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Chronic Pancreatitis

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Abstract

Purpose of review—We review important new clinical observations in chronic pancreatitis (CP) reported in 2011.

Recent findings—Smoking increases the risk of non-gallstone acute pancreatitis (AP) and the progression of AP to CP. Binge drinking during Oktoberfest did not associate with increased hospital admissions for AP. The unfolded protein response is an adaptive mechanism to maintain pancreatic health in response to noxious stimuli such as alcohol. Onset of diabetes mellitus in CP is likely due to progressive disease rather than individual variables. Insufficient pancreatic enzyme dosing is common for treatment of pancreatic steatorrhea; 90,000 USP U of lipase should be given with meals. Surgical drainage provides sustained, superior pain relief compared to endoscopic treatment in patients advanced CP with a dilated main duct +/- pancreatic stones. The central acting gabapentoid pregabalin affords a modest 12% pain reduction in patients with CP but ~30% of patients have significant side effects.

Summary—Patients with non-gallstone related AP or CP of any etiology should cease smoking. Results of this year's investigations further elucidated the pancreatic pathobiology due to alcohol, onset of diabetes mellitus in CP, and the mechanisms and treatment of neuropathic pain in CP.

Keywords

chronic pancreatitis; exocrine pancreatic insufficiency; diabetes mellitus; pain

Introduction

Currently, there is no definite medical treatment for pancreatic inflammation, fibrosis or pain of chronic pancreatitis (CP). In this review we focus on epidemiology, association between smoking and non-gallstone acute pancreatitis (AP) and progression from AP to CP,

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Conflicts of interest

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pancreatic pathology due to binge drinking and impaired adaptive intracellular responses, onset of diabetes mellitus in CP, dosing of pancreatic enzyme products (PEP) to treat exocrine pancreatic insufficiency (EPI), neuropathic pain mechanisms and treatments, and pancreatic fibrosis and fibrolysis.

Epidemiology

In Olmsted County (Minnesota) (1) the incidence and prevalence of CP are low, ~ 4 and 42/100,000 persons years, respectively. Moreover, the overall incidence is stable over 3 decades (1977–2006) and the survival of CP patients is significantly lower than the white population. Investigators identified 106 incident persons with CP meeting Mayo criteria. The increased incidence of clinical cases (89/106 persons) from 2.4 to 4.35/100,000 person-years over 3 decades is likely due to a dramatic fall in autopsy rates (38 to 2% of the CP diagnoses) and the increased frequency of the clinical diagnosis of CP (62 to 98% of CP diagnoses) probably because of advances in pancreatic imaging leading to earlier diagnosis of CP. The authors claim that ~50% of CP in this population is due to alcohol abuse, and the increased incidence of clinical cases is due to an increase in alcoholic pancreatitis in women. This interpretation is questionable because the authors “defined etiology based on the treating physician’s diagnosis”; it is uncertain how physician’s opinions relate to alcohol intake.

Cigarette smoking

Clearly, cigarette smoking associates with pancreatitis. In the past year two groups further defined the relationship among smoking, AP and CP, emphasizing that patients with non-gallstone related AP or CP of any etiology should cease smoking.

In a Swedish population (2), current smoking increased non-gallstone AP risk two-fold compared to never smokers and four-fold in current smokers who drank > 400g alcohol/month compared to lower alcohol quantities. In addition smoking duration rather than the daily number of cigarettes increased the risk of non-gallstone-related AP, and after stopping smoking for 20 years the risk of non-gallstone AP was similar to non-smokers. There was no association between smoking and gallstone-related AP.

In a Danish study (3) 24% of persons with AP progressed to CP; the etiology of AP was distributed equally between alcohol (48%) and idiopathic (47%). Independent of etiology, smoking was the most important factor influencing progression of AP to CP. The mortality for persons with progressive AP was ~ 6-fold greater than the normal population and ~ 3-fold greater than persons with non-progressive AP. Only one patient with gallstone AP progressed to CP, confirming that gallstone AP does not lead to CP (4).

Pancreatitis and binge drinking

In a large German study (5) the consumption of beer during the Munich Oktoberfest did not associate with increased hospital admissions for AP. The accompanying editorial (6), however, emphasized that attacks of “acute pancreatitis” may be precipitated by the withdrawal of alcohol after binge drinking rather than the acute ingestion of alcohol and there are several unanswered, longstanding questions about “drunkard’s pancreas” (7). “How much chronic alcohol ingestion can cause alcoholic chronic pancreatitis? Can increased alcohol ingestion (bingeing) by persons with alcoholic chronic pancreatitis induce an attack of “acute pancreatitis?” Does binge drinking induce an attack of acute pancreatitis in persons without an alcohol history, no history of previous attacks, no chronic pancreatitis, and no other etiology for pancreatitis?”

Alcohol pathobiology

Why does alcoholic pancreatitis develop in only ~ 3% of adult Americans with alcohol dependence or abuse (8, 9) and total alcohol consumption is not greater among heavy drinkers who develop pancreatitis vs those who do not (10–13)? Additional cofactors are necessary, as discussed elsewhere (6, 14). In experimental pancreatitis alcohol exposure alone causes minimal pancreatic damage but sensitizes pancreatic acini to injury due to other stressors (15–18). For example, a defective intracellular adaptive unfolded protein response (UPR) may influence alcohol induced pancreatic pathology (19). In health the UPR is important to manage mis- or unfolded proteins occurring in response to a variety of cell stresses and is composed of three endoplasmic reticulum (ER) stress response elements (ERSE). In disease, such as diabetes mellitus or cardiovascular disease, the duration or magnitude of the cell stress exceeds the adaptive capacity of cells and triggers cell death. Not surprisingly, the UPR is pivotal for the health of pancreatic acini. Chronic alcohol feeding to mice induces pancreatic oxidative stress and activates the UPR but genetically induced deficiency of one of the three ERSE pathway downstream effectors, the X-box binding protein 1 (XBP1), results in a defective UPR and increased acinar cell death (19). In addition conditional disruption of XBP1 activates the two other ERSEs leading to extensive pancreatic acinar apoptosis followed by a rapid pancreas regeneration arising from cells with failed inactivation of XBP1 (20, 21). Thus, alcohol requires additional cellular cofactors to evoke a pathological response and conceivably, genetic and/or environmental factors may alter cell protective/adaptive capacity to alcohol exposure leading to cell death.

Genetics in sentinel and recurrent acute pancreatitis (AP)

Genetic mutations of the *CFTR* and *SPINK1* genes associate with forms of CP and idiopathic recurrent AP but not with single episodes of human AP (22, 23). In support of the concept that persons with these genetic mutations have or will develop CP, Masumune et al (24) reported that mutations in the genes *PRSS1* (R122H), *SPINK1* (N34S) and *PRSS3* (E32del) associated with recurrent but not single attacks of AP. The reader is referred to an update of the genetics of idiopathic CP and other pancreatic diseases in the present edition of Current Opinion.

Autoimmune pancreatitis (AIP)

Due to the large number of publications on CP this year and space limitations, we do not discuss the topic of autoimmune pancreatitis (AIP) but refer the reader to publications focused on subclassifications of AIP (25–27), diagnostic criteria for IgG4-related disease (28), diagnostic utility of fine needle aspiration (FNA) (29–31) and endoscopic retrograde cholangiopancreatography (ERCP) (32–34), poor diagnostic value of IgG4 immunostaining of mucosal biopsies in AIP (35), differentiation of AIP from pancreatic cancer (31, 34, 36, 37), association of sclerosing cholangitis with IgG4-related systemic disease (38) and risk factors for developing pancreatic calcifications (39).

Onset of diabetes mellitus in chronic pancreatitis

Current guidelines categorize pancreatic diabetes as type III.C.1. (40) and due to insulinopenia (41, 42). There is evidence, however, that glucose intolerance and insulin resistance frequently coexist with insulinopenia (43–46). In a recent single center Chinese study (47) of 445 patients with CP the prevalence of diabetes mellitus was 52% at 20-years after onset of CP and 28% after receiving either endoscopic or surgical intervention. These data are consistent with the overall prevalence of diabetes of 47% in CP (48) and the increasing incidence of diabetes over time, ranging 0% to 22% at onset of symptoms (49) and increasing to more than 80% 25 years after onset (50). In addition the Chinese

investigators extended current knowledge that there are two independent predictors of diabetes (pancreatic calcifications and distal pancreatectomy) (50) by stratifying risk based on surgical history. They found that patients with prior surgery had two independent predictors of diabetes (distal pancreatectomy and smoking) and those without surgery had four (pancreatic calcifications, age at the onset of CP, smoking and chronic pain). Similar to Malka et al (50), the authors concluded that the risk of diabetes is likely attributable to progression of CP rather than individual factors.

Treating exocrine pancreatic insufficiency (EPI)

Currently 5 pancreatic enzyme product (PEPs) are approved by the Food and Drug Administration (FDA) through the Investigational New Drug (IND) process and commercially available (51). They are Creon Creon (Abbott Laboratories, Abbott Park, IL), Pancreaze (Johnson and Johnson, New Brunswick, NJ), Zenpep, Ultresa and Viokace (all three Aptalis Pharmaceutical Technologies, Birmingham, AL). All contain pancrelipase, a mixture of porcine lipase, amylase and proteases. All except Viokace are delayed release encapsulated preparations. Viokace is approved for use in conjunction with a proton pump inhibitor.

Unfortunately, inadequate doses of lipase were used in almost all studies performed for the IND process leading to recommendations for lower doses than required to abolish steatorrhea. For example in 2 reviews Dominguez-Munoz (52, 53) recommended 40–50,000 lipase United States Pharmacopeia (USP) units per meal.

In contrast the senior author showed by gastrointestinal intubation and fat balance studies that persons with severe CP and exocrine pancreatic insufficiency (EPI) require 30,000 international units (IU) (90,000 USP units) of lipase with meals containing 25g of fat (54–58) to achieve a postprandial intraduodenal concentration of 25 IU of lipase (equal to 75 USP Units), the concentration which corrects steatorrhea. These results were obtained with nonenteric/nonencapsulated pancreatin and a concomitant H₂ blocker (56–58). The approved PEPs, except Viokace, are microencapsulated delayed release pancrelipase to protect against acid denaturation of lipase. The failure of 40–50,000 lipase USP units in these preparations to uniformly correct steatorrhea suggests that this is inadequate dose of lipase in most patients. We suggest the dose should be doubled to ~ 90,000 lipase USP units with meals containing 25g of fat. Several studies lend support for this suggestion.

Two studies were fully funded and analyzed by Abbott. The first study (59) was a double-blind, randomized, placebo-controlled, two-arm, parallel-group trial compared pancrelipase delayed-release 12,000 lipase USP unit capsules (Creon) with placebo in subjects with EPI due to CP or pancreatic surgery. Pancrelipase (72,000 lipase USP units/ meal and 36,000 lipase USP units/ snack) treatment showed significantly less fat malabsorption (increasing the coefficient of fat absorption [CFA] 54.4 to 85.6) compared to placebo. In a 6 month open labeled study (60) of ingesting a mean of ~ 180,000 lipase USP units per day study (24,000 lipase USP unit capsules), the preparation was well tolerated and associated with significant, but small weight gain and reduced stool frequency by 1 per day. In this second study, there were no direct tests of absorption. The normal CFA is 93% so in both studies, malabsorption was reduced but likely not corrected in most patients, suggesting inadequate dosage of lipase.

In another study (61) the pharmaceutical company Aptalis designed analyzed and participated in the editorial process of a study in patients with severe EPI (mean CFA 65%) and found that Zenpep (an enteric coated porcine pancrelipase delayed-release capsules) improved fat absorption more with 40,000 lipase USP units per meal (CFA 84.4%) compared to 10,000 lipase USP units per meal (CFA 80.8%). Patients with mild steatorrhea

(CFA 82%) improved fat absorption to near normal values with both doses of pancrelipase. The results of this study suggest that a confounding factor in the treatment of EPI is the degree of fat malabsorption; persons with severe EPI (a mean CFA of 65% in the above study and ~40% in the senior author's studies) require lipase doses ranging up to 2x the current recommended dose to abolish steatorrhea.

Pain patterns

Ammann (62, 63) classified abdominal pain in CP as either short episodes/relapsing (Type A) or constant/prolonged episodes of pain (Type B) (62). Type A pain predominates in late-onset idiopathic CP and hereditary CP and is managed without invasive procedures. Type B predominates in alcoholic CP and early-onset idiopathic CP, associates with local complications (primarily pseudocysts or obstructive cholestasis) and requires surgery in ~60%. Investigators of a multicenter study (64) confirmed presence of two major pain patterns in CP, the association of alcohol with constant pain and persons with constant pain compared to intermittent pain "had higher rates of disability, hospitalization and pain medication use" and lower quality of life. Future analyses of these data should confirm Ammann's findings (62, 63) that constant pain associates with local complications that require intervention.

Treatment of Pain

Unrelenting pain occurs in a subset of patients with CP who may not have anatomic complications or respond to conventional therapies. Therapeutic options reported this year include outcomes of surgical vs endoscopic drainage (65), celiac plexus blockade (CPB) (66), and total pancreatectomy with auto islet transplanation (67, 68). To evaluate these treatments the diagnosis of CP must be certain. We review some studies in which the conclusions pertain to CP but in others the conclusions have questionable relevance to CP, largely because the diagnosis is uncertain.

Patients with painful advanced CP with a dilated main duct +/- pancreatic stones and severe intermittent or continuous pain for ~ 1 ½ years unrelieved by non-narcotic analgesics or requiring opiates should undergo surgical drainage in preference to endoscopic therapy. Cahen et al (69) randomized 39 patients with advanced CP to either endoscopic drainage following lithotripsy clearance of pancreatic duct stones or surgical pancreaticojejunostomy. In the first study (69) surgical drainage more effectively relieved pain over 2 years than endoscopic therapy (complete or partial pain relief, 75 vs 32%). In 2011 the authors reported that after 5 years 47% of patients endoscopically treated required surgery. Furthermore, more patients who underwent surgery continued to have pain relief (80% vs 38%) and required far fewer additional drainage procedures (5% vs 68%).

In contrast to the studies of Cahen et al (65, 69) where the diagnosis of CP was certain and outcomes can be definitely related to the diagnosis, Stevens et al (66) purported to show that adding triamcinolone to bupivacaine during endoscopic ultrasound (EUS) guided celiac plexus block (CPB) did not reduce pain in CP. This is an unexpected observation, because, CBP (bupivacaine + triamcinolone) provides short pain relief in a subset of patients with CP as shown in three randomized controlled trials (70–72), a meta-analysis (73) and a systematic review (74). In the study by Stevens et al (66) the diagnosis of CP is problematic. Their patients had abdominal pain and the diagnosis of CP was ascertained by grading the appearance of the pancreas at EUS as "indeterminate," "suggestive," or "most consistent" for CP based on the non-validated Rosemont classification. The majority of patients in the bupivacaine and bupivacaine + triamcinolone groups (15/21 and 13/19, respectively) were either indeterminate or suggestive. The authors acknowledge this weakness: "the inclusion of patients with mild EUS changes ...[raises the] ... possibility that some patients lacking

real CP were included. However, all subjects had severe pancreatic pain and a strong clinical suspicion of CP based on past AP, heavy alcohol use, or other risk factors". Nevertheless, it is likely many patients did not have CP, and at best the summary should be that EUS-CPB with bupivacaine or bupivacaine + triamcinolone may not be effective in alleviating pain in patients with clinically suspected but unproven CP. The author of the accompanying editorial (75) commented that the majority of studies evaluating CPB "show pain relief in approximately half the patients, a reduction in pain is rarely associated with a significant drop in narcotic use, and it is not long-lasting. Because this is a lifelong disease, even using a treatment that provides only a very short-lived response is not inherently logical". A counterargument to this conclusion is that according to the natural history of CP many patients with CP eventually experience cessation of pain and pain relief, even if temporary, may bridge time to pain relief and preclude the necessity of invasive procedures.

An emerging surgical treatment for painful CP is total pancreatectomy combined with islet cell autotransplantation in "early CP" before development of central pain pathways and to prevent pancreatogenic diabetes. For several reasons the value of this procedure is uncertain and we urge caution. Patients selected for this treatment may have abdominal pain from causes other than CP. The long-term results are unknown. Although there may be a very modest improvement in quality of life scores in the short term, most patients continue narcotic use, and many become insulin dependent and all need PEP to treat malabsorption—usually not mentioned. To harvest sufficient islets from the pancreas, "ideal" patients undergoing this procedure have "early" CP before there is extensive pancreatic damage. Thus, many patients lack the classical clinical and pathology findings of CP raising the possibility of submitting patients without CP to operation. For example, of the 33 adult patients who underwent this procedure by Morgan et al (67) more than half had questionable causes of CP (14 had sphincter of Oddi dysfunction, 3 had pancreas divisum). The authors of this study and one by Bellin et al (68) (who enrolled children 13/19 of whom had genetic or hereditary causes of CP [ages ~5–18 at transplant]) report significantly improved quality of life. However, in both studies there were significant post-operative complications (48% (67), 22% (68)) and the operation converted many patients from insulin independence to requiring some insulin (~70% (67), 60% (68)) and continued narcotic use (~88% (67), 22% (68)).

Central and peripheral sensitization to pain

This year, investigators increased our knowledge of central alterations of neuropathic pain by using imaging techniques (76, 77) and assessing the therapeutic responses to the central acting gabapentoid pregabalin (78) and peripheral sensitization by using an experimental model with peripheral inhibition of nerve growth factor (NGF) signalling (79).

Patients with definite CP based on Mayo Clinic criteria and longstanding pain have visceral hypersensitivity and magnetic resonance imaging (MRI) microstructural changes (76), including reduced cortical thickness of the brain areas involved in processing of pain (77) compared to normal persons. Thus, cortical thickness might be a surrogate for overall pain system dysfunction in CP, as it is in other causes of chronic pain. It is unknown whether treatment of neuropathic pain normalizes these brain imaging abnormalities in CP. If so, this technology is potentially useful not only to verify the presence of centralized neuropathic pain but also to monitor the response to treatment.

Olesen et al (78) conducted a double blind randomized control trial of 150 to 300 mg/day of pregabalin (a gabapentoid effective in treating other causes of neuropathic pain) for 3-weeks as adjunct therapy for pain treatment in 64 patients who met the Mayo criteria for CP. They found pregabalin was superior to placebo and concluded "pregabalin can be used in

combination with other analgesics or interventional therapies to obtain better control of the disabling pain in CP.” However, pregabalin treated patients only had 12% reduction of pain, likely because there was a large 25% placebo response. Pregabalin also caused adverse CNS adverse events in ~30% consisting of feeling drunk and light-headedness, similar to other gabapentoids. These investigators also found that “pregabalin was superior to placebo for attenuation of experimental visceral pain in CP patients and suggested its antinociceptive effects... [were] ...mediated primarily through sub-cortical mechanisms” (80). Although these studies with pregabalin are promising for its use as adjuvant treatment of painful CP, it is unknown if it is effective for longer than 3 weeks, as a first line treatment, or improves the quality of life.

Neuropathic pain in AP and CP likely develops from sensitization of primary nociceptors (peripheral sensitization) and involves activation of capsaicin-sensitive afferent sensory neurons and release of proinflammatory neuropeptides and nociceptive signalling (81). NGF has pathophysiologic effects on peripheral sensitization in CP (79). NGF mediates peripheral sensitization (82) and signals through its receptor TrkA and a downstream NGF-responsive gene product, vanilloid receptor TRPV1, which is a central transducer of noxious stimuli. In experimental rat CP blockade of NGF signalling by anti-NGF antibody attenuated pancreatic hyperalgesia and referred somatic pain and decreased pancreatic sensory neuron TRPV1 current and expression (79). Hence, NGF may be a target for treatment of pain in CP.

Pancreatic fibrosis and fibrolysis

Investigators in the past year characterized pancreatic stellate cells (PSCs) by a proteomics approach (83) and by interrogating calcium-dependent signal transduction pathways (84). Strikingly, pancreatic fibrosis in mice requires a myeloid rather than pancreatic source of the RelA/p65 component of the transcription factor nuclear factor (NF)-kappa B (85). The gaseous transmitter hydrogen sulfide (H₂S) suppresses PSC activation (from myofibroblasts), proliferation and synthesis of extracellular matrix (86). Relevant to anti-oxidant treatment of clinical CP, anti-oxidants have a cytotoxic (apoptosis-inducing) impact on activated (but not quiescent PSCs (myofibroblasts) and have anti-inflammatory and anti-fibrotic effects during *in vivo* experimental models of CP (87–89), but these effects may be independent of anti-oxidant mechanisms (88). Anti-oxidant properties of statins may also explain their attenuation of pancreatic inflammation and fibrosis in experimental CP (90). As the mediator of the renin-angiotensin system, angiotensin II activates PSCs but its two downstream receptors 1 (AT1R) and 2 (AT2R) have differential effects on pancreatic fibrogenesis; inhibition of AT1R prevents and reverses pancreatic experimental pancreatic fibrosis and inhibition of both receptors prevents development of fibrosis but does not reverse established fibrosis (91). As partial support for the potential reversibility of pancreatic damage after alcohol cessation, Vonlaufen et al (92) found that withdrawal of alcohol promotes PSC apoptosis and regression of fibrosis in an experimental model of lipopolysaccharide and alcohol induced pancreatic fibrosis. Finally, pancreatic stone protein, which may participate in formation of pancreatic calcifications, may ameliorate fibrosis because it reduces PSC activity and stimulates fibrolysis (93).

Conclusion

This year’s literature contained moderate advances to further elucidate the influence of smoking on AP and CP, pancreatic pathobiology due to alcohol, onset of diabetes mellitus in CP and mechanisms and treatment of neuropathic pain in CP.

Abbreviations

AIP	Autoimmune pancreatitis
AP	acute pancreatitis
AT1R	angiotensin receptor 1
AT2R	angiotensin receptor 2
PRSS1	cationic trypsinogen or serine protease I
PRSS3	mesotrypsinogen or serine protease III
CPB	celiac plexus blockade
CP	chronic pancreatitis
CFA	coefficient of fat absorption
CFTR	cystic fibrosis transmembrane conductance regulator
ERSE	endoplasmic reticulum stress response element
EUS	endoscopic ultrasonography
EPI	exocrine pancreatic insufficiency
H2S	hydrogen sulfide
IU	international units
NGF	nerve growth factor
PEP	pancreatic enzyme products
PSC	pancreatic stellate cell
RAS	renin-angiotensin system
SPINK1	serine protease inhibitor Kazal type 1
UPR	unfolded protein response
USP	United States Pharmacopeia
XBP1	X-box binding protein 1

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- Of outstanding interest

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of the X-box binding protein 1 (XBP1), a major effector of one of three arms of the UPR. A complementary study (ref 20) underscores that conditional disruption of XBP1 activates the two other arms of the UPR and leads to extensive pancreatic acinar apoptosis followed by a rapid pancreas regeneration arising from cells with residual XBP1. [PubMed: 21111739]

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aspirate (FNA; 22 gauge) and 19 (43%) had tissue aspirate evidence to support a diagnosis of type 1 AIP (see refs 25–26); 17 had lymphoplasmacytic sclerosing pancreatitis and 5 had IgG4-positive plasma cells. Although diagnostic yield of FNA for AIP is lower than for pancreatic true cut biopsy, FNA might be useful as a relatively safe and reliable diagnostic test in patients with atypical features of AIP. [PubMed: 22019795]

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Key Points

- The UPR may serve as a pivotal adaptive mechanism to maintain pancreatic health in response to noxious stimuli such as alcohol.
- Four variables independently predict diabetes mellitus in CP patients without surgery (pancreatic calcifications, age at the onset of CP, smoking and chronic pain) and two variables predict diabetes mellitus in CP patients with prior surgery (distal pancreatectomy and smoking).
- The appropriate dose of pancreatic enzymes is 90,000 USP units of lipase with meals containing 25 mg of fat.
- Surgical drainage is superior to endoscopic treatment in patients with advanced CP with a dilated main duct +/- pancreatic stones to ameliorate chronic severe intermittent or continuous pain unrelieved by analgesics.
- The central acting gabapentoid pregabalin affords a modest 12% pain reduction in patients with CP but ~30% of patients had significant side effects.