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Managing Chronic Pancreatitis: Beyond Opioids

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Chronic pancreatitis severely impacts the quality of life for affected patients and is a major burden on the health care system. Of all of the complications associated with chronic pancreatitis, chronic pain is one of the most difficult to manage. Historically, clinicians have used opioids as part of a long-term management strategy to keep patients out of the hospital and manage pain. With the growing opioid epidemic in the United States and mounting evidence that opioids can ultimately worsen patient outcomes, clinicians should be aware of the medical, nutritional, endoscopic and surgical alternatives that are available for managing pain resulting from chronic pancreatitis. These options should increasingly be utilized in the initial treatment and management of chronic pancreatitis rather than as salvage options when increasingly high doses of opioids become ineffective.

INTRODUCTION

Chronic pancreatitis (CP) is a fibro-inflammatory condition that affects the exocrine and endocrine function of the pancreas and can also cause a chronic pain syndrome that adversely impacts the lives of patients. Epidemiologic studies suggest that CP occurs more frequently in blacks than other ethnicities and is more common in men than women.[1-3] Risk factors for the development of CP include genetic mutations (such as *PRSS1* and *SPINK1*), autoimmune conditions, obstruction of the main pancreatic duct, recurrent acute pancreatitis, smoking and chronic alcohol use. In many cases, the etiology of the recurrent pancreatitis is never identified. The incidence of CP ranges from 4 to 13 cases per 100,000 patient-years.[4-6] Although few widespread population studies have been performed, available data suggests that the incidence of CP is on the rise.[7]

In early stages of CP, patients experience recurrent symptoms consistent with acute pancreatitis (i.e. severe mid-upper abdominal pain that radiates to the back, nausea, and vomiting). If flares of inflammation persist over several years, the pancreatic tissue becomes fibrotic and calcified. Typically patients will experience symptoms consistent with CP once 15% or less of functional pancreas remains.[8] Classic symptoms that patients with CP will experience can be separated into three categories – those related to exocrine insufficiency, those related to endocrine insufficiency and abdominal pain.

Exocrine insufficiency of the pancreas is manifested as steatorrhea, diarrhea, and poor nutrition due to malabsorption. Endocrine

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insufficiency is characterized by the loss of insulin-producing beta cells due to atrophy of pancreatic islets resulting in an insulin-dependent phenotype of diabetes. Chronic pain, perhaps the most significant sequelae of CP patients, severely impacts quality of life and levies major financial burdens on the health care system (estimated to be over $600 million dollars annually).[9] Chronic pain is very prevalent in CP, occurring in 85% of patients.[10-12] Approximately 90% of patients with CP will be admitted at least once to the hospital for management of chronic abdominal pain and, on average, more than 10 times over the course of their lives.[13]

Managing pain and the other sequelae of CP can be challenging. Historically, opioids have been a cornerstone of management of CP with over 50% of patients receiving at least one prescription for an opiate during their disease process.[14] Given the growing epidemic of opioid overuse and the presence of literature that suggests that opiates may not only just be ineffective for chronic pain, but may also perpetuate a cycle of chronic pain symptoms by worsening symptoms of chronic pancreatitis and changing pain thresholds, it is clear that alternative strategies must be considered when managing CP.[15,16]

The goal of this review is to provide a summary of medical, nutritional, endoscopic, and surgical alternatives for the management of CP so that clinicians are aware of what options exist beyond prescribing opiates.

Medical and Nutritional Therapy

CP patients will suffer from severe post-prandial pain due to the release of cholecystokinin once a food bolus enters the duodenum. After cholecystokinin is released, the pancreas begins secreting enzymes into the gastrointestinal lumen. CP patients subsequently can develop significant pain as a result of increased pressure within the pancreatic duct (ductal hypertension) as well as effects of trypsin on nociceptive receptors surrounding the pancreas. The oxidative-stress incurred by recurrent parenchymal inflammation may also adapt the central nervous system pain receptors such that some CP patients will also develop a component of neuropathic pain that becomes independent of the pancreas.

To counteract this, physicians have a variety of tools that target specific factors contributing to pain in CP patients. Antioxidants alongside pregabalin, for example, have been shown to improve pain control for CP patients, presumably by preventing the neural changes that result in the development of neuropathic pain.[17,18] Alternatively, pancreatic enzyme replacement therapy (PERT) is useful by limiting the release of cholecystokinin in the duodenal lumen and reducing the amount of pancreatic exocrine stimulation that occurs during meals, thereby improving ductal hypertension and reducing pain. A review of randomized controlled trials studying the effect of PERT for the purpose of pain control in CP demonstrated that only pancreatic enzyme formulations that were uncoated (i.e. not acid protected) resulted in improvement in pain.[19-24] Based on these studies, it is recommended that uncoated formulations of enzymes be used to manage chronic pain and that the enzymes are administered at high doses (>25,000, United States Pharmacopeia—USP) four to eight times per day.[25] Patients receiving these medications must receive anti-secretory therapy (i.e. proton pump inhibitors) to avoid the non-enteric coated enzymes from being inactivated by gastric acid.

Patients suffering from symptoms of exocrine insufficiency also benefit from enzyme supplementation. Compared to CP patients where pain is the predominant symptom, patients with severe exocrine insufficiency can benefit from enteric coated formulations of PERT as the enzymes are released in the jejunum and ileum to assist with absorption. Doses of PERT are titrated based on patient weight, symptom severity, and meal size. For average sized meals, doses should range from 50,000-90,000 USP.[26] If patients have persistent symptoms of malabsorption, clinicians should consider upping the PERT dose and adding a proton pump inhibitor in order increase the enzyme concentration in the distal small bowel.[27]

In conjunction with PERT, CP patients with malnutrition will often require dietary alterations and nutritional supplementation to improve malabsorption symptoms. As the natural history of CP progresses and patients limit oral intake, it is key that patients understand what to prioritize in their diet to avoid becoming malnourished. Traditionally, due to concerns of fat malabsorption, CP patients have been told to avoid fatty foods and, instead,

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focus on high fiber diets. We now know that fat is an essential source of energy for CP patients and, alternatively, high fiber diets have actually been shown to inhibit lipase secretion, which may worsen malabsorption.[28,29] Consultation with an experienced dietician should be considered as studies have shown that expert advice regarding nutritional supplements has been shown to improve outcomes for CP patients.[30] In order to maximize the effects of all of these interventions, CP patients should also be counseled to completely abstain from alcohol and to stop smoking to limit progression of disease.

Endoscopic Therapies

Over the past several of years, innovations in endoscopic technology have advanced the role of endoscopy in the management of chronic pancreatitis. Now, clinicians can rely on endoscopic therapy as a valuable and effective tool to address structural issues related to CP and to avoid or defer more invasive surgical procedures.

Pancreatic duct stones, or pancreatic calculi (PC), are an example of structural complications in CP patients that are amenable to endoscopic therapy. PC are made up of calcium carbonate (along with other minerals found in pancreatic juices) and develop in approximately 50% of CP patients.[33] These stones can obstruct the main pancreatic duct resulting in intraductal hypertension along with pain and inflammation that can accelerate the progression of parenchymal fibrosis.[34] Through endoscopic retrograde cholangiopancreatography (ERCP), endoscopists are able to obtain retrograde access to the main pancreatic duct. The goal of endoscopic treatment in these cases is to remove stones, resolve obstructions, and improve intraductal flow. For smaller stones this can be achieved by performing a sphincterotomy or by using extraction balloons, forceps, or baskets. In the cases where larger stones are present, lithotripsy may be required. Extracorporeal shockwave lithotripsy is a potential first step for the management of larger stones as it has shown to be cost effective. It important to note, however, that this technology is not available in all medical centers.[27] Alternatively, endoscopic advancements now allow for mechanical, electrohydraulic and laser lithotripsy to be performed through an endoscope. Mechanical lithotripsy involves inserting a catheter or basket into the pancreatic duct, crushing an obstructing stone, and removing the fragments from the duct. In laser or electrohydraulic lithotripsy, a smaller 10 French scope is inserted through the duodenoscope

Table 1. Pros and Cons of Different Medical Treatments for Chronic Pancreatitis

Treatment	Pros	Cons	Notes
Pregabalin	Associated with reduction in amount of opiate use. Improves short term pain.	Increased adverse events (i.e. sleepiness, blurry vision) compared to placebo. [31]	Long-term benefits are unknown Only low quality level of evidence available.[31]
Antioxidants	Results in a small reduction in pain relief. May prevent central pain dysregulation.	16% of patients report having headaches, nausea or constipation while on therapy.[32]	No data available regarding improvement in quality of life.[32]
Pancreatic Enzyme Replacement Therapy	Has been shown to improve exocrine insufficiency and sometimes pain.	Complicated dosing regimen that requires patients to titrate dose based on meal size. Six types of enzyme supplements are available. No comparative studies exist.	Non-enteric coated pancreatic enzymes (compared to enteric coated) appear to have improved results for improving pain. Enteric coated enzymes should be used for malabsorption

and into the pancreatic duct to direct laser or electrohydraulic treatment to obstructing stones. All of these techniques have shown efficacy in studies; however, longer term studies regarding efficacy and safety are still needed. Importantly, knowing which stones to attempt therapy on is a critical issue that is not always readily apparent. The presence of a caliber change in the pancreatic duct with dilation of the duct upstream from the stone is a useful criteria that is often utilized as an appropriate indication for treatment.

Similar to pancreatic duct stones, main pancreatic duct strictures (PDS) are obstructive complications of CP that cause chronic pain by preventing drainage of the main pancreatic duct and increasing intraductal pressures. The first step in managing a newly identified pancreatic duct stricture is to rule out underlying malignancy. This can be done non-invasively by obtaining a magnetic resonance imaging (MRI) or computerized tomography (CT) scan of the pancreas or invasively by endoscopic ultrasound with fine needle aspiration. Once malignancy has been ruled out, management of symptomatic benign strictures can be pursued. The goal of treatment in these cases is decompress the pancreatic duct by relieving the obstruction and improving pain. In current practice, treatment of CP strictures occurs via three techniques: pancreatic sphincterotomy, stricture dilation, and stenting. Execution of these maneuvers is effective in sustaining pain relief in 32%-68% of cases.[35,36] While pancreatic sphincterotomy and dilation are well-established steps in the management of PDS, research is currently focusing on how to best maximize the benefit of endoscopic interventions by studying different stenting practices. There is

Table 2. Endoscopic Treatments for Chronic Pancreatitis Separated by Indication with Listed Pros and Cons

Condition	Endoscopic Treatment(s)	Pros	Cons
Pancreatic Duct Calculi (PC)	Endoscopic laser/ electrohydraulic lithotripsy Endoscopic mechanical lithotripsy	Improvement in 65% of patients.[33]	Threefold higher complication rate from mechanical lithotripsy of PC compared to biliary stones.[46]
Pancreatic Duct Strictures	Endoscopic sphincterotomy Stricture dilation Stent placement	Improvement in pain occurs for the majority of patients.	Multiple procedures needed to exchange stents.
Biliary Strictures	Self-expanding metal stent placement Multiple plastic stent placement	Greater than 90% rate of stricture resolution.[39]	Associated with metal stent migration which, in severe cases, can lead to recurrent biliary obstruction.[39]
Chronic Pain without Duct Obstruction	Celiac plexus nerve block	Up to 60% of patients will experience pain relief following nerve block.[40,41]	Multiple procedures required as pain relief is only short term.
Pancreatic Pseudocyst	Endoscopic transmural drainage Endoscopic transpapillary drainage	Technical success in 90% of patients.[45] Effective alternative to an invasive surgery. New technologic advancements have made procedure less complicated.	Adverse events include bleeding, sepsis, and stent migration. Overall procedure-related complication rates are similar to surgery.[47]

Table 3. Categories and Types of Surgical Procedure for Chronic Pancreatitis with Reported Rates of Short-Term Pain Relief and Long-Term Adverse Events

Surgical Category	Surgical Procedure	Short Term Pain Relief	Long Term Adverse Events
Resection	Distal pancreatectomy	55-80%[60-62]	Significant risk of developing post-operative pancreatic fistulae. 29-69% of patients will develop endocrine or exocrine insufficiency.[60-62]
	Pancreaticoduodenectomy (Whipple) Duodenum preserving pancreatic head resection (Beger)	80-100%[54-58]	Postoperative morbidity (up to 53%) and mortality (3%). 12-51% will develop long term endocrine or exocrine insufficiency.[54-58,65]
	Total pancreatectomy	80-100%[66,67]	Postoperative morbidity of 40-50%. Without islet cell transplantation patients will develop insulin dependent diabetes.[66,67]
Drainage	Lateral Pancreaticojejuostomy (Peustow)	>90% [49-52]	Up to 25% of patients become insulin dependent after 5 years.[51,52] High rate of repeat hospitalizations for pain.[48]
Combined Drainage/Resection	Frey procedure	75-91% (long-term relief)[67-70]	Postoperative morbidity in 22%. Endocrine deficiency in 10-20%.[67-70]

a longer track record of research supporting the use of plastic stents in CP patients with strictures, however, newer data suggests that fully covered self-expanding metal stents (FC-SEMS) placed across PDS can improve ductal patency and keep patients asymptomatic longer. One study demonstrated that 89% of patients that were followed for more than 38 months after metal stent placement for PDS remained asymptomatic.[37] Future studies confirming the safety, efficacy and cost benefits of FC-SEMS over plastic stents will be important in making this standard practice.

In addition to strictures of the pancreatic duct, up to 46% of CP patients will develop strictures of the common bile duct their disease course.[38] Strictures often occur secondary to pancreatic parenchymal edema and progressively worsening fibrosis. Patients presenting with biliary strictures may be jaundiced or even have symptoms of cholangitis. Similar to PDS, biliary strictures must be first be investigated for possible malignancy; once that has been ruled out, patients can be considered for endoscopic treatment. Endoscopists can choose to place multiple plastic stents across the biliary strictures or opt for the placement of a FC-SEMS. A recent randomized controlled trial, however, suggests that compared to placing plastic stents, placement of FC-SEMS results in increased rates of stricture resolution while requiring fewer procedures.[39]

For patients where no focal anatomical changes can be attributed as a cause of recurrent pancreatic-type pain, celiac nerve blocks (CNB) or celiac neurolysis can be considered. During a CNB procedure, an endoscopist uses an echoendoscope to directly inject a steroid-anesthetic mixture into a celiac ganglion or the area around the celiac axis

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if no ganglion is seen. Celiac neurolysis is a similar procedure; however, the injection is a mixture of alcohol and an anesthetic and this mixture has not typically been utilized in patients with benign pancreatic disease. For CP patients with chronic pain, CNB is effective in 50-60% of cases; however, additional treatments will likely be required as the treatment effect often diminishes over the course of a few months.[40,41]

A final complication of CP that can be managed endoscopically are pancreatic pseudocysts. Pancreatic pseudocysts are walled-off, encapsulated collections of pancreatic fluid that are commonly seen in both acute pancreatitis and CP. Unlike in acute pancreatitis, most CP pseudocysts do not often resolve spontaneously. However, they also do not tend to cause many symptoms. If pseudocysts in CP cause symptoms due to mass effect on nearby organs or because they become infected, treatment is warranted. The goal of endoscopic treatment in these causes is to drain the cyst and have it collapse and ultimately resolve. Endoscopic drainage techniques have been shown to be successful in resolving pseudocysts in up to 90% of cases and also improve quality of life for CP patients. Compared to surgical or percutaneous drainage, endoscopic approaches have been associated with less procedural risk, decreased hospitalizations, and costs.[42-45] Endoscopic drainage of pseudocysts can be performed by a transmural approach (if the pseudocyst is near the stomach or duodenum) or by a transpapillary approach (if the pseudocyst has a direct communication to the pancreatic duct). Endoscopic transmural drainage of pseudocysts has been made simpler by the development of lumen apposing metal stents and these stents have become the primary method of endoscopic therapy of pancreatic fluid collections. Using a single device specifically created for this aim, these stents are able to puncture the cyst and connect the cyst cavity to the lumen of the GI tract to facilitate drainage. By simplifying this process, endoscopists have achieved success rates comparable to surgery while significantly reducing procedure times and cost.

Surgical Management

In cases of CP where less invasive treatment strategies have failed, surgical management can be considered. Surgical treatment of chronic pancreatitis can be broken down into drainage procedures, resection procedures, and combined drainage/resection procedures.

Surgical drainage procedures are indicated in CP patients with refractory, chronic pain who have evidence of a persistently obstructed and distended ($\geq$ 6 mm) main pancreatic duct or occasionally in CP patients who are found to have a disconnected pancreatic duct. Surgical management in these cases involves bringing a loop of jejunum up to the pancreas and creating a direct anastomosis with the dilated pancreatic duct to facilitate drainage. This procedure is known a lateral pancreaticojejunostomy (also often referred to as a Puestow procedure). Pancreaticojejunostomies are effective (providing initial pain relief in 90% of cases) and safe (mortality of 0-4%).[48-51] Despite achieving high rates of pain relief initially, 40% of CP patients will eventually require hospitalization after surgery for pain management and, potentially, additional procedures such as pancreatic resection will be necessary. Finally, although this technique is advantageous in that no gland is resected, as many as 25% of CP patients will develop glandular dysfunction and become insulin dependent after surgery, despite the lack of resection of the gland.[51,52]

When CP patients are experiencing pain but the main pancreatic duct is not dilated, pancreatic resection procedures are considered. Other situations where a surgeon may choose a resection procedure includen if a CP patient has a focal lesion which may represent malignancy or if the patient has had an attempt at a drainage procedure in the past which has failed. There are three main types of surgical resections that are utilized for CP patients based on what parts of the pancreatic parenchyma are most diseased/involved.

For the majority of CP patients, chronic inflammatory changes are focused at the head of the pancreas. The preferred surgical procedure in this setting is a pancreaticoduodenectomy (also known as a Whipple procedure) or a duodenal preserving pancreatic head resectiton (Beger procedure). For cases where the majority of the body and the tail of the pancreas are calcified a distal pancreatectomy is performed. In this procedure, the distal pancreas (neck, body and tail) is resected, while the pancreas head and uncinate process are preserved. Finally, a complete resection of the

pancreas (i.e. total pancreatectomy) is indicated in CP patients who are found to have extensive main-duct intraductal papillary mucinous neoplasms or hereditary pancreatitis due to the significant risk of malignant transformation within the entire gland. All of these resection procedures are associated with good initial pain relief. As would be expected, to varying degrees, each surgery is associated with post-operative morbidity as well as significant rates of endocrine insufficiency. For example, following total pancreatectomy, patients will develop insulin-dependent diabetes that can be very difficult to manage. To improve post-operative glycemic control, surgeons have utilized auto-islet cell transplantation (where the pancreas is removed, emulsified, purified to extract islet cells and then injected back into the patient). Studies of auto-islet cell transplantation demonstrate promising results; however, this procedure is available only in expert centers and can be very expensive.[53-63] It also appears to be less efficacious in patients with more advanced disease, in whom fewer available islet cells are available for extraction.

Finally, combined resection/drainage procedures, like the Frey procedure, are often performed in patients with a dilated pancreatic duct associated with an enlarged pancreatic head. During a Frey procedure, the affected areas of the pancreatic head are cored out and a lateral pancreaticojejunostomy is performed. Compared with standard drainage procedures, combined procedures such as the Frey procedure are associated with improved long-term pain relief.[64]

CONCLUSION

This review has covered the management strategies of chronic pancreatitis that exist beyond opioid prescription – medical/nutritional therapy, endoscopic therapy, and surgical treatment. It is key that clinicians are aware of alternatives to opiates for the management of CP. Opiates should not be considered a long-term solution to pain management in CP as they may be a driver towards the development of centrally-mediated neuropathic pain. The development of this centrally-mediated pain is believed to result in reduced efficacy of subsequent endoscopic and surgical treatments. With advances in available medical, surgical and endoscopic therapy, clinicians have even more options available to them to better manage CP and should utilize these approaches earlier in managing pain associated with CP. The next steps in optimizing the management of CP is to gain a better understanding of which specific scenarios would benefit from endoscopic management versus surgical management. Future trials directly comparing these different techniques and combination therapies will be vital in providing direction to clinicians managing these patients. ■

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