Mechanism-based pain management in chronic pancreatitis - is it time for a paradigm shift?

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Review

Mechanism-based pain management in chronic pancreatitis - is it time for a paradigm shift?

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Abstract

Introduction
Pain is the most common symptom in chronic pancreatitis and treatment remains a challenge. Management of visceral pain in general, is only sparsely documented, and treatment in the clinic is typically based on empirical knowledge from somatic pain conditions. This may be problematic, as many aspects of the neurobiology differ significantly from somatic pain, and organs such as the gut and liver play a major role in tolerability to analgesics. On the other hand, clinical awareness and new methods for quantitative assessment of pain mechanisms, will likely increase our understanding of the visceral pain system and guide more individualized pain management.

Areas covered
This review includes an overview of known pain mechanisms in chronic pancreatitis and how to characterize them using quantitative sensory testing. The aim is to provide a mechanism-oriented approach to analgesic treatment, including treatment of psychological factors affecting pain perception and consideration of side effects in the management plan.

Expert opinion
A mechanism-based examination and profiling of pain in chronic pancreatitis will enable investigators to provide a well-substantiated approach to effective management. This mechanisms-based, individualized regime will pave the road to better pain relief and spare the patient from unnecessary trial-and-error approaches and unwanted side effects.

Keywords: Chronic pancreatitis; Chronic Pain; Pain Management; Pain Measurements; Neurophysiology; Analgesics; Symptom Assessment
1. Introduction

Chronic pancreatitis (CP) is a fibro-inflammatory disease where the pancreatic parenchyma is progressively replaced by fibrous connective tissue, potentially leading to exocrine and endocrine pancreatic insufficiency. The most common symptom in CP is abdominal pain which is present in about 70% of the patients. The typical description of the pain is a constant dull ache in the epigastrium with referral to the back (including referred muscle hyperalgesia) that often increases with food intake, but it can manifest in a variety of ways, ranging from patients with limited, intermittent pain to those with constant, intense, and severe pain [1]. Previously it was believed that pancreatic pain would “burn-out” as the disease process evolved with destruction of the pancreatic tissue [2]. Today the “burn-out” theory is regarded obsolete as evidence against it has been provided in large retrospective studies [3,4]. Thus, it is not advisable with a “wait-and-see” approach to patients with on-going pain. Unfortunately, management of pancreatic pain remains a considerable therapeutic challenge [5]. 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 the central sensitization processes and the more difficult it is to treat [6].

Different management regimes for visceral pain are only sparsely documented as compared with its somatic counterpart. As a consequence, the approach used in treatment of somatic pain is typically used as framework for visceral pain management, with analgesic use based on the World Health Organization (WHO) ladder [7,8]. Although visceral, somatic, neuropathic and inflammatory chronic pain conditions share common mechanistic features, visceral and somatic pain has several important differences that should be considered when initiating analgesic treatment [6]. Hence, visceral pain is more diffuse and difficult to localize. This can lead to malpractice, as failing to localize the origin of the pain can hinder for example surgical treatment. It is also accompanied by symptoms arising from the autonomic and enteric nervous system that may need specific management, including nausea and gastrointestinal disturbances [9]. Chronic visceral pain also induce peripheral and central sensitization more frequent than in somatic pain conditions [10]. Finally, when drug absorption and metabolism is considered, the gut and liver are of major importance, but they are often malfunctioning in CP due to steatorrhea, bile duct stenosis, duodenal stenosis and comorbidities including alcoholic liver disease [11]. These organs are also the main targets to side effects.

As a new dimension, characterization of the pain mechanisms underlying painful CP can theoretically facilitate individualized treatment targeting the involved mechanism, and thereby enable personalized pharmacological treatment, improve patient outcome, and reduce unwanted side effects. Therefore, the aim of this paper is to review the involved pain mechanisms in chronic
pancreatic pain and discuss the future of mechanism-based analgesic treatment. This will be done by evaluating studies that have used quantitative sensory testing (QST) to phenotype/profile patients and evaluate treatment response.

2. Pain mechanisms and quantitative sensory testing

There are several reasons for chronic pain in patients with chronic pancreatitis, for review see [5]. The pain can be nociceptive, inflammatory and/or neuropathic and thereby arise from an actual or threatened damage to the tissues. This can occur due to a number of complications to CP, and many of them are treatable. The initial step in treating pancreatic pain is to examine whether any of these complications are present and treat appropriately. If there are no anatomical complications, or if treatment of these complications does not relieve the patient’s symptoms, the pain could be of predominantly neuropathic origin and a different approach must be taken. In case of no obvious organic identifiable reasons but the patients show hyperalgesic reactions, the new descriptor **neuroplastic pain** may be used [12]. Like all other kinds of chronic pain, pancreatic pain can affect the peripheral and central nervous system leading to neuropathy and sensitization. For example, exposure to several chemical agents released following cellular damage in the pancreas, including H+, K+, inflammatory molecules and trypsin, lead to increased spontaneous activity and excitability manifested as peripheral sensitization. These peripheral changes result in an ongoing and vigorous nociceptive input to the spinal cord that may result in an altered function of the central pain pathways due to neuroplasticity (central sensitization) [13,14].

***Figure 1 near here***

Sensitization is characterized by hyperalgesia, where pain detection threshold is decreased compared to that in patients without chronic pain. The hyperalgesia can be detected either locally as seen in peripheral sensitization or generalized as seen in central widespread sensitization. General sensitization can also induce alldynia, where even stimuli that normally does not induce pain, can feel painful. This is obviously difficult to assess from structures as the pancreas but often those chronic visceral pain conditions manifest somatic hyperalgesia and alldynia in the referred somatic areas [15]. Although hypothetical, symptoms such as postprandial pain may be a manifestation of alldynia [16].
In central pain processing, there is a closely regulated balance between descending excitatory and inhibitory drives. In chronic pain patients it has been suggested that an imbalance between inhibitory and facilitatory descending pain modulatory systems can occur, favoring increased gain of incoming nociceptive signals [17]. Multiple studies have shown, that the balance between descending pain inhibition and facilitation is disturbed in patients with chronic pain and it has been proposed as a significant factor in the chronification of pain [18–21]. Similar modulatory pathways can perhaps also play a role in “temporal summation” of pain. Temporal summation is the perception of increased pain as a response to repetitive nociceptive stimulations with the same intensity due to a wind-up effect in the spinal dorsal horn [22]. A train of stimuli with a frequency of 0.33 Hz or higher induces cumulative depolarizations of the post-synaptic membrane thus resulting in wind-up of action potentials [23,24]. Temporal summation is facilitated in case of central sensitization [25]. Central sensitization can in some cases be detected without the presence of enhanced temporal summation, which shows that the interaction between the two is a complex interplay [26].

The function of pain processing and some of the underlying mechanisms can be characterized using QST. QST is comprised of a variety of stimulation modalities, at specific anatomical structures and using various evaluation methods. Well defined stimulations of skin and muscle are widely used, as the structures are easily accessible. Modalities may include mechanical stimulation (including touch, pinprick, and pressure) as well as thermal and electrical stimulation. In contrast, visceral QST, with stimulation of the gastrointestinal tract or other internal organs are unpleasant to the patient due to the invasive nature of the stimulus and more comprehensive and time consuming to conduct [27]. Rectal distension with an electric “Barostat” is occasionally used clinically in patients with e.g., irritable bowel syndrome, but beyond this visceral QST has mainly been limited to research settings [28,29].

On the other hand, central pain processing is the same whether the pain is visceral or somatic of origin. Hence, convergence between somatic and visceral nerves makes it possible to use somatic QST as a proxy of central referred pain mechanisms in the context of visceral pain [30]. The QST protocol we use for patients with CP is shown in figure 1. There is a static part that determines pain detection and pain tolerance thresholds to accurately calibrated phasic and tonic stimuli, and a dynamic part that determines the function of e.g. descending pain modulation and temporal summation. It has been shown to be sensitive for quantifying sensory abnormalities on an individual patient level and be predictive for outcome of management [31–33]. The dynamic parts of the QST paradigm is designed to evaluate changes in pain perception due to descending modulation and temporal summation. The descending modulation can be studied by the conditioned pain modulation (CPM) paradigm, where a painful conditioning stimulus at a remote area, attenuates pain responses to a test pain stimulus.
Figure 1 shows the involved pain mechanisms that can be evaluated in a QST examination for CP patients and Table 1 shows an overview of the different QST parameters:

- **Segmental and generalized hyperalgesia.** Sensitization of the nervous system can be explored by examining pressure pain detection and tolerance thresholds and comparing data with data from age and gender matched healthy volunteers. The pain detection threshold shall be assessed from several anatomical locations, including the pancreatic dermatome (Th10) and control dermatomes (e.g. C5, L4 etc.). Figure 2 shows an example of pressure pain detection thresholds in a patient with generalized hyperalgesia compared to a healthy control population [34].

- **CPM.** This can be assessed by applying a painful conditioning stimulus in between two identical test pain stimuli and the difference in the result of the two stimuli would then be a measure of the CPM efficacy [35]. The CPM effect can be expressed both as a relative and an absolute value. The conditioning stimulus can for example be the cold pressor test, where the extremity is exposed to cold water as used in our protocol. Ischemic pain, chemically induced pain, heat, and electrical induced pain can also be used. The test pain stimuli can for example be mechanical pressure, electrical stimulation, heat stimulation, and cold stimulation. There is currently no consensus how CPM should be assessed and unfortunately CMP seems to vary between repeated assessments and between patients/volunteers [36].

- **Temporal summation** is evoked by a series of e.g. 5 painful stimuli delivered by one per second [37]. Temporal summation magnitude is the difference between the sensory rating of the first and last stimuli. The stimulation can e.g. be heat, cold, mechanical pressure or electrical stimulation. Again, there is no golden standard how to assess temporal summation.

3. **Mechanism-oriented pain treatment**

3.1. **Initial approach**

When treating a patient with painful CP, the primary focus should be on treating the causality of pain in a mechanistic way. Patients with CP can have several complications that cause pain, including
pancreatic pseudocysts, peptic ulcers, pancreatic cancer, duodenal stenosis, and duct obstruction due to stones or stenosis [38,39]. Nutrition should be optimized, as high fat foods can provoke pancreatic pain in lack of pancreatic enzymes, and patients should be advised against smoking and drinking [1]. Whether pancreatic enzymes works as an analgesic is debatable, please see the appendix in Drewes 2017 for clarification [5]. Alcohol is a risk factor for CP, and cessation of alcohol consumption has been shown to be protective against developing pancreatic dysfunction as well as recurrent pancreatitis [40]. Smoking is an independent risk factor for CP and more than 80% of patients with chronic pancreatitis are smokers [41]. Tobacco can potentiate alcohol toxicity in a dose-dependent way, and a recent study has shown that smoking cessation increases the chance of successful outcome of pain relieving surgery [5,41,42].

Although treatment of the aforementioned complications along with successful smoking and alcohol cessation may result in pain relief in a proportion of patients, many patients will require additional pain management [43]. The patients could at this point possibly benefit from a mechanism-oriented pharmacological treatment of malfunctions in the pain processing pathways. If this approach fails to provide sufficient analgesia, a multidisciplinary approach adding alternative treatments including e.g., spinal cord stimulation and acupuncture may be useful.

Although not validated, an example of a mechanism-based treatment algorithm is presented in figure 3, and the rationale explained below.

***Figure 3 near here***

3.2. Neurophysiological evaluation of the response to analgesics

3.2.1. Sensitization

Sensitization is an important factor in the chronification of pain and a study has shown that treatment can be guided from this feature. N-methyl-D-aspartate (NMDA)-receptor antagonists, tricyclic antidepressant agents (TCA) and gabapentinoids have often been used to treat patients with sensitization and their potential use in patients with chronic pancreatic pain with sensitization will be reviewed here. Gabapentinoids is a group of anticonvulsant agents that acts by binding to the α2-δ unit of voltage-gated calcium channels in the central neural pathways, whereby it reduces the release of excitatory neurotransmitters [44]. The group includes gabapentin and pregabalin. Olesen et al. examined the effect of pregabalin on painful CP and found that lower electrical pain detection threshold at the abdominal pancreatic area had high accuracy to separate responders from
non-responders [45]. The classification accuracy was 80.6%, which is significantly above the effect of random selection. From the same study, Bouwense et al. reported that treatment with pregabalin in patients with CP leads to a greater increase in electrical pain thresholds at the C5 dermatome than placebo treatment, but not in the pancreatic “viscerotome” (dorsal and ventral T10 dermatome) suggesting a possible prevention on spreading hyperalgesia to higher segmental levels [46]. Pregabalin did also increase pain detection threshold and tolerance threshold in rectal stimulation [47]. This supports findings in previous studies where pregabalin reduces visceral hyperalgesia [48,49].

Many studies have examined the effect of ketamine on different types of pain. Ketamine is a NMDA receptor antagonist and thereby a possible treatment modality for central sensitization. Arendt-Nielsen et al. likewise found that ketamine increased the temporal summation pain threshold in healthy volunteers compared to placebo [50]. Several studies have tried to unravel the long-term effect of different administration forms of ketamine in patients suffering from various pain syndromes, but with inconsistent results. Currently large studies are ongoing in Australia examining the effects of low dose ketamine in managing and preventing chronic pain [51]. Generally the studies showed that infusion of ketamine provides immediate analgesic effect, which attenuates over time [52,53]. In CP, Bouwense et al. found that ketamine increases the sum of pressure pain detection threshold immediately after infusion, but the effect was not significant one hour after infusion [54].

TCA probably relieves pain through multimodal mechanisms of action, involving inhibition of serotonin and noradrenaline reuptake, blockage of sodium channels as well as blocking of the NMDA-receptors. The effects on pain thresholds are therefore likely to attenuate central sensitization. Enggaard et al. examined TCA’s effect on QST results in healthy volunteers and found that it increased pressure pain thresholds and decreased temporal summation [55]. It has also been examined in patients with painful polyneuropathy by Holbech et al., who found that pain intensity decreased significantly and that it improved both temporal summation by mechanical repetitive stimuli as well as cold pain [56]. TCA has not been tested in CP patients, but as the affected pain mechanisms of CP resembles those affected by other chronic pain conditions, it makes sense to use findings in other conditions when knowledge is limited in CP.

3.2.2. Impaired descending pain inhibition

Descending pain inhibition is an important pain processing pathway and it is decreased in many chronic pain conditions [57]. Olesen et al. has shown that conditioned pain modulation function is reduced in patients with painful CP compared to healthy volunteers [21]. Treatment targeted this pain
mechanisms could therefore be used to manage pancreatic pain. Bouwense et al. has looked at the effect of pregabalin compared with placebo on CPM function in CP patients [58]. They found that pregabalin responders (patients with a decrease of more than 30% on their average daily pain intensity after 3 weeks of pregabalin treatment) had a significant increase in CPM function from baseline measures. This indicates that pregabalin could have a direct anti-facilitatory effect on CPM or an indirect reduction of the transmission in the ascending pain pathways [58]. Even though this was a posthoc analysis, data are supported from preclinical studies, studies in healthy volunteers and from different patient categories than CP. From these studies, we can be inspired to find other treatments that could be helpful when treating pancreatic pain. As serotonin, noradrenaline, and opioid peptides are important neurotransmitters in relation to descending pain inhibition, many studies have examined the effect of serotonin and norepinephrine reuptake inhibitors (SNRI), TCA, and opioids in relation to defective pain modulation.

In two rat studies, TCA and low dose of opioids, respectively, have been shown to enhance endogenous pain modulation [59,60]. The noradrenergic system plays an important role in endogenous pain modulation and is influenced by TCA [60]. The authors of the opioid study speculated that opioids target supraspinal structures such as the periaqueductal grey and ventromedial medulla and thereby enhance descending modulation [59]. In humans, studies of opioids effects on descending modulation are more contradictory [61–64]. Olesen et al. examined morphine’s effect on different experimental pain models in healthy volunteers and did not find that morphine increased CPM effect [65]. Arendt-Nielsen et al. found that buprenorphine and fentanyl both increased the CPM function significantly compared to placebo in healthy volunteers after 72 hours treatment [63]. Hermans et al. found that morphine had no effect on CPM in patients with either rheumatoid arthritis or fibromyalgia combined with evidence of central sensitization [66]. However, the study only consisted of a single subcutaneous injection of morphine and does not tell us anything about the long-term effects of morphine treatment. Tapentadol, which has a dual effect on opioid receptors and noradrenalin reuptake, was examined in healthy volunteers in two studies, and it was shown not to affect CPM or experimentally induced heat, cold or mechanical hyperalgesia [61,64]. On the other hand, in patients with diabetic neuropathy where the pain system had undergone pathological changes, Niesters et al. found that tapentadol increased CPM function after 4 weeks of treatment [62]. Tapentadol both activates the μ-opioid receptor as well as inhibits neuronal norepinephrine reuptake. It therefore makes sense also to examine whether norepinephrine reuptake inhibitors also increase CPM function in patients. This has been done by Yarnitsky et al. who has found that CPM function predicts treatment effect of duloxetine [67].
3.2.3. Temporal summation

Chronic pain can induce enhanced temporal summation. The NMDA receptor is also believed to play a key role in this mechanism through a release of both peptides and glutamate that may lead to hyper excitability of spinothalamic tract neurons, and this characterizes central sensitization [23,68].

Different opioids have shown to inhibit temporal summation, including codeine and morphine [55,69]. Anticonvulsants drugs including the gabapentinoids and carbamazepine have also been shown to inhibit temporal summation in healthy subjects [50,70,71]. Amitriptyline (TCA) is thought to block the NMDA receptor, and this would theoretically lead to a decrease in temporal summation. However, a study surprisingly found that it significantly increased temporal summation, and speculates that this probably is caused by amitriptyline’s augmentation of glutamate release, making it less effective as a NMDA receptor antagonist [70].

As expected from a pathophysiological level, other NMDA antagonists are found to inhibit temporal summation. Ketamine was found to decrease temporal summation in healthy volunteers [50]. In another study, the effect of dextromethorphan on temporal summation was examined in patients suffering from abdominal pain due to irritable bowel syndrome. Here, the drug decreased temporal summation from a pathological baseline limit [72]. The authors did not report the effect of dextromethorphan on the patients’ pain ratings, and one could question whether the effect was clinically relevant.

3.2.4. Choosing analgesic treatment

In the clinic, many patients with severe pain will have several malfunctions when evaluating their QST results. An example from our clinic is that there is a substantial overlap of between abnormal mechanisms in 56% of the patients. This can be a challenge, because several treatments could potentially be beneficial. In preliminary results from our pain clinic, 57% of the patients have deficient CPM, 52% have segmental hyperalgesia and 43% of the patients have temporal summation. In this case, we suggest to treat the most deviant mechanism first and if management is insufficient to retest the algorithm on treatment and add supplementary therapies depending on the new findings. However, the algorithm can also be a supportive tool in the management strategy, and treatment shall always be based on the patients and doctors’ preferences, side-effect profile etc.

If the results of the QST examination is conflicting, it may make sense to use a more traditional analgesic strategy instead of the QST-guided regimen.
We are not able to say whether this method for choosing analgesic treatment is more cost-effective than using the WHO treatment ladder, as this will require a large number of treatments in different combinations. However, analgesic treatment costs only represent less than 1% of the socio-economic burden of chronic pain, and a small increase or decrease of the treatment cost will therefore seldomly have a significant impact on the total chronic pain related cost [73].

3.3. Psychological evaluation

The patients’ mental condition has great influence on the experience of pain as well as treatment outcomes [74]. Pain catastrophizing is when a patient describes the pain in exaggerated terms, ruminates on it and feels increasingly helpless about the situation. Several studies have shown that high pain catastrophizing predicts poorer treatment outcome in various chronic pain conditions [75,76]. At this stage, it is not clear which of the individual factors composing the manifestation of catastrophizing can be modulated by analgesics and e.g., cognitive therapy.

Depression is closely related to pain symptoms and studies have found that it has a significant influence on quality of life in patients with chronic pain [77]. The response to pharmacological pain treatment is also closely linked to the presence of depression [78,79]. Psychological interventions as mindfulness and cognitive-behavioral therapy can have a positive influence on catastrophizing scores and can raise the patients’ quality of life [80–82]. Pharmacological antidepressant treatments can also decrease pain intensity, however it is not clear whether this effect is based on the improvement of mental health rather than direct effects on malfunctioning pain system as discussed above [83].

3.4. Complementary treatment

Besides pharmacological management, many other pain treatment modalities exist. Acupuncture has been used to alleviate pain for many years, although the scientific results have been inconsistent [84–86]. It is difficult to examine the result of acupuncture in a randomized placebo-controlled study, as sham treatments are difficult to control. Hence, sham acupuncture needles are only different from actual acupuncture needles by the fact that it does not puncture the skin, but the tactile stimulation is still present and can possibly induce some of the effects from acupuncture [87]. However, in a sham controlled study examining the analgesic effect of acupuncture on painful CP, an effect on pain intensity was seen, although a short lasting response limits its clinical use [84].
Different kinds of neuromodulation have also been evaluated. Spinal cord stimulation has shown promising results in different types of chronic pain including CP [88,89], but as numbness during stimulation can be felt, no real sham controlled studies have been done. The mechanisms involved remains unclear, but several effects including blockage of nerve conduction, release of inhibitory neuromodulators, and direct stimulation on the dorsal column pathways has been proposed [89]. A study examining transcranial magnetic stimulation on the secondary somatosensory cortex in patients with CP found a significant decline in pain ratings after treatment. The effect was correlated to an increase in glutamate and N-acetyl-aspartate levels in the somatosensory cortices, and low baseline glutamate level was predictive for a positive treatment outcome [90]. This field is current under development as high frequency stimulators have been proposed to exert more specific effects [91].

Vagal nerve stimulation has been examined for a number of conditions with chronic visceral pain often with good results [92,93]. No clearly defined mechanism has been discovered, but theories point to anti-inflammatory effects in conjunction with pain modulatory effects [94]. Juel et al. has examined acute accentuation of vagal tone on the auricular vagal branch in CP patients, but found no effect on experimental pain thresholds. [95]. This may relate to the short stimulation period, as only 60 minutes stimulation was performed. It could also be because the analgesic potency of this type of stimulation was not powerful enough to induce measurable effects. Further studies are needed where longer stimulation periods with multiple stimulations are performed, and perhaps the stimulation should be in closer relation to the vagal nerve than just the auricular branch.

At this level, complementary treatment cannot be used in a mechanism-based treatment, as the effect on different pain processing mechanisms is unknown and the effects are not validated.

3.5. Gastrointestinal side effects of analgesics

No treatment with analgesics is without risks, and due to changes in exocrine pancreatic function, motility and gut blood supply, patients with CP are especially prone to develop gastrointestinal adverse effects, for details see [96]. Acetaminophen is generally well tolerated, but its treatment carries a risk of acute liver failure if the instructed dosages are not complied. Furthermore long term use of acetaminophen may cause medicine overuse headache [97]. NSAIDs is linked to non-variceal upper gastrointestinal bleeding, lower gastrointestinal bleeding, gut perforation and strictures, and protein-losing enteropathy. There are several risk factors for developing gastrointestinal side effects to NSAID use including high age, female sex, smoking, former peptic ulcer, and concurrent use of steroids, anticoagulants, or selective serotonin reuptake inhibitors, and in these cases NSAID treatment should be avoided [98]. The risk of peptic ulcer seems to be especially high in CP patients.
likely due to compromised blood supply of the stomach after attacks of acute pancreatitis as well as increased infection rates with H Pylory [99].

Opioids, both weak and strong, have a potent pain-relieving effect, but are associated with addiction and major side effects where the gastrointestinal includes anorexia, nausea, vomiting and constipation [100,101]. In this context, new drugs such as peripherally-acting μ-opioid receptor antagonists have proven valuable in the treatment of opioid-induced bowel dysfunction as they block the μ-opioid receptors locally in the gut without affecting the central analgesic effect. [102].

Although long-term use of opioids may be necessary in CP and can provide potent pain control, it can also lead to opioid-induced hyperalgesia, which is characterized by a paradox of increased perception of pain, without a progression in the disease or opioid withdrawal [103].

Adjuvant analgesics such as antidepressants and anticonvulsants, are all known for having a long list of potential gastrointestinal side effects, some more severe than others. These include abdominal pain, diarrhea, constipation, dyspepsia, nausea, vomiting, hepatitis, and liver failure. They should typically be started in a low dose and titrated up, to find an optimal balance between beneficial effects and side effects [104]. Therefore, the risks of potential side effects shall be considered in the algorithm proposed in figure 3, and often this limits dosing and optimized pain control.

4. Conclusion

Pain management in CP remains a significant challenge, and no single analgesic is the best match for every patient. To achieve optimal pain management, quantitative assessment of affected pain mechanisms provides a platform for individualized and multimodal pain management, which may lead to a more rational and precise use of analgesics. This is exemplified in figure 3 where a suggestion for a mechanism-based approach for pain management is illustrated. The flowchart is based on proposed mechanisms mainly found in basic cross-sectional studies. Although different treatment studies in CP and other painful conditions have confirmed the value of the different steps in the algorithm, it needs to be tested further as an overall concept in clinical practice, preferably in a randomized fashion. This will hopefully give data from mechanistic clinical studies, where analgesic treatments are supported by the different steps in the algorithm, allowing us to adapt it to the results. Other features such as genetic profiling, drug kinetics and assessment of the autonomic response may be important as well, but the suggested tests can be used bedside with minimal costs."
5. Expert opinion

Pain treatment in CP has for years mainly been based on knowledge of somatic pain. Although the mechanisms (and hence the effect of analgesics) are to some degree similar, there are also differences. An increasing number of mechanism-based studies on pain treatment has elucidated a number of relevant mechanisms that can be treated with specific analgesics. Our knowledge is expanding, but there are still significant gaps that need to be explored. Quantitative sensory testing can be used to characterize pain processing and delineate relevant pain mechanisms on an individual patient basis, but many QST protocols used in clinical studies are quite extensive and not easily transferred to the clinic. There is therefore a need for a simple and feasible QST examination protocol with appropriate reference material. The QST protocol should include examinations providing information on the presence of segmental and widespread hyperalgesia, temporal summation (serving as proxies for central sensitization), and conditioned pain modulation as shown in figure 1. From this protocol, the ultimate goal is to develop a treatment algorithm such as proposed in figure 3, which will enable us to tailor the best-suited treatment plan for each patient. Before this is possible, additional drugs should be examined to establish their effect on pain mechanisms. This could include more studies on e.g. ketamine, cannabinoids, opioids, and antidepressant agents.

Treatment of psychological factors and the accompanying effect on pain ratings and quality-of-life should be documented. This could include both pharmacological management as well as cognitive behavioral therapy and help to evoke beneficial coping mechanisms. Quality of life is equally as important as pain ratings when assessing effect of treatment, as complete pain relief often is a too ambitious goal, and quality of life can be enhanced despite minor changes in pain intensity.

6. Article highlights

- Although pain is the most frequent symptom in chronic pancreatitis, pain management is an ongoing challenge
- In chronic pain conditions, several pain mechanisms can be affected, and pain can therefore affect each individual differently
- Although still in a developmental phase, somatic quantitative sensory testing can be used to diagnose visceral pain mechanisms
- Many analgesics are targeting specific pain mechanisms
- By individualizing pain treatment, pain control is achieved faster, and the patient need not test several analgesics, each accompanied by different side effects
There are several psychological factors that influence pain perception, and these should be treated alongside the pain to achieve sufficient pain control.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.
References

Papers of special note have been highlighted as:

* of interest
** of considerable interest


* A comprehensive review of the newest research in pancreatic pain


* A review concerning the neurobiological mechanisms of pancreatic pain


* A comprehensive article concerning descending pain modulation


* An article showing how patients with CP differ from healthy controls by having deficient pain modulation


[36] Vaegter HB, Petersen KK, Mørch CD, Imai Y, Arendt-Nielsen L. Assessment of CPM reliability:


** A study that proved that QST can predict the efficacy of pregabalin in CP patients


* A study that proves that QST can predict the efficacy of duloxetine in diabetic neuropathy


Harding LM, Kristensen JD, Baranowski AP. Differential effects of neuropathic analgesics on


Figure legends

Figure 1. Illustration of the bedside method used for objective assessment of the pain system in a patient with chronic pancreatitis without the use of visceral stimulations. Due to convergence between afferents from the pancreas and those of the skin in the Th10 dermatome (abdomen and back), any increased afferent barrage from the pancreas may result in local neuronal sensitization at this level. This will result in a lowering of the pain threshold (hyperalgesia) to experimental pain stimuli of the skin and deep tissue (QST 1). In the left insert showing the dermatomes, this is illustrated as white circles, whereas the remaining test sites are illustrated as black circles. If the sensitization spreads along the neuraxis there will also be a lowering of pain thresholds in other areas (QST 2; black circles in the dermatome-figure).

The efficacy of inhibitory bulbo-spinal descending pathways (black arrow) is tested as a change in the pain threshold to pressure stimulation before and after the descending pathways are activated with a tonic heterotopic stimulus. Finally, neuronal sensitization is also assessed as an increased response to repeated pinprick stimuli (temporal summation). This is illustrated in the right insert.

Figure 2. A fictive example of pressure pain detection thresholds in a patient with generalized sensitization compared with preliminary data from a healthy reference population.

Figure 3. If smoking cessation and alcohol abstinence do not provide pain relief, the flowchart exemplifies a mechanism-based treatment algorithm that can be used to guide management of pain in patients with chronic pancreatitis. Simple analgesics include non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen, complementary treatments include acupuncture, vagal nerve stimulations etc. Abbreviations: Gaba = gabapentinoids, QST = Quantitative Sensory Testing, SNRI = Serotonin and Norepinephrine Reuptake Inhibitor, TCA = Tricyclic Antidepressants

Table 1. An overview of QST modalities studied in this review including which pain mechanism the test is designed to examine.
Table 1:

<table>
<thead>
<tr>
<th>QST</th>
<th>Method</th>
<th>Stimulation</th>
<th>Pain mechanism</th>
</tr>
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<tbody>
<tr>
<td>Conditioned pain modulation</td>
<td>Conditioning stimulus in between to test pain stimuli</td>
<td>Conditioning stimulus: Cold pressor test, ischemic pain, heat, chemically induced pain, electrical induced pain.</td>
<td>Test pain stimulus: Mechanical pressure, electrical stimulation, heat, cold. Descending pain inhibition.</td>
</tr>
<tr>
<td>Windup phenomenon</td>
<td>A series of identical noxious stimuli of a frequency of 0.33 Hz or higher</td>
<td>Pin prick, electrical stimulation, heat, cold</td>
<td>Temporal summation</td>
</tr>
<tr>
<td>Pain detection/tolerance threshold</td>
<td>Pain detection threshold and pain tolerance threshold at various sites including control sites</td>
<td>Mechanical pressure, electrical stimulation, heat, cold</td>
<td>Sensitization (both peripheral and central)</td>
</tr>
</tbody>
</table>
Figure 2
Figure 3