Endoscopic treatment of pain in chronic pancreatitis

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Purpose of review
Pain is the most common symptom of chronic pancreatitis, having a profound effect on patients and a broad socioeconomic impact. Endoscopy is guideline recommended as first-line management for chronic pancreatitis pain in certain clinical scenarios. Herein, we provide an evidence-based review of the endoscopic treatment of pain due to chronic pancreatitis while highlighting some important confounders in the measurement of this outcome in clinical practice and research.

Recent findings
Multiple recent studies have reported on the efficacy of current endoscopic therapies for chronic pancreatitis pain. Despite the high technical success rates of these procedures, pain outcomes remain disappointing. Complex mechanisms beyond ductal hypertension, such as central sensitization, visceral hypersensitivity and inflammatory neuritis account for some of the discordance observed between the rates of technical and clinical success. In addition, the sham effect is increasingly recognized as a confounder when interpreting the procedural benefit. Nevertheless, there are multiple promising innovations in the field of pancreatic endoscopy that are aimed to improve technical and clinical outcomes, but rigorous investigation is necessary to establish their role in clinical practice.

Summary
Endoscopic therapy for chronic pancreatitis pain appears to be safe and effective in certain contexts and recent innovations in the field will hopefully further improve outcomes. In addition to evaluating the technical success of endotherapy in chronic pancreatitis, methodologically rigorous research focusing on patient-centered outcomes and accounting for the sham effect is necessary to advance this field.

Keywords
chronic pancreatitis, endoscopy, endoscopic retrograde cholangiopancreatography, pancreatic duct stones, pancreatic duct stricture, pseudocyst

INTRODUCTION

Pain is the most common symptom of chronic pancreatitis, affecting between 85 and 97% of patients during the course of their disease [1▪▪]. This pain results in diminished quality of life indices similar to other serious lung, heart, kidney and liver diseases [2–4]. In addition, the socioeconomic impact is significant, as patients affected with chronic pancreatitis have poorer employment status, incur excess healthcare costs, and experience high levels of disability [2–5]. According to the latest consensus guidelines on the management of pain in chronic pancreatitis, published in 2017, endoscopic intervention is considered first-line treatment for an obstructing stricture or stone in the distal (head/neck) main pancreatic duct (MPD) [1▪▪]. Some endoscopic therapies, however, such as celiac plexus block (CPB) should only be considered after medical management of pain has failed. In addition, complications of chronic pancreatitis, including pseudocysts and biliary obstruction, may become symptomatic and require endoscopic intervention.

The current review will provide a synopsis of the pathophysiology of pain in chronic pancreatitis and confounders in the assessment of pain outcomes. This will be followed by a detailed discussion of the endoscopic management of MPD stones and

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KEY POINTS

- Pain is the most common symptom and the main indication for endoscopic intervention in chronic pancreatitis.
- Visceral hypersensitivity and the sham effect of endoscopy may explain the discrepancy between the observed technical and clinical success of endoscopic interventions in chronic pancreatitis.
- For the management of pain in chronic pancreatitis, endoscopic retrograde pancreatoscopy with or without extracorporeal shock wave lithotripsy is an important part of the management algorithm.
- The benefit of endoscopic ultrasound with celiac plexus block to treat pain in chronic pancreatitis is unclear.

strictures, endoscopic ultrasound (EUS)-guided CPB, and pseudocyst drainage (Table 1).

MECHANISMS OF PAIN IN CHRONIC PANCREATITIS

An earlier and more rudimentary pathophysiological explanation for pain in chronic pancreatitis was ductal obstruction resulting in increased acinar pressure [6]. Accordingly, endoscopic and surgical therapies for managing pain in chronic pancreatitis traditionally focused on addressing intraductal hypertension by removing stones and treating strictures. Ductal hypertension, or blocked 'plumbing' however, only represents one component of the underlying pathophysiology of pain in chronic pancreatitis. Abnormal 'wiring' due to visceral hypersensitivity and neural sensitization – which can occur at a peripheral and/or central level in chronic pancreatitis – is now accepted as the main driver of chronic pain in this patient population [6,7▪]. Indeed, preoperative visceral hypersensitivity has been associated with inferior pain outcomes following pancreatic surgery in chronic pancreatitis and is the probable explanation for an incomplete pain response in patients who have undergone total pancreatectomy [8▪▪,9,10▪,11]. Thus, in chronic pancreatitis patients, the discordance between technical success in resolving a pancreatic anatomical abnormality and the lack of an expected improvement in pain can be accounted for by the presence of these neurogenic abnormalities.

Generally speaking, the target anatomy for endoscopic therapy is large duct disease, albeit there are limited epidemiological studies looking at its prevalence. Ductal dilation to at least 5 mm was

Table 1. Endoscopic interventions for pain in chronic pancreatitis

Intervention	Results based on systematic review and meta-analysis	Sham comparison	Technical success	Pain response	Recommended by guidelines[a]
ESWL & ERCP for MPD stones	Yes	No	70.7%[b]	52.7%[b]	Yes
ERCP and stenting for MPD strictures	Yes	No	85–95%[b]	32–68%[b]	Yes
D-SOP with EHL/laser lithotripsy for MPD stones	No	No	90%[c]	Not reported	No, only recently described, insufficient data
EUS-guided MPD drainage	No	No	100%[c]	82–92%[c]	Yes, in cases of failed ERCP and altered anatomy
EUS-guided celiac plexus block	Yes	No	100%[b]	51–59%[b]	No (only recommended after alternative methods for managing pain have failed)
EUS-guided pseudocyst drainage (plastic stents)	Yes	No	97%[b]	Composite endpoints reported	Yes (optimal prosthesis unknown)
EUS-guided pseudocyst drainage (LAMS)	Yes	No	94%[b]	Composite endpoints reported	Yes (optimal prosthesis unknown)

D-SOP, digital single-operator pancreatoscopy; EHL, electrohydraulic lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography; ESGE, European Society of Gastrointestinal Endoscopy; ESWL, extracorporeal shock wave lithotripsy; EUS, endoscopic ultrasound; LAMS, lumen apposing metal stents; MPD, main pancreatic duct.
[a]Guidelines include: consensus guidelines on managing pain in chronic pancreatitis; ESGE guidelines on managing chronic pancreatitis; international consensus guidelines on indications for interventional EUS.
[b]Results based on meta-analysis.
[c]Results bases on limited small retrospective studies.

present in only 30% of all patients with calcific chronic pancreatitis at a single large tertiary referral center [12]. The population of patients who may benefit from endoscopic decompression is therefore limited, underscoring the importance of developing effective treatment options for those with small duct disease.

ASSESSMENT OF PAIN OUTCOMES

An important consideration when assessing pain outcomes after chronic pancreatitis treatment is the sham effect. The EPISOD trial was one of the first studies in interventional endoscopy to employ a comparative sham arm [13▪▪]. Its results changed the management of sphincter of Oddi dysfunction by demonstrating that the sham effect of endoscopic retrograde cholangiopancreatography (ERCP) in this cohort is substantial. Improvement in the primary composite pain outcome was seen in 37% of the sham group (no sphincterotomy) as compared with 23% of the interventional group (sphincterotomy). To date, there are no sham-controlled trials in chronic pancreatitis endotherapy and the true sham effect on pain outcomes in chronic pancreatitis remains unknown. A meta-analysis of 55 randomized controlled trails (RCTs) of intervention (surgical, endoscopic and percutaneous) vs. sham for the management of a range of conditions demonstrated no difference in outcomes between intervention and sham for the management of chronic pain [14▪▪]. This study estimated that the nonspecific – or sham – effect, accounted for 78% of the active benefit in chronic pain conditions. This phenomenon is also widely recognized as the placebo effect in nonintervention trails, which accounts for 40% of the active treatment benefit in chronic pain conditions [15]. The importance of the sham effect is an increasingly recognized entity in evaluating outcomes in chronic pain and along with neuropathic pain, must be accounted for when assessing pain outcomes in chronic pancreatitis. Moving forward, sham and placebo controlled trials are critical in developing truly salutary interventions for chronic pancreatitis pain.

ENDOSCOPIC MANAGEMENT OF MAIN PANCREATIC DUCT OBSTRUCTION

Impaired pancreatic ductal drainage due to stones or strictures is the primary target of most endoscopic interventions in chronic pancreatitis. Two large observational studies evaluating response to ERCP in chronic pancreatitis reported a long-term clinical success, defined as complete pain relief, of 51–60% [16,17]. This was discordant with the reported technical success rate, which stood at 85–86% in these studies. Focusing on the proper patient-centered outcomes and accounting for the sham effect is not only important to ensure that chronic pancreatitis patients – who are often desperate for relief – are only subjected to the risks of truly beneficial procedures, but also to contain the soaring costs of endoscopic management for chronic pancreatitis [18].

Main pancreatic duct stones

The majority of small MPD stones (<5 mm) can be removed by ERCP with pancreatic sphincterotomy and standard stone extraction maneuvers [19▪]. In contrast, mechanical clearance of larger MPD stones (≥5 mm) using the standard approach is associated with a high failure rate [19▪]. There is limited enthusiasm for mechanical lithotriptsy to remove large MPD stones, owing to a three-fold increased rate of complications as compared with its use in the biliary system [20].

Digital single-operator cholangioscopy combined with electrohydraulic lithotripsy (EHL) or laser lithotripsy has proven to be very effective for complex common bile duct stones [21▪]. Similarly, a recent multicenter experience of 109 patients demonstrated that digital single-operator pancreatoscopy (D-SOP) combined with EHL or laser lithotripsy was 90% effective in clearing MPD stones [22]. Stone clearance was achieved in 73% of patients in a single session and only six patients in this study required extracorporeal shock wave lithotripsy (ESWL). Accounting for the inherent limitations of retrospective self-reported data, D-SOP combined with EHL or laser lithotripsy appears to represent a viable option for larger MPD stones that are accessible with a pancreatoscope. In our practice, we preferentially perform D-SOP–EHL for stones less than 1 cm that cannot be removed by standard extraction techniques but can be reached with the pancreatoscope. In some cases, an antecedent period of pancreatic stent placement is necessary to dilate the downstream pancreatic duct and provide sufficient working space for stone access.

ESWL is associated with fragmentation of large MPD in up to 100% of cases, allowing for either spontaneous passage of the fragments or clearance during subsequent ERCP [19▪]. ESWL combined with ERCP for clearance of MPD stones was associated with a technical success rate of 70.7% and complete resolution of pain in 52.7% in a meta-analysis of 27 studies [23]. The study also demonstrated improved quality of life indices in treated patients. An important consideration is that only six

included studies were prospective and none had a sham arm. Nevertheless, the European Society of Gastrointestinal Endoscopy recommends ESWL to fragment MPD stones at least 5 mm followed by ERCP with stone extraction [19▪]. In clinical practice and in most of the published literature on the use of ESWL, it is combined with ERCP, however two retrospective studies have demonstrated that ESWL alone, without ERCP, may provide long-term technical success and pain relief in 70–88% and 78% of patients, respectively [24,25]. A single European RCT enrolling 55 patients showed no difference in resolution of pain at 2 years between ESWL and ERCP vs. ESWL alone (45 vs. 38%) [26]. These findings have not been validated in the 11 years since the study's publication and the authors acknowledge that over 300 patients would be required for an adequately powered comparative effectiveness study. Given the associated logistical difficulties in the United States, we generally reserve ESWL for stones more than 1 cm or those for which pancreatoscopic access is not feasible.

Main pancreatic duct strictures

In a multicenter retrospective study of over 1000 patients undergoing endoscopic treatment of chronic pancreatitis, MPD strictures were present in 79%, making it the most common indication for decompression [27]. Evaluation of a new MPD stricture for underlying malignancy must always be considered due to increased risk of pancreatic cancer in chronic pancreatitis [28].

The frequently employed modern definition for technical success in treating MPD strictures is: 'complete runoff of contrast material and the ability to pass an inflated extraction balloon through the stricture' [29,30▪]. The historically reported technical success for treating MPD strictures is high (85–95%), but similar to MPD stones, long term pain outcomes are less impressive, with compete relief reported in only 32–68% [31]. Another challenge is the durability of treatment as up to 38% of strictures recur at 2 years [32].

Management of MPD strictures typically involves ERCP with pancreatic sphincterotomy, balloon dilation, and plastic stent placement across the stricture, aiming with time to upsize to larger or multiple stents. Ten French diameter plastic stents have been associated with a lower rate of occlusion and are recommended if the stricture can accommodate their diameter [19▪]. Stents are typically exchanged every 2–3 months due to the risk of occlusion, which can result in a recrudescence of pain and occasional suppurative pancreatic duct infection. Ongoing stent exchanges are recommended for at least 1 year as shorter periods of treatment are associated with inferior outcomes [19▪,33].

Since this approach is time and effort intensive as well as costly, there is increasing interest in metallic and biodegradable stents. As in the treatment of benign biliary strictures, for which fully covered self-expanding metallic stent (fcSEMS) have demonstrated similar efficacy to plastic stents with faster stricture resolution and fewer ERCPs [34], the larger diameter of metallic stents may allow a longer exchange-free dwell time, promoting stricture remodeling after the first ERCP. Indeed, case series have suggested that fcSEMS may be safe and effective in the pancreatic duct [35]. A new 6-mm fcSEMS designed for the MPD was associated with successful stent deployment in 100% of cases, stricture improvement on fluoroscopy in 83.3%, and long-term reduction in pain scores in 72% [29]. To prevent migration, which was observed in two out of 11 patients during a pilot study, plastic stents were placed within the fcSEMS [36]. Stents were removed at a median of 7.5 months without any cases of migration and a low reported complication rate. Pancreatic duct sidebranches, however, are occluded by the fully covered prosthesis and thus progressive small duct and parenchymal disease remains a conceptual concern. Additional prospective cohort studies are needed to elucidate the role of fcSEMS for chronic pancreatitis-induced pancreatic duct strictures.

Biodegradable pancreatic stents, designed to disintegrate in 3–6 months, with a similar design and delivery mechanism to an uncovered SEMS, were tested in a pilot study of 19 patients who failed conventional endoscopic management for MPD strictures [30▪]. Stricture resolution occurred in 58% of cases, and 53% of patients required no further endoscopic intervention for pain at 1 year. Complications included two stent occlusions, one stent disintegration at deployment, one case of cholecystitis, and one episode of abdominal pain requiring admission. Although these results could be perceived as disappointing, the study enrolled patients with recalcitrant MPD strictures that had failed prior endoscopic therapy. The use of biodegradable stents and fcSEMS have the potential for significant cost savings by reducing the need for repeat ERCPs. More data are required to determine if fcSEMS and biodegradable stents can supplant plastic stents for treating MPD strictures.

Endoscopic ultrasound-guided pancreatic duct drainage

In cases of unsuccessful cannulation or altered anatomy, EUS-guided access to and drainage of the MPD

is currently recommended as the next step by interventional EUS consensus guidelines [37▪▪,38,39]. This approach is particularly useful in chronic pancreatitis patients with varices due to underlying splenic/portal vein thrombosis, limiting surgical options. In a large series of EUS-guided drainage procedures among a mixed cohort of 94 patients with an obstructed MPD, technical success at draining the MPD was 100%, mean procedure time was 21 min, and resolution of abdominal pain occurred in 82% [40]. A new single pigtail plastic stent developed for use in the MPD was reported on by Matsunami *et al*. [41] in a mixed cohort containing only six chronic pancreatitis patients, with 92% of patients reporting resolution of symptoms on follow-up. A limitation of this study is that stent replacement was required every 3–4 months and 24% of patients had spontaneous stent dislodgement during the first year. A modified fcSEMS utilized for transmural drainage, with proximal and distal antimigration flanges has been described in a cohort containing chronic pancreatitis and recurrent acute pancreatitis patients [42]. Technical success was 100%, improvement in pain scores by at least 50% occurred in 92% of patients and 44% of patients stopping analgesic pain medication. A median stent patency of 4.5 months was reported, slightly above that expected for plastic stents.

EUS-guided pancreatic duct drainage offers an important treatment option in patients who have failed conventional ERCP or have altered anatomy. As experience grows and dedicated tools are developed, this approach will likely play a growing role in managing this difficult to treat patient population. For the time being, consensus guidelines recommend that EUS-guided drainage only be performed by expert endoscopists at tertiary centers due to its high level of technical complexity and the associated complication rate of 20% [37▪▪,38,39].

Endotherapy vs. surgery

Two RCTs have compared surgical with endoscopic decompression in chronic pancreatitis [43,44]. Up front surgical decompression was associated with higher levels of complete pain relief (34–40% vs. 15–16%) at 2–5-year follow-up. Longer term follow of the Dutch study comprising 39 patients reported a high rate of crossover to surgery (47%) in the endoscopy arm and surgical patients required less total procedures (median 4 vs. 12) [45▪]. Improvement in quality of life indices favoring surgery and complete pain relief at 24 months, however, were no longer significant at 79 months. Surgery for chronic pancreatitis was associated with a three times higher complication rate than endoscopy in a study evaluating over 20 000 inpatients with chronic pancreatitis [46]. A small retrospective study of MPD strictures showed that narcotic independence after lateral pancreaticojejunostomy is more likely to occur in patients who become narcotic independent following ERCP [47]. Endoscopic response thus could be used as a selection tool for surgery. However, if patients respond to endoscopic therapy, it is unclear if surgery as opposed to ongoing endotherapy is the best treatment option.

Patients with a single stone or stones in the head of the pancreas have a higher rate of MPD clearance with nonsurgical approaches [48,49]. Failure of conventional endoscopic therapy to clear the MPD of stones has been associated with a dilated duct (>8 mm) and pancreatic stones at least 12 mm [50]. In our opinion, endoscopic management for pancreatic duct stones should be considered first for patients with a single stone and those located in the head. For patients with more complex disease, a multidisciplinary approach, considering local expertise is ideal prior to deciding on surgical or endoscopic decompression.

ENDOSCOPIC ULTRASOUNDED-GUIDED CELIAC PLEXUS BLOCK

CPB targets the nerves supplying the nociceptive afferent signals from the pancreas with a local anesthetic and steroid. EUS delivery has emerged as the preferred method for CPB due to better pain response and patient preference [51,52]. Although the combination of local anesthetic and steroid is commonly employed, no incremental benefit was demonstrated by adding steroid to local anesthetic in a small RCT [53]. Although targeting the celiac ganglia may be conceptually superior as shown in celiac plexus neurolysis for cancer pain, existing data for CPB suggest that a diffuse injection above the superior mesenteric vein may produce more favorable pain outcomes [54–56]. Duration of pain response is limited to a median of only 10 weeks with no clear benefit associated with repeated injections in those who do not initially respond [57]. The results of CPB for pain relief are substantially less impressive then those reported for neurolysis, with meta-analyses demonstrating disappointing response rates of 51–59% [58▪,59]. Clinical practice guidelines recommend against CPB as a first-line treatment since the overall efficacy is unclear due to the lack of sham controlled trails. In addition, the benefits are only short lived and significant complications are observed in up to 40% of cases, including acute worsening of pain, diarrhea, and hypotension [60].

ENDOSCOPIC MANAGEMENT OF PANCREATIC PSEUDOCYSTS

Pancreatic pseudocysts occur in 20–40% of chronic pancreatitis patients over the course of their disease [61]. Drainage should be restricted to those with clinically important sequelae such as abdominal pain, infection, gastric outlet obstruction, early satiety, weight loss, or jaundice [19▪]. For pancreatic pseuodocysts, endoscopic management is preferred to surgery based on clinical trial data and is guideline recommended on the basis of its high success rate, lower mortality, lower morbidity, and reduced cost [19▪,62,63,64▪].

Pancreatic pseudocysts associated with chronic pancreatitis can be managed by transapillary or transmural (transgastric or transduodenal) drainage, or both [19▪]. In general, collections smaller than 5 cm in size are ideal for treatment via ERCP with transpapillary pancreatic stent placement because they are likely to respond and may not provide sufficient working space for transmural drainage. Limited data suggest that bridging the pancreatic duct leak with the stent if possible increases the likelihood of success [65,66].

For larger pseudocysts, RCT data demonstrate that EUS-guided transmural drainage is superior to endoscopic drainage alone and has the added benefits of identifying and avoiding puncture of interceding vascular or luminal structures [62,67]. Traditionally, the cystgastrostomy or cystduodenoscopy fistula tract is maintained by double pigtail stents. Recently, however, fcSEMS and lumen apposing metal stents (LAMS) have become popular for this indication based on their ease of use, reduced procedure time, and larger lumens. A small pilot RCT showed shorter procedure times associated with fcSEMS but no difference in outcomes, whereas a larger retrospective comparative effectiveness study demonstrated improved clinical outcomes and reduced adverse events associated with biliary fcSEMS in 230 patients with pseudocyst [68,69]. The 'hot' or electrocautery assisted LAMS reduces procedure time even further because the access and deployment platform allows near simultaneous cyst puncture and stent deployment using the same delivery system without the need for prior fine needle puncture and wire placement. However, some experts prefer antecedent puncture and wire placement which respectively allow the exclusion of blood in the cyst and endoscopic salvage of an errantly deployment stent. A recent cost-effectiveness analysis, incorporating meta-analytic data, demonstrated that while both prostheses are clinically effective (97% plastic stents vs. 94% LAMS), plastic stents are more cost-effective at 6 months (US$10 403 vs. 18 129) [70]. Additional studies are necessary to define the optimal prosthesis for the drainage of pancreatic pseudocysts, which do not contain debris or require entry into the cavity.

Larger cysts with associated pancreatic ductal disruption have a higher likelihood of recurrence after transmural drainage alone and may require adjunctive ERCP with transapillary drainage [37▪▪,71]. It has been observed, however, that transmural drainage alone may provide mechanical closure of the leak in some cases and a fraction of pseudocysts are no longer in communication with the pancreatic duct once they become mature. The routine addition of transpapillary drainage to transmural drainage did not improve pseudocyst resolution in a retrospective study including 375 patients [72]. Although these data support the concept that not every pancreatic fluid collection requires adjunctive transpapillary drainage, some collections do mandate ductal source control, especially those associated with obstructive chronic pancreatitis. A better understanding of the clinical and radiographic predictors of a persistent leak and the role of magnetic resonance cholangiopancreatography in clinical decision-making is needed.

CONCLUSION

Neuropathic pain with associated nervous system alterations and the sham effect of endoscopic intervention help to explain the discordance between the technical and long-term clinical success of endotherapy for chronic pancreatitis. Based on existing guideline recommendations, ERCP ± ESWL for management of pancreaticolithiasis, ERCP with pancreatic duct stenting for MPD strictures, and transmural or transpapillary drainage for symptomatic pseudocysts should be considered first-line for the management of painful chronic pancreatitis in the appropriate clinical setting. The efficacy of CPB is unclear and is not recommended by multiple guidelines as first-line treatment. EUS-guided MPD access/drainage and D-SOP with EHL/laser lithotripsy are emerging procedures that have expanding potential in managing chronic pancreatitis, provided long-term outcomes prove favorable and endoscopic innovation in these areas continue.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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