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EDITORIAL

Pain in chronic pancreatitis: Managing beyond the pancreatic duct

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Abstract

Chronic pancreatitis (CP) continues to be a clinical challenge. Persistent or recurrent abdominal pain is the most compelling symptom that drives patients to seek medical care. Unfortunately, in spite of using several treatment approaches in the clinical setting, there is no single specific treatment modality that can be earmarked as a cure for this disease. Traditionally, ductal hypertension has been associated with causation of pain in CP; and patients are often subjected to endotherapy and surgery with a goal to decompress the pancreatic duct. Recent studies on humans (clinical and laboratory based) and experimental models have put forward several mechanisms, including neuroimmune alterations, which could be responsible for pain. This might explain the partial or no response to single modality treatment in a significant proportion of patients. The current review discusses the recent concepts of pain generation in CP and evidence based therapeutic approaches (other than ductal decompression) to handle persistent or recurrent pain. We focus primarily on parenchymal and neural components; and discuss the role of antioxidants and the existing controversies, drugs that interfere with neural transmission, pancreatic enzyme supplementation, celiac neurolysis, and pancreatic resection procedures. The review concludes with the treatment approach that we follow at our institute.

Key words: Pain; Chronic pancreatitis; Nociception; Neuroplasticity; Antioxidant micronutrients; Pregabalin; Pancreatic enzymes

Core tip: Pain in chronic pancreatitis (CP) has multiple but simultaneously occurring mechanisms. Recent data have shown expression of nociceptors and neurotrophic factors in different neural locations. The expression of these and other neural chemokines (fractalkine) have positive correlation with pain. Pain also results from global sensitization. Among the therapeutic modalities, beneficial effects have been demonstrated with methionine containing antioxidant micronutrients supplements and pregabalin. Of the pancreatic enzymes, only non-enteric coated preparations might benefit a subgroup of patients. The threshold for performing celiac neurolysis should be high in view of variable response across clinical trials.

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INTRODUCTION

Pain in chronic pancreatitis (CP) is as enigmatic as the disease itself. There is currently no definitive cure for the illness; and treatment usually centers on pain relief and

management of exocrine and endocrine dysfunction. 85%-90% patient will have abdominal pain at presentation[1]; and in our experience over two-third of patients would present with ductal calculi and/or stricture (unpublished data). Traditionally, pain in CP has been largely associated with ductal hypertension. However, as evident from the literature, recurrence of pain is common even after ductal decompression in the form of extracorporeal shock wave lithotripsy (ESWL), endoscopic retrograde cholangiopan-creatography (ERCP) or lateral pancreaticojejunostomy. Over the past several years, a host of pain mechanisms have been proposed and demonstrated directly or indirectly in humans[2]. Most important among these are oxidative stress and inflammation induced pancreatic nociception, pancreatic neuropathy/neuroplasticity and central neuroplasticity. There appears to be significant cross talk among the different mechanisms, which could explain the partial or no success of single modality treatment approaches. This mandates a holistic and conceptualized approach to pain management in CP, aided by the little evidence available.

This review addresses the current concepts of genesis of pain in CP and evidence based management approaches focusing primarily on the parenchymal and neural components.

PAIN MECHANISMS

Nociception

Nociception refers to the perception of pain sensation as a result of activation of pain receptors (nociceptors). The proteinase-activated receptor 2 (PAR-2) and the transient receptor potential vanilloid 1 receptors are two discrete types of nociceptors that have been shown to be present in the pancreas specific sensory nerves and dorsal root ganglia[3,4]. It is now known from experimental models that even sub-inflammatory doses of trypsin could bind to the PAR-2 receptor, thereby suggesting trypsin as a potential nociceptive stimulus, independent of its inflammatory role[4]. Other nociceptive stimuli that have been proven or speculated to stimulate pancreatic nociceptors include tryptase, alcohol metabolites, protons, bradykinin, hydrogen sulphide, serotonin and calcium[5]. The primary sources of intrapancreatic tryptase are the mast cells that infiltrate the pancreatic nerves in CP. The latter mediators are known to be released by injured acinar cells. Recently, another nociceptor namely the ligand-gated cation channel Transient receptor potential ankyrin 1 has also been shown to cause pancreatic inflammation and visceral hypersensitivity[6].

Other than the above-mentioned ligands, several neurotrophic factors like nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), glial-derived neurotrophic factor and artemin are expressed locally in the pancreas in response to inflammation and bind to specific receptors at different regions within the nerves (Figure 1)[7-10]. These factors, after binding to the respective receptors cause nociceptive sensitization and neural proliferation. Interestingly, the expression of TrkA, BDNF and artemin has been found to correlate with the severity of pain in patients with CP[2].

Even though ductal hypertension had been considered to be a major cause of pain in CP, the mechanism was not known clearly. Recently, it was shown in experimental models that increase in pressure can activate pancreatic stellate cells (PSC), which in turn can generate oxidative stress[11]. Furthermore, ethanol and smoking can by itself lead to oxidative stress within the PSCs[12,13]. Oxidative stress is capable of generating a pro-inflammatory state by means of activating immune cells, increasing expression of pro-inflammatory cytokines, and activating cytokine receptors and transcription factors (*e.g.*, tumor necrosis factor alpha, NF-κB)[2]. This could indirectly or directly sensitize the intrapancreatic pain receptors. The response of pain in CP along with normalization of circulating oxidant stress markers after treatment with high-dose anti-oxidants is a testimony to this.

Once activated, the pain receptors generate an action potential in the first order sensory neurons of spinal levels T5 to T9. The action potential travel forward (antegrade) to the dorsal horn (gray matter) of the spinal cord where it results in the release of the neurotransmitters glutamate, calcitonin gene related peptide (CGRP) and substance P[14]; which subsequently excites the second order neurons in the dorsal horn *via* *N*-methyl *D*-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors and the neurokinin 1 (NK-1) receptors[15]. The nociceptive transmission is then propagated through the ascending pathways in the spinal cord white mater to the thalamus, from where third order neurons relay to the sensory cortex, limbic system and the thalamus for cognitive and affective integration of pain. The sympathetic efferent cell body is the other sensory component to which the first order pancreatic nociceptive neurons project. This in turn relays to the celiac plexus *via* the greater splanchnic nerves and finally synapses with the second order sympathetic neurons. Axons of these sympathetic neurons then travel cephalad in the vagal trunks[2].

Neural mechanisms

Several neuroimmune and neuroplastic mechanisms have been described in CP pain over the recent years in humans and experimental models. The most conspicuous neural changes in the intrapancreatic nerves include: (1) infiltration of inflammatory cells (especially mast cells and eosinophils)[16]; (2) neural edema and perineural disruption[17]; (3) Schwann cell (glial cell in peripheral nerves) proliferation[18]; and (4) neural hypertrophy and sprouting[19], to name a few. The magnitude of these changes has been shown to correlate with the severity of pain, thereby ascribing them a causal role for neuropathic pain in CP. Possible factors that could be responsible for neural inflammation in the pancreatic nerves include glutamine, CGRP, substance P, and fractalkine. Some of these mediators can travel retrograde (antidromic) from the dorsal horn to the intrapancreatic nerve end-

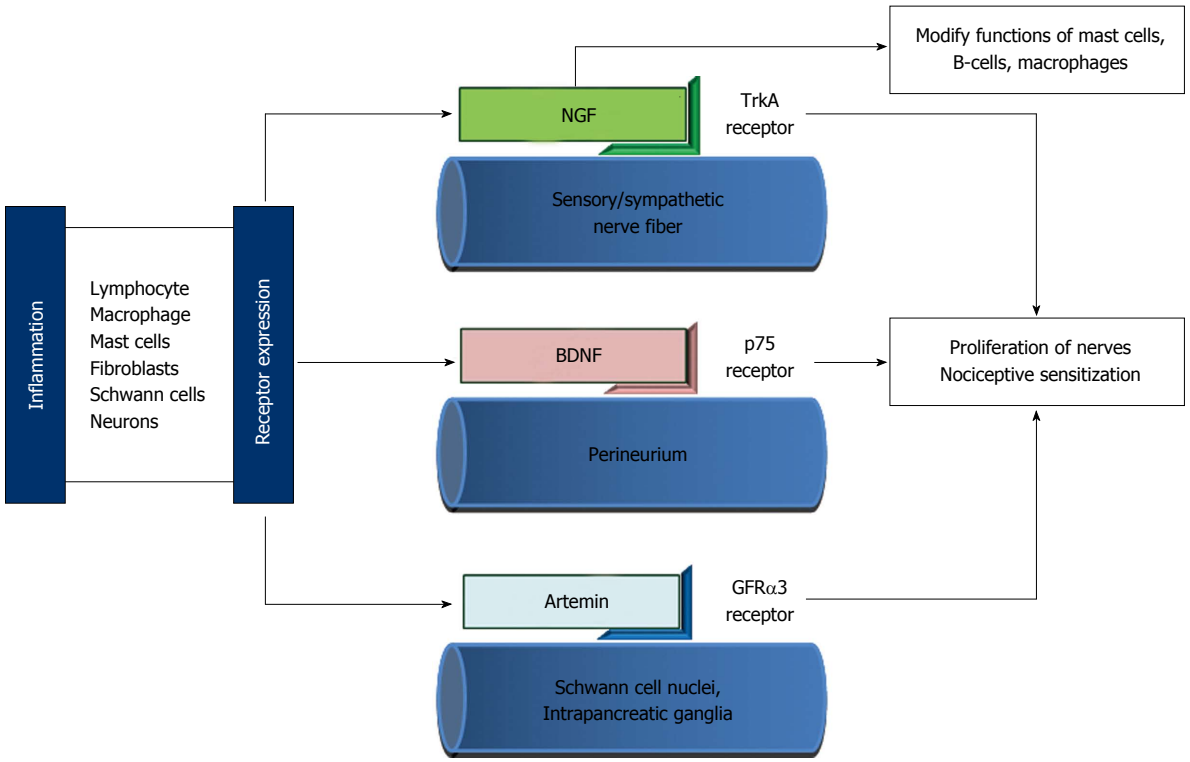

Figure 1 Schematic diagram representing neuroimmune mechanisms of pain in patients with chronic pancreatitis. The TrkA receptors (for nerve growth factor, NGF) are expressed on the sensory and sympathetic nerve fibres, p75 (for brain derived neurotropic factor, BDNF) on the perineurium and glial cell line-derived neurotrophic factor receptor α3 (GFRα3) (for Artemin) on the Schwann cell nuclei and intrapancreatic ganglia. The receptor expression is mediated by inflammation involving inflammatory cells and neural elements.

ing and induce chemotaxis of inflammatory cells[2,20,21]. Furthermore, overexpression of two important markers, namely, nestin and growth-associated protein-43 has been demonstrated in pancreas of human CP[19]. These two are markers of neuroplasticity/neural regeneration and are responsible for Schwann cell and neural growth. The composite of these findings and the associated pain clearly points towards profound neural remodeling within the pancreas (pancreatic neuroplasticity). These changes have important bearing on pain processing in central nervous system both at the level of the spinal cord and higher centers. Continuous sensitization of the intrapancreatic nociceptors due to persistent inflammation results in continuous stimulation of second order neurons present the dorsal horn of the spinal cord, a phenomenon called global sensitization[22]. The clinical surrogate of global sensitization is an increase in the area of referred pain due to convergence of afferent fibres from different visceral and somatic organs on the same hyperexcitable secondary spinal neurons. This has been demonstrated recently in patients with CP, in whom the areas involved in referred pain in response to esophageal, gastric and duodenal stimulation were significantly higher than those in controls[23]. Global sensitization results in two important phenomenon, mechanical allodynia (generation of pain after a physiological or non-noxious stimulus) and inflammatory hyperalgesia (amplified pain response to normal or minimal pain stimuli). The other manifestation of global sensitization is an increasingly painful response to repetitive but isointense stimuli. This is known as temporal summation, which has been clearly demonstrated in patients with CP[24,25]. It has also been demonstrated that early event-related brain potentials are altered in several key pain processing areas in the cerebral cortex in response to visceral stimulation in patients with CP[23]. This, along with a posteromedial shift in the electrical dipoles indicates significant neural reorganization in the cerebral cortical pain processing architecture. This is central neuroplasticity. Other evidence of central neuroplasticity in CP has come from clinical studies that have shown increase in theta activity on electroencephalogram (EEG) and increased activity in the right secondary somatosensory area on magnetic resonance spectroscopy[26,27]. Furthermore, abnormalities have been demonstrated in the descending inhibitory pathways from the cortex, which tilts the balance between these and ascending excitatory pathways in favour of more central pain processing abnormalities[28].

Figure 2 depicts a conceptual model of pain in patients with CP.

CLINICAL EVALUATION

Even though different mechanisms for pain in CP have been proposed and demonstrated, there are currently no easily available and clinically validated tools to identify the type of pain. A clinical history of new or wider areas of referred pain could be an indicator of the develop-

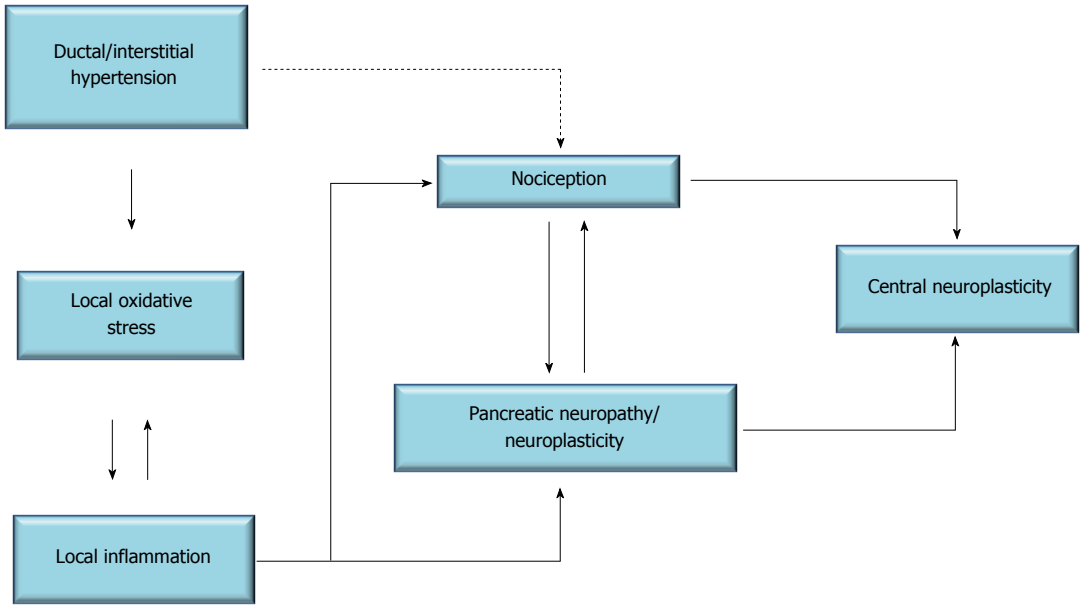

Figure 2 Schematic representation of the conceptual framework of pain mechanisms in chronic pancreatitis.

ment of neuropathy. An objective questionnaire based tool namely painDETECT has been used to evaluate neuropathic pain in the context of radiculopathy[29]. This questionnaire evaluates components pertaining to neuropathic pain (for *e.g.*, burning/tingling nature of pain); and could have a potential use in patients with CP to assess the neuropathic component of the total pain. Persistence of theta wave on EEG is another proven feature of development of central neuroplasticity[26]. However, this has not been tested and validated in large multicenter studies to be recommended for use in the routine clinical setting. Furthermore, even though few groups have used quantitative sensory testing for evaluation of pain in CP, this may not be feasible widely[30].

PAIN MANAGEMENT BEYOND DUCTAL DECOMPRESSION

In routine pancreatology practice, usually three broad categories of CP patients with recurrent or persistent pain are encountered, namely those with ductal obstruction (with calculi or stricture), those after ductal decompression (post-endotherapy/surgery) with a dilated duct and those with a non-dilated duct but only parenchymal changes. In the first category, ductal decompression in the form of endotherapy (ESWL with/without ERCP and ductal stenting) is the current standard of care[31,32]. Discussion of management of this group of patients is out of the scope of the current review. In the second category, it is important to rule out recurrent stones (which may be radiolucent), stricture, local complications (like inflammatory mass, biliary obstruction, pseudocysts), and cancer. In the absence of these, recurrent pain in this group of patients (and also in the third group) is most likely to be associated with predominant neural mechanisms resulting from interstitial hypertension, tissue ischaemia, and neural inflammation. For the management of chronic and recurrent pain in CP, following treatment modalities have been practiced.

Analgesics

For short-term relief of pain in CP, the World Health Organization pain ladder, starting with an nonsteroidal anti-inflammatory drugs may be followed[33]. It is a common practice in many western countries to use opiates long-term to ameliorate chronic and recurrent pain. However, even though high potency opiates like morphine and analogues are effective, they should be avoided as a first line drug as far as possible due to the risk of drug dependence and potentiation of side effects, including narcotic bowel syndrome. Furthermore, morphine and codeine can cause activation and degranulation of mast cells, thereby overriding the beneficial effect while worsening the inflammation and pain[34]. Tramadol, though a low potency selective μ-opiate receptor agonist, has been shown to be as effective as higher potency narcotics but with a significantly better safety profile[35]. Other effective alternatives for severe continuing pain include epidural buprenorphine and transdermal fentanyl (patch)[36].

Antioxidant micronutrients

The primary aim of antioxidant micronutrient therapy in CP is to supply methyl and thiol moieties for the transsulfuration pathway, which is essential for protection against reactive oxygen species (ROS) mediated electrophilic stress[37]. It has been demonstrated in clinical studies that there is a significant reduction in antioxidant defense in patients with CP. Studies from the United Kingdom, India and Spain have used a antioxidant cocktail consisting of methionine, organic selenium, ascorbic acid, β-carotene, and α-tocopherol; out of which 2-4 g/d of methionine (which preserves the transsulfuration path-

Table 1 Studies evaluating the role of antioxidant micronutrients on clinical outcomes, including pain, in patients with chronic pancreatitis

Ref.	Study type	Antioxidant micronutrients used	Indications; study duration	Outcomes
Uden *et al*[38] 1990	DB double dummy cross over	Vit C; Vit E; Beta carotene; Selenium; Methionine	*n* = 20 (ACP, ICP, IAP) 20 wk	↓ in VAS
De las Heras Castaño *et al*[39] 2000	Open label	Vit C; Vit E; Beta carotene; Selenium; Methionine	*n* = 19 (ACP, ICP, RAP) 12 mo	↓ in VAS, ↓ admission, ↑ exocrine fn
Dite *et al*[40] 2003	Open label	Vit C; Vit E	*n* = 70 (ACP, ICP) 12 mo	Pain abolished in 44%
Kirk *et al*[41] 2006	DB RCT cross over	Vit C; Vit E; Beta carotene; Selenium; Methionine	*n* = 19 (all ACP) 20 wk	↑ QOL
Bhardwaj *et al*[42] 2009	DB RCT	Vit C; Vit E; Beta carotene; Selenium; Methionine	*n* = 127 (ACP, ICP); 80% power; 6 mo	32% patients pain free ↓ No. of painful days ↓ analgesic need
Siriwardena *et al*[43] 2012	DB RCT	Vit C; Vit E; Beta carotene; Selenium; Methionine	*n* = 70 (ACP, ICP); 80% power; 6 mo	↔ pain ↔ QOL

↓: Indicates reduction; ↑: Indicates improvement; ↔: Indicates equivocal. DB: Double blind; RCT: Randomized controlled trial; QOL: Quality of life; Vit: Vitamin; ACP: Alcoholic chronic pancreatitis; IAP: Idiopathic acute pancreatitis; RAP: Recurrent acute pancreatitis; fn.: Function; ICP: Idiopathic chronic pancreatitis.

way in acinar cells) is believed to be the most important. Table 1 shows the clinical trials that have evaluated the effect of antioxidant micronutrient supplementation on pain relief in CP[38-43]. The largest randomized controlled trial (from India) with 127 patients that used organic selenium (600 μg), ascorbic acid (0.54 g), β-carotene (6000 IU), α-tocopherol (270 IU) and methionine (2 g) for six months demonstrated a significant reduction in the number of painful days compared to placebo (7.4 ± 6.8 d *vs* 3.2 ± 4.0 d, respectively; $P < 0.001$) and use of analgesic tablets per month[42]. There was also significant concomitant reduction in markers of oxidative/electrophilic stress like TBARS and improvement in antioxidant capacity. However, the clinical efficacy found in this trial was negated by the most recent randomized trial from Manchester (ANTICIPATE study), which concluded that even though micronutrients increased the antioxidant levels in blood, they did not produce adequate pain relief[43]. It is important to note that in contrary to the Indian study, patients in the ANTICIPATE study were on high dose of narcotics, many continued to consume alcohol and many did not respond to other forms of therapy either[44,45]. We believe that the optimal dose of antioxidant micronutrients confers definite benefit in terms of pain relief in carefully selected patients with CP. Even though it is advisable to monitor plasma glutathione and micronutrient concentrations, and titrate doses accordingly, in practice this may not be feasible.

In addition to the fixed dose antioxidant cocktail regimen, it is also important to give dietary advise on intake of anti-oxidant rich diet, and avoid practices that can adversely affect the bioavailability of dietary antioxidants (*e.g.*, vegetables cooked in high temperature)[46]. Folate deficiency can hinder with methionine recovery for the transsulfuration pathway[2,47]. Therefore folic acid supplementation could provide additional benefits especially to the alcoholic CP patients.

Drugs that interfere with neural transmission

In clinical practice, tricyclic antidepressants (like amitriptiline) and serotonin-norepinephrine reuptake inhibitors (like duloxetine) are frequently used for refractory pain in CP, based on the observed benefits in other neuropathic states. Similarly, anticonvulsants like gabapentin and pregabalin, which are first line drugs for diabetic neuropathy have also been used. However, among all these agents, only pregabalin have been tested in a randomized controlled setting. A recent randomized controlled trial (RCT) evaluated the effect of increasing doses (150-600 mg/d) of pregabalin for three weeks on pain in 64 patients with CP; and demonstrated that there was significant reduction in pain score in the pregabalin arm [-36% (95%CI: -43 - -29)] *vs* -24% (95%CI: -31 - -16); $P = 0.02$][48]. Significant improvement was also observed in the patient's global impression of change at the end of the study. Ninety-one percent of patients had some adverse events in this trial, of which the most common were neurological (feeling drunk in 35%, and light-headedness in 12%). Rest of the adverse events was similar to those in the placebo arm. The number (proportion) of patients with serious adverse events in the pregabalin and placebo patients was 4 (12%) and 2 (7%) respectively; and this difference was not statistically significant. Pregabalin is α2δ receptor blocker that decreases presynaptic release of glutamate, noradrenaline and substance P; and has been shown to improve pain in CP by inhibiting central sensitization[49]. Studies have shown that the inhibition of central sensitization is manifested by normalization of the theta band on EEG, particularly in the parietal lobe[50]. These studies does give a comprehensive mechanistic insight of the beneficial role of pregabalin on chronic pain in CP. Further long-term follow-up studies would complement the current evidence and provide data on the long term efficacy of the drug.

Pancreatic enzymes

Pancreatic enzymes have been often used to control pain in CP. This is based on the hypothesis that proteases in the enzyme supplement would inhibit overstimulation of duodenal cholecystokinin (CCK) receptors, which will

in turn inhibit the food induced feedback loop thereby putting the pancreas to rest. However, meta-analysis of six double-blinded RCTs from 1983-1995 involving 186 patients concluded that pancreatic enzymes confer no benefit in pain relief[51]. Similarly, a Cochrane Systematic Review of 10 RCTs (2 parallel design and 8 cross over) involving 361 patients found equivocal pain relief, fecal fat excretion and improvement in quality of life in the pooled analysis[52]. However, the individual trials in the two studies that used non-enteric coated preparations did show significant improvement in pain[53,54], thereby fitting into the notion of reducing post-prandial pancreatic secretion by CCK receptor inhibition. This does not happen with the enteric-coated preparations because the release of these enzyme preparations (which should happen at a pH of 5.5) in the duodenum is erratic and non-uniform due to reduced ductal bicarbonate secretion in CP. The enzymes from the enteric-coated preparations are generally released more distally in the jejunum and ileum. Unfortunately, almost all currently available enzyme preparations are enteric coated and should not be prescribed for pain relief as a sole indication. Non-enteric coated enzyme preparations (wherever available) can be of some benefit to a subgroup of patients with post-prandial pain. It is important to prescribe non-enteric preparations along with a proton pump inhibitor or H2 receptor blocker in order to prevent gastric acid mediated degradation of the enzymes in the stomach.

Celiac plexus block

Celiac plexus block with a local anesthetic (bupivacaine) with or without a combination of steroid (triamcinolone) is another modality for treatment for pain in chronic pancreatitis. Even though this can also be performed percutaneously, endoscopic ultrasound (EUS) based procedure has better results and negligible risk of developing paraplegia, which is associated with the percutaneous technique[55]. However, the overall benefits of celiac plexus block are about 55% after 4-8 wk and a dismal 26% and 10% after 12 and 24 wk respectively[56]. Therefore, this modality should be kept as rescue therapy for patients who do not respond to conventional medical and endoscopic therapy and are not ideal surgical candidates. EUS guided celiac ganglion neurolysis with absolute alcohol is another option, but is too extreme for a benign disease, especially in the presence of additional central mechanisms of chronic pain[57].

Side-effects of celiac block are seen in 10%-33% of patients. The most common side effects include transient self-limiting diarrhea and orthostatic hypotension, owing to the sympathetic blockade with relatively unopposed visceral parasympathetic activity[56,58]. Diarrhea usually settles in 48 h. Occasionally the patient may complain of an increase in the pain. Serious complications like retroperitoneal bleeding and peripancreatic abscess have infrequently been reported. An additional problem with the use of alcohol is the development of dense desmoplasia, which might make future pancreatic surgery difficult.

Surgery

Other than drainage procedures, surgical interventions for pain control in CP includes resectional procedures like classical (Kausch Whipple) or pylorus preserving (Traverso-Longmire) pancreaticoduodenectomy, distal pancreatectomy and total pancreatectomy. Pancreaticoduodenectomy is particularly useful in pain with an associated inflammatory head mass. Even though long-term pain relief has been demonstrated in 75%-95% of patients, this procedure is associated with worsening of exocrine and endocrine functions[59,60]. Similarly, endocrine and exocrine insufficiency is seen in 80%-95% patients undergoing distal pancreatectomy[61]; and is therefore currently performed only for recurrent pain with localized disease (such as a stricture in the upstream duct not amenable to endotherapy). Total pancreatectomy is also infrequently performed in view of the associated significant morbidity. However, with the development of islet transplantation, there has been a renewed interest in select centers in total pancreatectomy with autoislet transplantation in patients with end stage CP. However, it should be borne in mind that even after removing the entire pancreas, as high as 40% of patients could still require analgesics even after 2 years of follow-up[62]. Many a time, a resectional procedure is combined with a drainage procedure, like Frey's, Beger's, Berne's and the V-shaped procedure, in order to provide the benefit of both ductal decompression and removal of a part of the inflamed pancreas (especially an inflammatory mass).

Bilateral thoracic splanchnicectomy is yet another infrequently used surgical modality that could ameliorate chronic pain in patients with CP; and have recently been shown to inhibit pain by predominantly impairing adrenomedullary function[63].

Miscellaneous

Both short and long acting octreotide have been attempted in pain management in advanced CP in small-scale studies[64,65]. Even though satisfactory pain relief has been documented, the results need to be verified in larger trials. Furthermore, whether the pain relief is better in patients with or without ductal obstruction also needs to be examined. Other than octreotide, secretin infusion has also been evaluated in a recent phase Ⅱ trial with equivocal results[66]. Few of the modalities that have been used as adjuncts to medical/surgical therapy include spinal cord stimulation[67], cognitive-behavioral therapy, and other alternative approaches for chronic pain states. However, none of these are backed by sufficient good-quality evidence to be currently recommended specifically for pain in CP.

HURDLES IN MANAGING PAIN IN CP

Even though much have been understood on pain mechanisms in CP, there are still several hurdles in pain management in clinical practice. Firstly, several mechanisms might be simultaneously operating at any particular time

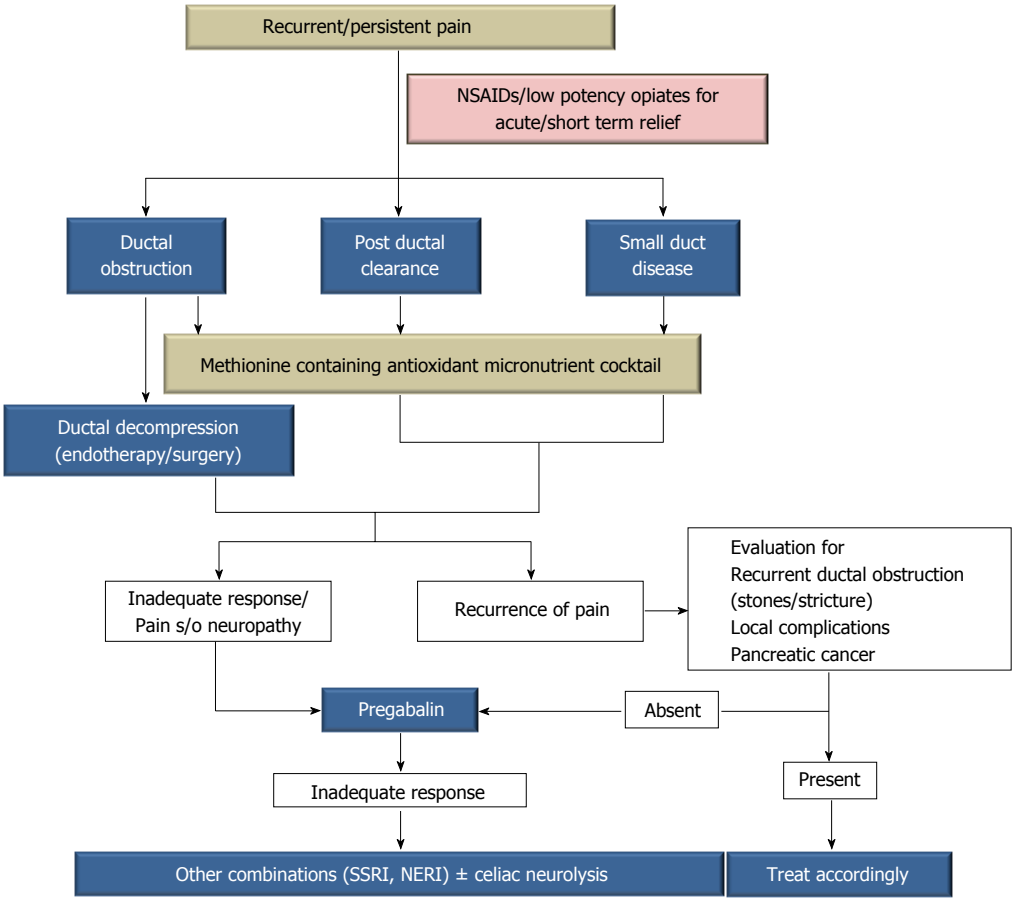

Figure 3 Management approach for recurrent and/or persistent pain in patients with chronic pancreatitis at the Asian Institute of Gastroenterology. SSRIs: Selective serotonin reuptake inhibitors; NERI: Norepinephrine reuptake inhibitor; NSAIDs: Nonsteroidal anti-inflammatory drugs.

point in a particular patient, thereby posing a question on selecting the most appropriate and optimal modality. Secondly, there are no validated objective tools that can identify the pain type, thereby precluding a fixed treatment regimen. Thirdly, there are no data to suggest an optimal duration of treatment with antioxidant and/or pregabalin in order to achieve long-term pain relief; as a result of which patients might run the risk of undertreatment or of building up excessive antioxidant micronutrients in circulation, which could impede with the physiological roles of ROS. Finally, there are no data on the efficacy or adversity of combination therapy for refractory pain.

APPROACH TO PAIN MANAGEMENT IN CP AT ASIAN INSTITUTE OF GASTROENTEROLOGY

Figure 3 shows the treatment approach that is followed at Asian Institute of Gastroenterology. This is a composite of clinical evidence; concepts build on experimental data; and clinical experience. Methionine containing antioxidants micronutrient cocktail is started early on after the diagnosis of CP. Dose and duration of treatment is titrated according to clinical response and patient's tolerance to treatment. Patient with recurrent pain with ductal obstruction are subjected to ductal clearance by endotherapy (ESWL with or without ERCP) or surgery (in select patients). Pregabalin is added to the regimen for patients who do not show satisfactory response to antioxidant micronutrient therapy and ductal decompression; and in those who shows clinical signs suggestive of neuropathy. In patients who have recurrence of intractable pain are evaluated for recurrence of ductal obstruction, development of local complications or cancer; and treated with additional pregabalin in the absence of these. Patients who respond sub-optimally to these regimens are treated additionally with combination of SSRI and NERI like duloxetine with or without celiac plexus block. It is important to counsel the patients thoroughly on diet and lifestyle changes like quitting alcohol and smoking all along the treatment sessions.

CONCLUSION

Pain in CP is complex, and several independent and interdependent mechanisms may manifest simultaneously in a patient. Therefore, pain management in CP should be individualized for each patient rather than follow a fixed regimen. Recent laboratory data from human and experimental CP have opened up avenues to explore new and target specific antagonists against TRPV1, NGF, PAR2,

NK-1, CGRP and substance P.

REFERENCES

1 **Braganza JM**, Lee SH, McCloy RF, McMahon MJ. Chronic pancreatitis. *Lancet* 2011; **377**: 1184-1197 [PMID: 21397320 DOI: 10.1016/S0140-6736(10)61852-1]
2 **Talukdar R**. Pathogenesis of acute and chronic pancreatitis. In: Reddy DN. Recent Advances in Pancreas. New Delhi: Elsevier 2012; 27-53
3 **Hoogerwerf WA**, Shenoy M, Winston JH, Xiao SY, He Z, Pasricha PJ. Trypsin mediates nociception via the proteinase-activated receptor 2: a potentially novel role in pancreatic pain. *Gastroenterology* 2004; **127**: 883-891 [PMID: 15362043]
4 **Xu GY**, Winston JH, Shenoy M, Yin H, Pendyala S, Pasricha PJ. Transient receptor potential vanilloid 1 mediates hyperalgesia and is up-regulated in rats with chronic pancreatitis. *Gastroenterology* 2007; **133**: 1282-1292 [PMID: 17698068]
5 **Drewes AM**, Krarup AL, Detlefsen S, Malmstrøm ML, Dimcevski G, Funch-Jensen P. Pain in chronic pancreatitis: the role of neuropathic pain mechanisms. *Gut* 2008; **57**: 1616-1627 [PMID: 18566105 DOI: 10.1136/gut.2007.146621]
6 **Cattaruzza F**, Johnson C, Leggit A, Grady E, Schenk AK, Cevikbas F, Cedron W, Bondada S, Kirkwood R, Malone B, Steinhoff M, Bunnett N, Kirkwood KS. Transient receptor potential ankyrin 1 mediates chronic pancreatitis pain in mice. *Am J Physiol Gastrointest Liver Physiol* 2013; **304**: G1002-G1012 [PMID: 23558009 DOI: 10.1152/ajpgi.00005.2013]
7 **Friess H**, Zhu ZW, di Mola FF, Kulli C, Graber HU, Andren-Sandberg A, Zimmermann A, Korc M, Reinshagen M, Büchler MW. Nerve growth factor and its high-affinity receptor in chronic pancreatitis. *Ann Surg* 1999; **230**: 615-624 [PMID: 10561084]
8 **Zhu ZW**, Friess H, Wang L, Zimmermann A, Büchler MW. Brain-derived neurotrophic factor (BDNF) is upregulated and associated with pain in chronic pancreatitis. *Dig Dis Sci* 2001; **46**: 1633-1639 [PMID: 11508661]
9 **Demir IE**, Wang K, Tieftrunk E, Giese NA, Xing B, Friess H, Kehl T, Ceyhan GO. Neuronal plasticity in chronic pancreatitis is mediated via the neurturin/GFRα2 axis. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G1017-G1028 [PMID: 22961804 DOI: 10.1152/ajpgi.00517.2011]
10 **Ceyhan GO**, Bergmann F, Kadihasanoglu M, Erkan M, Park W, Hinz U, Giese T, Müller MW, Büchler MW, Giese NA, Friess H. The neurotrophic factor artemin influences the extent of neural damage and growth in chronic pancreatitis. *Gut* 2007; **56**: 534-544 [PMID: 17047099]
11 **Asaumi H**, Watanabe S, Taguchi M, Tashiro M, Otsuki M. Externally applied pressure activates pancreatic stellate cells through the generation of intracellular reactive oxygen species. *Am J Physiol Gastrointest Liver Physiol* 2007; **293**: G972-G978 [PMID: 17761838]
12 **Asaumi H**, Watanabe S, Taguchi M, Tashiro M, Nagashio Y, Nomiyama Y, Nakamura H, Otsuki M. Green tea polyphenol (-)-epigallocatechin-3-gallate inhibits ethanol-induced activation of pancreatic stellate cells. *Eur J Clin Invest* 2006; **36**: 113-122 [PMID: 16436093]
13 **Jianyu-Hao**, Guang-Li, Baosen-pang. Evidence for cigarette smoke-induced oxidative stress in the rat pancreas. *Inhal Toxicol* 2009; **21**: 1007-1012 [PMID: 19635036 DOI: 10.1080/08958370802665937]
14 **Anaparthy R**, Pasricha PJ. Pain and chronic pancreatitis: is it the plumbing or the wiring? *Curr Gastroenterol Rep* 2008; **10**: 101-106 [PMID: 18462594]
15 **Winston JH**, He ZJ, Shenoy M, Xiao SY, Pasricha PJ. Molecular and behavioral changes in nociception in a novel rat model of chronic pancreatitis for the study of pain. *Pain* 2005; **117**: 214-222 [PMID: 16098667]
16 **Keith RG**, Keshavjee SH, Kerenyi NR. Neuropathology of chronic pancreatitis in humans. *Can J Surg* 1985; **28**: 207-211 [PMID: 3995416]
17 **Bockman DE**, Buchler M, Malfertheiner P, Beger HG. Analysis of nerves in chronic pancreatitis. *Gastroenterology* 1988; **94**: 1459-1469 [PMID: 3360267]
18 **Ceyhan GO**, Demir IE, Rauch U, Bergmann F, Müller MW, Büchler MW, Friess H, Schäfer KH. Pancreatic neuropathy results in "neural remodeling" and altered pancreatic innervation in chronic pancreatitis and pancreatic cancer. *Am J Gastroenterol* 2009; **104**: 2555-2565 [PMID: 19568227 DOI: 10.1038/ajg.2009.380]
19 **Ceyhan GO**, Bergmann F, Kadihasanoglu M, Altintas B, Demir IE, Hinz U, Müller MW, Giese T, Büchler MW, Giese NA, Friess H. Pancreatic neuropathy and neuropathic pain--a comprehensive pathomorphological study of 546 cases. *Gastroenterology* 2009; **136**: 177-186.e1 [PMID: 18992743]
20 **Ceyhan GO**, Deucker S, Demir IE, Erkan M, Schmelz M, Bergmann F, Müller MW, Giese T, Büchler MW, Giese NA, Friess H. Neural fractalkine expression is closely linked to pain and pancreatic neuritis in human chronic pancreatitis. *Lab Invest* 2009; **89**: 347-361 [PMID: 19153557 DOI: 10.1053/j.gastro.2008.09.029]
21 **D'Haese JG**, Demir IE, Friess H, Ceyhan GO. Fractalkine/CX3CR1: why a single chemokine-receptor duo bears a major and unique therapeutic potential. *Expert Opin Ther Targets* 2010; **14**: 207-219 [PMID: 20055718 DOI: 10.1517/14728220903540265]
22 **Devor M**. Centralization, central sensitization and neuropathic pain. Focus on "sciatic chronic constriction injury produces cell-type-specific changes in the electrophysiological properties of rat substantia gelatinosa neurons". *J Neurophysiol* 2006; **96**: 522-523 [PMID: 16835360]
23 **Dimcevski G**, Sami SA, Funch-Jensen P, Le Pera D, Valeriani M, Arendt-Nielsen L, Drewes AM. Pain in chronic pancreatitis: the role of reorganization in the central nervous system. *Gastroenterology* 2007; **132**: 1546-1556 [PMID: 17408654]
24 **Pedersen JL**, Andersen OK, Arendt-Nielsen L, Kehlet H. Hyperalgesia and temporal summation of pain after heat injury in man. *Pain* 1998; **74**: 189-197 [PMID: 9520233]
25 **Dimcevski G**, Staahl C, Andersen SD, Thorsgaard N, Funch-Jensen P, Arendt-Nielsen L, Drewes AM. Assessment of experimental pain from skin, muscle, and esophagus in patients with chronic pancreatitis. *Pancreas* 2007; **35**: 22-29 [PMID: 17575541]
26 **Drewes AM**, Gratkowski M, Sami SA, Dimcevski G, Funch-Jensen P, Arendt-Nielsen L. Is the pain in chronic pancreatitis of neuropathic origin? Support from EEG studies during experimental pain. *World J Gastroenterol* 2008; **14**: 4020-4027 [PMID: 18609686]
27 **Fregni F**, Pascual-Leone A, Freedman SD. Pain in chronic pancreatitis: a salutogenic mechanism or a maladaptive brain response? *Pancreatology* 2007; **7**: 411-422 [PMID: 17898531]
28 **Olesen SS**, Brock C, Krarup AL, Funch-Jensen P, Arendt-Nielsen L, Wilder-Smith OH, Drewes AM. Descending inhibitory pain modulation is impaired in patients with chronic pancreatitis. *Clin Gastroenterol Hepatol* 2010; **8**: 724-730 [PMID: 20304100 DOI: 10.1016/j.cgh.2010.03.005]
29 **Rados I**, Sakic Zdravcevic K, Hrgovic Z. painDETECT questionnaire and lumbar epidural steroid injection for chronic radiculopathy. *Eur Neurol* 2013; **69**: 27-32 [PMID: 23128915 DOI: 10.1159/000338265]
30 **Olesen SS**, van Goor H, Bouwense SA, Wilder-Smith OH, Drewes AM. Reliability of static and dynamic quantitative sensory testing in patients with painful chronic pancreatitis. *Reg Anesth Pain Med* 2012; **37**: 530-536 [PMID: 22854397 DOI: 10.1097/AAP.0b013e3182632c40]
31 **Reddy DN**, Ramchandani MJ, Talukdar R. Individualizing therapy for chronic pancreatitis. *Clin Gastroenterol*

Hepatol 2012; **10**: 803-804 [PMID: 22504003 DOI: 10.1016/j.cgh.2012.03.022]
32 **Tandan M**, Reddy DN, Talukdar R, Vinod K, Santosh D, Lakhtakia L, Gupta R, Ramchandani MJ, Banerjee R, Rakesh K, Varadaraj G, Rao GV. Long-term clinical outcomes of extracorporeal shock wave lithotripsy (ESWL) in painful chronic calcific pancreatitis. *Gastrointest Endosc* 2013; In press [DOI: 10.1016/j.gie.2013.05.012]
33 **World Health Organization**. Cancer Pain Relief and Palliative Care: Report of a WHO Expert Committee. Geneva: World Health Organization, 1990
34 **Sheen CH**, Schleimer RP, Kulka M. Codeine induces human mast cell chemokine and cytokine production: involvement of G-protein activation. *Allergy* 2007; **62**: 532-538 [PMID: 17441793]
35 **Wilder-Smith CH**, Hill L, Osler W, O'Keefe S. Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. *Dig Dis Sci* 1999; **44**: 1107-1116 [PMID: 10389680]
36 **Desai PM**. Pain relief in chronic pancreatitis with epidural buprenorphine injection. *Indian J Gastroenterol* 1997; **16**: 12-13 [PMID: 9167372]
37 **Braganza JM**, Dormandy TL. Micronutrient therapy for chronic pancreatitis: rationale and impact. *JOP* 2010; **11**: 99-112 [PMID: 20208316]
38 **Uden S**, Bilton D, Nathan L, Hunt LP, Main C, Braganza JM. Antioxidant therapy for recurrent pancreatitis: placebo-controlled trial. *Aliment Pharmacol Ther* 1990; **4**: 357-371 [PMID: 2103755]
39 **De las Heras Castaño G**, García de la Paz A, Fernández MD, Fernández Forcelledo JL. Use of antioxidants to treat pain in chronic pancreatitis. *Rev Esp Enferm Dig* 2000; **92**: 375-385 [PMID: 10985097]
40 **Dite P**, Precechtelova M, Novotny I, Soska V, Zakova A, Lata J. Changes of reactive oxidative substances in patients with morphologically different degrees of chronic pancreatitis and effects of long-term therapy with natural antioxidants. *Gastroenterologia Polska* 2003; **33**: 58-62
41 **Kirk GR**, White JS, McKie L, Stevenson M, Young I, Clements WD, Rowlands BJ. Combined antioxidant therapy reduces pain and improves quality of life in chronic pancreatitis. *J Gastrointest Surg* 2006; **10**: 499-503 [PMID: 16627214]
42 **Bhardwaj P**, Garg PK, Maulik SK, Saraya A, Tandon RK, Acharya SK. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. *Gastroenterology* 2009; **136**: 149-159.e2 [PMID: 18952082 DOI: 10.1053/j.gastro.2008.09.028]
43 **Siriwardena AK**, Mason JM, Sheen AJ, Makin AJ, Shah NS. Antioxidant therapy does not reduce pain in patients with chronic pancreatitis: the ANTICIPATE study. *Gastroenterology* 2012; **143**: 655-63.e1 [PMID: 22683257 DOI: 10.1053/j.gastro.2012.05.046]
44 **Talukdar R**, Nageshwar Reddy D. Is there a single therapeutic target for chronic pancreatitis pain? *Gastroenterology* 2013; **144**: e18 [PMID: 23357056 DOI: 10.1053/j.gastro.2012.12.033]
45 **Garg PK**. Antioxidants for chronic pancreatitis: reasons for disappointing results despite sound principles. *Gastroenterology* 2013; **144**: e19-e20 [PMID: 23352593 DOI: 10.1053/j.gastro.2012.12.031]
46 **Braganza JM**. A framework for the etiopathogenesis of chronic pancreatitis. *Digestion* 1998; **58** (suppl 4): 1-12 [DOI: 10.1159/000051438]
47 **Braganza JM**, Odom N, McCloy RF, Ubbink JB. Homocysteine and chronic pancreatitis. *Pancreas* 2010; **39**: 1303; author reply 1304 [PMID: 20944492 DOI: 10.1097/MPA.0b013e3181e2d567]
48 **Olesen SS**, Bouwense SA, Wilder-Smith OH, van Goor H, Drewes AM. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. *Gastroenterology* 2011; **141**: 536-543 [PMID: 21683078 DOI: 10.1053/j.gastro.2011.04.003]
49 **Bouwense SA**, Olesen SS, Drewes AM, Poley JW, van Goor H, Wilder-Smith OH. Effects of pregabalin on central sensitization in patients with chronic pancreatitis in a randomized, controlled trial. *PLoS One* 2012; **7**: e42096 [PMID: 22879908 DOI: 10.1371/journal.pone.0042096]
50 **Graversen C**, Olesen SS, Olesen AE, Steimle K, Farina D, Wilder-Smith OH, Bouwense SA, van Goor H, Drewes AM. The analgesic effect of pregabalin in patients with chronic pain is reflected by changes in pharmaco-EEG spectral indices. *Br J Clin Pharmacol* 2012; **73**: 363-372 [PMID: 21950372 DOI: 10.1111/j.1365-2125.2011.04104.x]
51 **Brown A**, Hughes M, Tenner S, Banks PA. Does pancreatic enzyme supplementation reduce pain in patients with chronic pancreatitis: a meta-analysis. *Am J Gastroenterol* 1997; **92**: 2032-2035 [PMID: 9362186]
52 **Shafiq N**, Rana S, Bhasin D, Pandhi P, Srivastava P, Sehmby SS, Kumar R, Malhotra S. Pancreatic enzymes for chronic pancreatitis. *Cochrane Database Syst Rev* 2009; (4): CD006302 [PMID: 19821359 DOI: 10.1002/14651858.CD006302.pub2]
53 **Isaksson G**, Ihse I. Pain reduction by an oral pancreatic enzyme preparation in chronic pancreatitis. *Dig Dis Sci* 1983; **28**: 97-102 [PMID: 6825540]
54 **Slaff J**, Jacobson D, Tillman CR, Curington C, Toskes P. Protease-specific suppression of pancreatic exocrine secretion. *Gastroenterology* 1984; **87**: 44-52 [PMID: 6202586]
55 **Gress F**, Schmitt C, Sherman S, Ikenberry S, Lehman G. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. *Am J Gastroenterol* 1999; **94**: 900-905 [PMID: 10201454]
56 **Gress F**, Schmitt C, Sherman S, Ciaccia D, Ikenberry S, Lehman G. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. *Am J Gastroenterol* 2001; **96**: 409-416 [PMID: 11232683]
57 **Levy MJ**, Topazian MD, Wiersema MJ, Clain JE, Rajan E, Wang KK, de la Mora JG, Gleeson FC, Pearson RK, Pelaez MC, Petersen BT, Vege SS, Chari ST. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct Ganglia neurolysis and block. *Am J Gastroenterol* 2008; **103**: 98-103 [PMID: 17970834]
58 **Kaufman M**, Singh G, Das S, Concha-Parra R, Erber J, Micames C, Gress F. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. *J Clin Gastroenterol* 2010; **44**: 127-134 [PMID: 19826273 DOI: 10.1097/MCG.0b013e3181bb854d]
59 **Frey CF**, Amikura K. Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy in the management of patients with chronic pancreatitis. *Ann Surg* 1994; **220**: 492-504; discussion 504-507 [PMID: 7524454]
60 **Izbicki JR**, Bloechle C, Knoefel WT, Kuechler T, Binmoeller KF, Broelsch CE. Duodenum-preserving resection of the head of the pancreas in chronic pancreatitis. A prospective, randomized trial. *Ann Surg* 1995; **221**: 350-358 [PMID: 7726670]
61 **Issa Y**, van Santvoort HC, van Goor H, Cahen DL, Bruno MJ, Boermeester MA. Surgical and Endoscopic Treatment of Pain in Chronic Pancreatitis: A Multidisciplinary Update. *Dig Surg* 2013; **30**: 35-50 [PMID: 23635532]
62 **Sutherland DE**, Radosevich DM, Bellin MD, Hering BJ, Beilman GJ, Dunn TB, Chinnakotla S, Vickers SM, Bland B, Balamurugan AN, Freeman ML, Pruett TL. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg* 2012; **214**: 409-24; discussion 424-6 [PMID: 22397977 DOI: 10.1016/j.jamcollsurg.2011.12.040]
63 **Buscher HC**, Lenders JW, Wilder-Smith OH, Sweep CG,

van Goor H. Bilateral thoracoscopic splanchnicectomy for pain in patients with chronic pancreatitis impairs adrenomedullary but not noradrenergic sympathetic function. *Surg Endosc* 2012; **26**: 2183-2188 [PMID: 22395951 DOI: 10.1007/s00464-012-2152-4]

64 **Toskes PP**, Forsmark CE, DeMeo MT, Prinz RA, Owyang C, Soudah H, DiMagno EP, Nealon WH, Vinayek R, Banks PA, Adams D, Warshaw A, and Katkov W. A multicenter controlled trial of octreotide for the pain of chronic pancreatitis. *Pancreas* 1993; **8**: Abstract 774

65 **Lieb JG**, Shuster JJ, Theriaque D, Curington C, Cintrón M, Toskes PP. A pilot study of Octreotide LAR vs. octreotide tid for pain and quality of life in chronic pancreatitis. *JOP* 2009; **10**: 518-522 [PMID: 19734628]

66 **Levenick JM**, Andrews CL, Purich ED, Gordon SR, Gardner TB. A phase II trial of human secretin infusion for refractory type B pain in chronic pancreatitis. *Pancreas* 2013; **42**: 596-600 [PMID: 23548879 DOI: 10.1097/MPA.0b013e318273f3ec]

67 **Puylaert M**, Kapural L, Van Zundert J, Peek D, Lataster A, Mekhail N, van Kleef M, Keulemans YC. 26. Pain in chronic pancreatitis. *Pain Pract* 2011; **11**: 492-505 [PMID: 21676159 DOI: 10.1111/j.1533-2500.2011.00474.x]

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