdermally (*i.e.*, patch formulation). In an open label randomized crossover trial, transdermal fentanyl plaster was compared to sustained release morphine tablets in an equipotent dosage regime<sup>[49]</sup>. No significant differences were found for pain control, patients' preference or quality of life, while 44% of patients treated with fentanyl plaster reported skin side effects. Taken together with the increased costs of patch formulation, the authors concluded that transdermal administration of opioids cannot be recommended as first line opioid therapy for CP, but should be reserved to patients having trouble with tablet ingestion<sup>[49]</sup>.

As discussed above, CP patients may be suffering from hyperalgesia due to sensitization of the central nervous system<sup>[14,19]</sup>. In general, opioids are not very effective in treating established central sensitization and may even cause hyperalgesia themselves (*i.e.*, opioid induced hyperalgesia)<sup>[50]</sup>. Furthermore, opioid induced bowel dysfunction is a common problem in clinical practice and typically manifests as abdominal discomfort or even diffuse abdominal pain<sup>[40]</sup>. Taken together, opioid based therapies often become ineffective and associated with gastrointestinal side effects in the context of advanced CP and hence other treatments are highly warranted.

### Adjuvant analgesics

Adjuvant analgesics are a heterogeneous group of drugs initially developed for indications other than pain. However, many have proven effective in painful conditions, which has now been widely recognised as a separate therapeutic indication. Adjuvant analgesics modify the nociceptive processes through several modes of action, including anxiolytic effects (benzodiazepines, alpha-2-delta ligands), antidepressive effects (antidepressants), and anti-hyperalgesic effects (antidepressants, alpha-2-delta ligands). Although they have been widely used to treat pain associated with CP, only the alpha-2-delta ligand pregabalin has been studied in the context of painful CP<sup>[2,51]</sup>. Hence, in a placebo controlled double blinded randomized trial, we recently demonstrated the efficacy of pregabalin as an adjuvant analgesic for pain in CP. We found that CP patients treated with pregabalin escalated to a maximal dose of 600 mg *bid* had a significant reduction in self-reported pain scores compared to placebo. Furthermore, the percentage of patients with much or very much improved health status score was higher in the pregabalin group compared to the placebo group. The side effects were relatively few and of mild to moderate severity; with a “drunk feeling” being the most prevalent side effect (35% of patients) and typically showing a ceiling effect after one or two weeks of treatment<sup>[51]</sup>.

The analgesic mechanisms of action underlying pregabalin analgesia are not completely understood, and it probably exerts a range of effects on pain transmission<sup>[52,53]</sup>. *In vitro* studies indicate that pregabalin binds selectively to the alpha-2-delta subunit of voltage-dependent calcium channels, thereby blocking the influx of calcium into pre-synaptic nerve terminals. This reduces release of excitatory neurotransmitters, including glutamate, noradrenalin and substance P, and dampens pain transmission<sup>[54,55]</sup>. These findings translate well to experimental pain studies in CP, where antinociceptive effects of pregabalin on electrical evoked pain from the gut and skin were observed, compatible with a reduction of central sensitization<sup>[56,57]</sup>.

### Ketamine

Introduced in 1965 as an anesthetic, today ketamine is used not only for anesthesia, but also as a potent analgesic in acute and chronic pain as well as an antihyperalgesic

used to reduce central sensitization in various chronic pain conditions. It is a noncompetitive *N*-Methyl-*D*-aspartate (NMDA) receptor antagonist, but it also exerts its analgesic effects through other mechanisms including opioid receptor activation<sup>[58]</sup>. Sensitization of the central nervous system has been documented in several studies of painful CP and is believed to play a prominent role in pain generation in this entity<sup>[15,16]</sup>. One of the best-characterized mechanisms in the early phase of central sensitization is activation of the NMDA receptors<sup>[59]</sup>. Multiple studies have consistently produced positive results regarding the use of ketamine in chronic pain patients with central sensitization and hyperalgesia and it thus comprises an interesting remedy to revert reduce central sensitization and its associated hyperalgesia in CP<sup>[60]</sup>. This was supported by a double-blinded crossover trial designed to evaluate the effect of ketamine infusion on hyperalgesia associated with CP<sup>[61]</sup>. Infusion of ketamine temporarily reversed pressure pain hyperalgesia and the underlying sensitized state of the pain system. However, only short-term effects were evaluated and no effect was seen on clinical endpoints. Hence, the use of ketamine for pain in CP is still in its infancy and prospective clinical trials are warranted to establish its role in the management of painful CP.

## SUPPLEMENTARY THERAPIES

### Pancreatic enzyme therapy

Pancreatic enzyme therapy for pain control in CP has been the subject of several randomized trials and meta-analyses (Table 3). The proposed mechanism of action is the ability to degrade cholecystokinin (CCK) releasing factor in the duodenum and thereby lower CCK<sup>[2]</sup>. An elevated level of CCK have been reported in CP patients and may generate pain by increasing the pressure in the pancreatic duct (CCK-A), but also through direct activation of nociceptive pathways in the central nervous system (CCK-B)<sup>[62,63]</sup>. Only non-enteric coated formulations have duodenal protease activity and studies using this type of enzymes have documented improvement in pain<sup>[64,65]</sup>. In contrast, most studies using enteric coated preparations (which are not active in the duodenum and hence cannot degrade CCK-releasing factor) have not shown any improvement on pain measures<sup>[66-69]</sup>. One study, however, showed pain relief of enteric coated enzymes during acid inhibition, but this study used a measurement of pain that included symptoms of mal-absorption (bloating, gas or cramping), rather than more traditional pain measures<sup>[70]</sup>. A meta-analysis combining all studies found no effect of enzymes on pain relief in CP<sup>[71]</sup>. Nevertheless, combining the two types of enzyme formulations in a meta-analysis is probably not appropriate given the proposed mechanism of action<sup>[72]</sup>.

### Somastotatin-analogues

Somastotatin-analogue inhibits pancreatic secretion by blocking CCK and secretin release and also by a direct

inhibitory effect on acinar cells<sup>[73]</sup>. As discussed above, these effects may alleviate pain through reduction of pancreatic ductal pressure and by lowering the central effects of CCK. There are conflicting data about the efficacy of somatostatin-analogues for pain in CP. While early pilot series of octreotide showed an effect on pain control, this effect could not be confirmed in a double-blind cross-over study enrolling 10 CP patients treated with octreotide (100 µg *tid*) or placebo for 3 d<sup>[74]</sup>. Although pancreatic secretion measured by fecal chymotrypsin was reduced by octreotide, no differences were seen in pain control or analgesic use. This study has been criticized for its relatively short follow-up and limited wash out period (48 h). Also, four patients had evidence of concretions in the pancreatic duct, which may have compromised the effect of octreotide. In a later pilot study, a long-acting version of octreotide (Octreotide LAR) administered once monthly, was compared to conventional subcutaneous octreotide treatment administered three times daily. Although not significant, there was a trend toward improved pain control for octreotide LAR<sup>[75]</sup>. These results, however, have never been subject to a formal placebo controlled trial and the role of octreotide treatment for painful CP has so far not been satisfactorily documented. Taken together with the numerous side effects and their cost, a general use of somatostatin-analogues for pain in CP cannot be recommended<sup>[76]</sup>.

### Antioxidants

The use of antioxidants for pain control in CP was presented two decades ago, but never gained widely clinical popularity. The proposed analgesic mechanism of action underlying this therapy is an anti-inflammatory and blocking effect on free radicals<sup>[77]</sup>. Propelled by an Indian randomized placebo controlled trial, antioxidant therapy recently had a rebirth for pain management in CP. In this trial, six months antioxidant therapy was associated with significant and prolonged pain relief compared to placebo<sup>[78]</sup>. However, these findings were not reproduced by a subsequent study from North America<sup>[79]</sup>. A possible explanation for this dichotomy may be that the patients included in the two trials were different. While the Indian study mostly included patients with trophic calcifying pancreatitis and malnutrition (and hence deficiency in antioxidants), the American study included a more elderly population who had alcohol as the leading etiology of CP and a normal nutritional condition. Hence, the efficacy of antioxidant therapy may be related to the etiology of CP and its associated malnutrition<sup>[80]</sup>. This idea was supported by a subgroup analysis of the patients with alcohol etiology in the Indian trial, who, in agreement with the American study, demonstrated no benefit of antioxidants<sup>[78]</sup>. Taken together, the evidence is not sufficient to recommend antioxidant therapy be used routinely for the typical Western CP patient with alcoholic pancreatitis.

### Other treatments

In addition to the abovementioned treatment options, various other pharmacological principles have been used

to treat pain associated with CP, including leukotriene antagonism and stimulation with secretin<sup>[81,82]</sup>. However, none of these treatments have documented any effect on pain and are regarded obsolete by most experts.

## INDIVIDUALISED PAIN THERAPY AND FUTURE ANALGESICS FOR PAIN IN CHRONIC PANCREATITIS

A major problem in pain medicine is the lack of knowledge about which treatment suits a specific patient. In a recent study, we tested the ability of quantitative sensory testing to predict the analgesic effect of pregabalin and placebo in patients with CP<sup>[83]</sup>. Pregabalin effect was associated with pretreatment sensitivity to electric tetanic stimulation of the upper abdominal area (sharing spinal segmental innervation with the pancreatic gland). Hence, patients expressing lower pain thresholds in the “pancreatic viscerotome” were more likely to benefit from pregabalin treatment compared to patients with normal sensitivity<sup>[83]</sup>. These findings suggest sensitization of spinal neurons in the segment innervated by pancreatic visceral afferents to be an important predictor of pregabalin efficacy in patients with painful CP. Interestingly, this method may be used to tailor pain medication based on patient’s individual sensory profile and thus comprises a significant step towards personalized pain medicine.

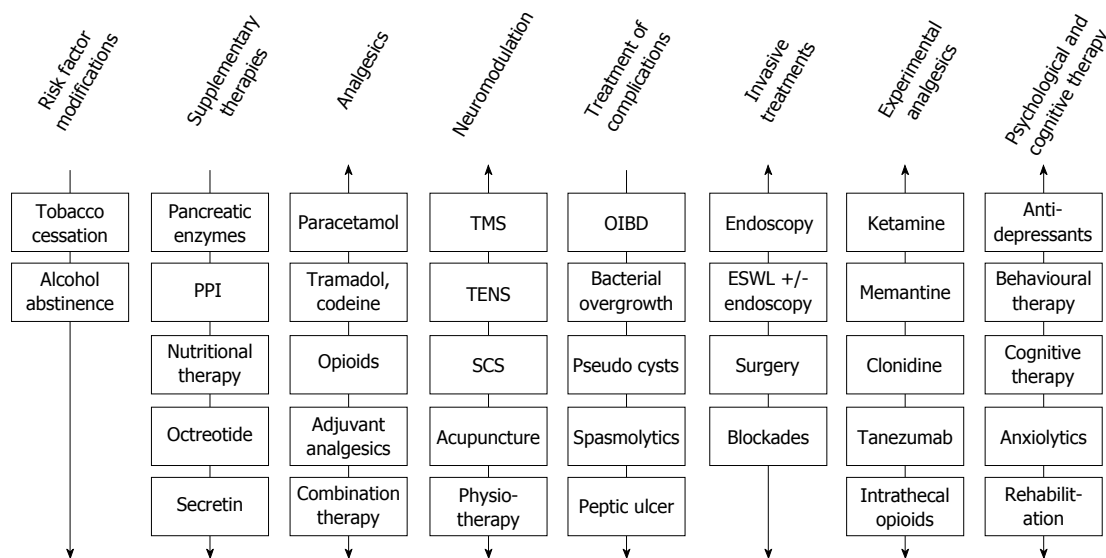
The novel and improved understanding of pain mechanisms in CP may pave the way for new treatments. Analgesics specifically targeting neural or humoral mediators of pain, such as nerve growth factor (NGF) and transient receptor potential vanilloid-1 antagonists, are currently being tested in clinical trials and hold promise for the future, although these drugs have yet to be tested in patients with CP<sup>[84,85]</sup>. Recently, a NGF-antagonist (Tanezumab) was shown to relieve pain in patients with knee pain due to gonarthrosis<sup>[84]</sup>. As NGF has been shown to be up-regulated in CP patients and is known to play a pivotal role in the process of peripheral sensitization, NGF-antagonism may be effective for pain relief in CP patients<sup>[86]</sup>.

### Multidisciplinary pain treatment

As discussed above the mechanisms underlying pain in CP are highly variable in the individual patient. Consequently, there is no single approach that is effective for all patients and choosing the right algorithm for pain treatment is highly depending of the pathogenesis of pain in the individual situation. Hence, a successful management of pain requires a multidisciplinary approach as illustrated in Figure 1. In addition, establishing a stable doctor-patient relationship is an important factor for a successful treatment outcome<sup>[80]</sup>.

## CONCLUSION

Intense abdominal pain is the most prominent feature of CP and its treatment remains a major clinical challenge.



**Figure 1** An illustration of the multidisciplinary approach recommended for managing pain in chronic pancreatitis. The mechanisms underlying pain in chronic pancreatitis (CP) are highly variable in the individual patient and there is no single approach that is effective for all patients. Hence, choosing the right algorithm for the pain treatment is highly depending of the pathogenesis of pain in the individual situation. Some treatments follow a typical step-up approach as indicated by the unidirectional arrows. Other treatments follow either a step-up or a top-down approach depending on the specific situation as illustrated by the bidirectional arrows. The latter is seen for example for analgesic therapies, where weak analgesics may be appropriate to control pain in one situation. On the other hand a more aggressive approach, using opioids combined with adjuvant analgesics as first line therapy (*i.e.*, top-down), is useful in patients with a more aggressive and debilitating pain pattern to control pain and prevent sensitization of central pain pathways. Often combination therapies of *e.g.*, opioids or adjuvant analgesics are used. Surgery, endoscopic therapies *etc.* are included in the figure for completeness, although these therapies are beyond the scope of this review. PPI: Proton pump inhibitor; TENS: Transcutaneous electrical nerve stimulation; SCS: Spinal cord stimulation; OIBD: Opioid-induced bowel dysfunction; TMS: Transcranial magnetic stimulation; ESWL: Extracorporeal shock wave lithotripsy.

Medical management requires a multidisciplinary approach including identification of risk factors associated with disease progression and appropriate modification. A systematically evaluation of extra pancreatic causes of pain and complications followed by appropriate treatments is essential in all patients. Analgesics are typically titrated according to the WHO ladder principle, but in some situations a top-down approach may be useful to control pain and avoid sensitization of central pain pathways. Also, adjuvant analgesics should be considered at an early stage and combinations of drugs are often used. Non-encapsulated enzyme therapy, somatostatin-analogues and antioxidants can be considered as supplements to conventional analgesics in special situations. An improved understanding of pain mechanisms in CP will undoubtedly pave the way for new treatments and future strategies should be based on modern mechanism based and personalized pain treatment.

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