# What is the Evidence for Endoscopic Therapy for Pain Relief in Chronic Pancreatitis?

Azreena Burukan, Joshua Skeens, Andrew Butler, Emily Vickery, Emily Tone, Jack Tyrrell, Niall O'Sullivan and Donal O'Connor

## Background

The objective of this study was to evaluate the efficacy of endoscopic therapy for pain relief in patients suffering from chronic pancreatitis. Following an initial search, 25 papers met the inclusion criteria and were selected and reviewed.

## Introduction

Chronic pancreatitis (CP) has two fold increased prevalence of 11.7 to 13.4 per 100,000 population (Duggan et al., 2016), and requires national attention. The highly variable levels of pain exhibited by patients (Manes et al., 1994) has led to investigation into the efficacy of pain management for CP.

Endoscopic therapy in pain management of CP involves Endoscopic Retrograde Cholangio-pancreatography (ERCP) and Endoscopic Ultrasound (EUS) procedures. All procedures require the use of an endoscope, which is passed through the mouth, oesophagus, stomach, and into the duodenum where it can access the Common Bile Duct (CBD) and Main Pancreatic Duct (MPD). ERCP involves the injection of contrast to visualise the biliary tree and pancreas for endoscopic sphincterectomy (CBD or MPD sphincter) and to insert duct stents for dilatation of strictures and the removal of calculi in the ducts. Extracorporeal shock wave lithotripsy (ESWL) is promoted for calculi larger than 5 mm, which encompass the use of magnetic waves to break down calculi for removal via ERCP. EUS can also be used for coeliac plexus block in order to achieve pain relief.

In this paper, a systematic review was performed to assess therapies for pain relief in CP. The objectives were: - 1) to assess current literature regarding the authenticity of endoscopic therapy and 2) whether other forms of intervention showed a greater efficacy in pain relief, with the aim of attaining the highest levels of evidence (IA) and recommendations (A), as stated in "The Oxford levels of Evidence 2". This paper analysed 25 papers; three were randomized control trials (IB), with the remaining papers representing targeted studies exhibited level IIB evidence. Therefore, through the homogeneity of the results provided below, this paper falls under level IIA evidence and Grade B recommendation.

## Chronic pancreatitis

Aetiology

CP is a chronic inflammatory disease of the pancreas that leads to fibrosis and scarring of pancreatic parenchymal tissue and pancreatic ducts. The disease progression typically causes pain, with Goulden et al. (2013) recording it as the primary symptom for 80-90% of recorded chronic pancreatitis hospital admissions.

Bornman et al. (2003) highlighted the large variation in the level of pain witnessed by patients with similar anatomical and morphological changes brought about by the disease, thereby demonstrating the classification of the disease as a complex pain syndrome. The pain is noted as radiating from the epigastric region to the back, with acute severe episodes. Most CP patients complain of postprandial pain. Pain as a result of CP can be due to anatomical reasons, such as: enlargement of pancreatic and common biliary duct, due to calcifications, which (Figure 1) can lead to increased intraductal pressure causing hypertension and ischemia, due to bile duct or pancreatic duct stenosis. Pain can also be caused by the involvement of neuronal tissues, as a result of inflammation of visceral tissue in disease progression, leading to increased nociceptive sensitisation of the tissue (Hoogerwerf et al., 2001). Furthermore, there has been a promotion that defective centres of the brain involved in the regular immune response mediated by inflammation cause further sensation of pain and visceral inflammation (Fregni et al., 2007). The unpredictable origin of pain makes further research in this area a necessity.

Chronic alcohol abuse is the most common cause of CP (Tsujimoto et al. 2008). It is theorised that the oxidation of ethanol to acetaldehyde activates pancreatic stellate cells prematurely resulting in increased oxidative stress and signalling of the fibrogenic pathway (Pezzelli et al., 2009). Other causes include familial pancreatitis, autoimmune diseases, and cystic fibrosis. It can also be idiopathic (PubMed Health, 2017).

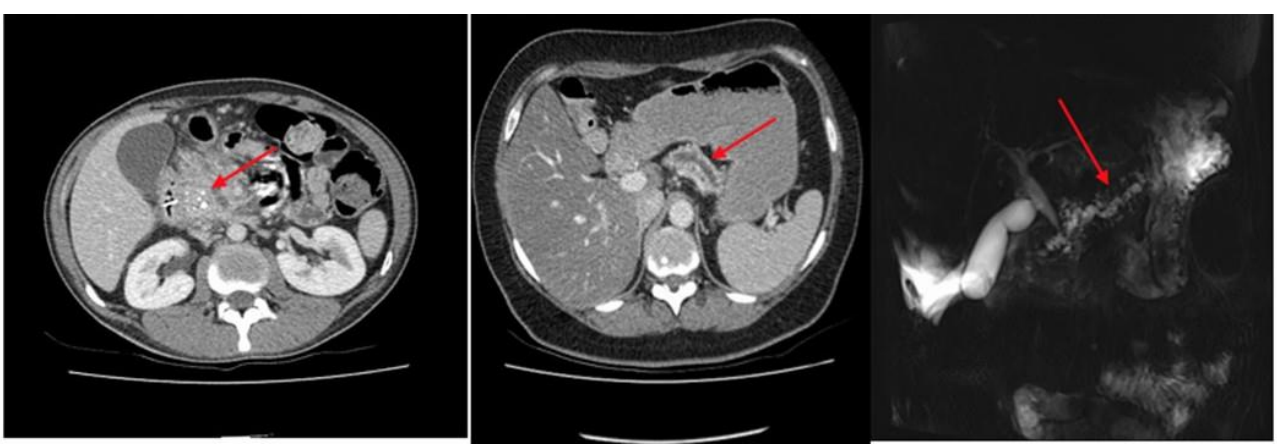

Figure 1. Computer Tomography (CT) showing calcifications and enlarged head of pancreas (left), dilated MPD and atrophic pancreas (centre) and dilated tortuous main pancreatic duct (right). Courtesy of Dr. Donal O'Connor; Senior registrar.

Complications

CP encompasses both mechanical and functional complications. Mechanical complications include chronic pseudocysts that develop in 10% of patients with CP, gastric outlet obstruction, and common bile duct stenosis (D Freedman et al., 2017). Less commonly reported complications include post-Endoscopic cancer.

Chronic pain is the most common complication associated with CP (EL, 1998). It can be the most challenging complication to treat (Gachago et al, 2008) and is associated with poorer psychological quality of life and endorsement of depressive symptoms (Balliet et al., 2012).

The mechanism underlying the pathogenesis of CP pain is still not precisely known. The most widely accepted "Plumbing" Theory states that fibrotic obstruction causes an increase in intraductal or parenchymal pressure (Schou Olesen et al., 2015),similar to "compartment-like syndrome". Patel et al., (1995) documented decreased blood flow and increased acidic metabolites of an animal CP model upon stimulation, which could account for pain. Swelling of the pancreatic head can also result in hypersensitisation of the celiac plexus and hence this is a common site for neurological blockade therapy. (Schou Olesen et al., 2015). Numerous other theories are summarised in Figure 2.

Pain Relief

As discussed above, we will be focusing on pain relief for CP via ERCP and EUS. There are, however, other forms of treatment such as pharmaceutical, neurological, and surgical treatments.

Proton pump inhibitors are thought to reduce intra-pancreatic pressure by suppressing acid secretion. Yoo J. et al (2012) found that the use of pantoprazole shorten hospital stays as well as the time taken for pain relief to take place.

It is advised to cease all alcohol intake completely, if possible, to avoid recurrent attacks. Opioid analgesics can also be used to relieve pain in chronic pancreatitis. Wilder-Smith et al (1999) found that 67% of patients rated their analgesia 'excellent' after 4 days of treatment with tramadol, but this amount was significantly lower in patients taking morphine (20%).

Neuropathic analgesics such as gabapentin and amitriptyline may also be used, although relief from pancreatic pain wouldn't be their primary indication for use. Neurological treatment includes endoscopic ultrasound coeliac plexus block (EUS-CPB). Santosh D. et al (2009) found that 70% of patients reported improved pain scores after undergoing EUS-CPB with bupivacaine and Triamcinolone.

There are a number of surgical interventions including the classic Whipple procedure to the newer duodenum preserving procedures developed by Frey and Beger, among others. In an 85 patient study, patients underwent either a classic Whipple procedure or a duodenum preserving procedure for pain in chronic pancreatitis. 67% of the patients who underwent the whipple procedure were pain free 66 months postoperatively and similarly 67% of patients who underwent the Frey and Beger procedure were pain free for the same length of time on average.

## Method

In order to gather evidence for the use of endoscopic therapy for pain relief in CP, we conducted a systematic literature review and focused on recently published guidelines for management of pain in CP. In accordance with HaPanEU guidelines, published in 2016, studies were sourced through the online search engine, PubMed. The terms used when searching the database were: chronic pancreatitis, pain management, and endoscopy. We also included current reviews from the Lancet, the World Journal of Gastroenterology, Elesivier, Science Direct, Cochrane library, Gastroendo News and the Gastrointestinal Endoscopy Clinics of North America. For the purpose of our investigation we included 25 papers, which studied the efficacy of endoscopic intervention in the management of pain in chronic pancreatitis. We were particularly interested in those, which compared their results using the Izbicki pain score (Izbicki et al. 1998). We excluded literature which discussed acute pancreatitis and pseudocyst drainage, and those which did not focus on management of chronic pain. We excluded all papers which discussed biliary obstruction. Due to limited material available we decided to exclude systematic literature reviews from our study material. All material used for the purpose of this review is lawfully sourced and referenced appropriately.

## Results

A systems-review of 25 papers evaluated the use of endoscopy in the treatment of chronic pancreatitis for pain relief as shown in Table 1. The total number of patients is 3892. Pain relief averaged 70.8% through endoscopy treatment where the highest rate of pain relief achieved was 94% while the lowest was 30.4%.
The endoscopic treatment that was looked in this study ranges from EUS, ERCP and ESWL. Significance on pain relief between the different types of endoscopic treatment cannot be commented.

Pain relief was not achieved in about 28.1% where the highest rate that failed to relieve pain was 69.9% and lowest was 6%. Further treatment is required in 41% of patients, in which 25.2% underwent surgery, 44.53% of the patients had repeated endoscopic treatment, and 30.25% had to use analgesia to control their pain. 27% of patients had an endoscopic- related complication.

According to Cervero F and Laird JSM 1999, the pain that is experienced by patients with CP is abdominal pain that radiates to the back and hypogastric region. The pain is exacerbated when they eat, hence they avoid eating. The pain does not resolve and is constant. They get unexpected pain suddenly and when this is not elevated by analgesia, patients seek medical attention. When endoscopic intervention does not relieve this pain, then further intervention is needed.

## Discussion

In a study by Dite P et al, 2003, complete relief was seen in 37% of the patients that underwent surgical intervention whilst only 14% was seen in endoscopic intervention. Cahen DL et al and Ahmed AU et al ., 2012 found long-term pain relief was higher amongst surgical patients 5 years post intervention compared to endoscopic patients. Longitudinal studies conducted by Ammann RW et al, 1984, 1994, showed that 40-75% of patients require surgery after endoscopic intervention due to continuing pain.

Rutter et al. (2010) reported endoscopic therapy in treatment of chronic pancreatitis improved overall quality of life. This included reduced hospital stays, reduced follow up procedures and a longer period between relapsing of symptoms in patients. Although surgery was deemed to have greater clinical outcomes with regard to improving overall quality of life (Rutter et al. 2010). Based on these findings and considering pain management in chronic pancreatitis as a whole, it would therefore be logical to assume surgery as a first line therapy in all patients with chronic pancreatitis. However, there are instances where endoscopic therapy supersedes all other treatments and these

are mainly due to an obstacle in the main pancreatic duct (Dumonceau 2010).

One way pain relief can be achieved is through endoscopic ultrasound (EUS)-guided celiac plexus block which is often reserved and used in patients with chronic pancreatitis. According to Le Blanc et al. 2009, EUS guided celiac plexus block gives an average pain relief for about 4 months and has an overall response rate of 50-55%, which is deemed to be short term pain relief. Puli SR et al. 2009 mentioned that the rate of complication of the neurolysis is very low and though it depends on technique about 60% of pain relief is seen. Ahmed Ali et al, 2015 and Cahen DL et al, 2007 agree that treatment given surgically has a better outcome compared to an endoscopic approach. Although there are various surgical methods that are available for CP, Diener MK et al. 2017 found that the pancreaticoduodenectomy and the duodenum preserving pancreatic head resection procedures have similar outcomes for pain relief.

Pancreatic Calculi can deposit in the Main Pancreatic Duct (MPD), its side branches or parenchyma and cause these areas to become hypertensive, potentially leading to pancreatic ischaemia and resulting in severe pain in some cases (Tandan et al. 2013). Three or more stones blocking the MPD and a Pancreatic Duct stone (PDS) with a diameter of ≤ 10mm indicates endoscopic treatment. Small calculi can be extracted by ERCP following initial fragmentation by Extracorporeal Shock wave lithotripsy (EWSL) to <3mm diameter (Liu et al. 2010). ESWL is a high intensity magnetic shock wave treatment performed that shatters pancreatic stones, and stones >5mm are indicated for its use (Tandan et al. 2010). Some studies suggest that ESWL is effective as a sole therapy for pancreatic caliculi, with higher costs and longer hospital stays associated with the adjunctive therapy (Tandan et al. 2013)

A prospective cohort study carried out over a 15 year period made an incredibly strong case for the use of ERCP to decompress the main pancreatic duct. Gabrielli et al (2005) achieved sufficient drainage and"complete clearance" of the MPD through the placement of these plastic stents- with a reduction in the diameter of the MPD and a complete relief of pain achieved in all patients. Only four patients were admitted to surgery after relapses of pain from the procedure, and there were 10 relapses of pain related to the placement of plastic stents. A more recent systematic literature review validates the findings of Gabrielli's study by suggesting that MPD strictures be treated with single large plastic stents for "1 year". In the case of unsuccessful ERCP, EUS-guided drainage of the pancreatic duct is recommended (Seican and Vultur 2014). Dumonceau stated that endoscopic therapy -ERCP with EUS-guided drainage of the MPD if unsuccessful - is a "first line therapy for painful chronic pancreatitis", when the MPD is obstructed. Dumonceau also recommends that in the case of an unsatisfactory clinical response, an MDT approach be adopted with the potential for surgery to be carried out on the patient at this stage.
As the role of endoscopic therapy has not yet been well defined in both treatment and control of pain in CP, one must consult the most recently published guidelines before making a clinical decision due to the invasive nature of the procedure. The Spanish Pancreatic club outlines how a clinician must be aware of the various limitations of endotherapies (E. de Madaria et al. 2010):

(i) There is no randomised control trial comparing pharmacological vs endoscopic or surgical treatment of pain in CP

(ii) It is difficult to ascertain how effective EDT in treating pain long term, as the long term pain profile with or without EDT is not well defined (Ammann and Muellhaupt, 1999).

(iii) Endoscopic therapy has to be carried out by extremely qualified and skilled clinicians. This challenge would potentially be avoided administering medication.

Izbicki JR et al. 1998 argues the reduction of pain in patients who received endoscopic treatment is because the treatment procedure was unclear and there was no evidence that pain was measured. There are only 2 randomised controlled studies in the literature comparing endoscopic therapy with surgical drainage of the pancreatic duct in CP. (Table 1).

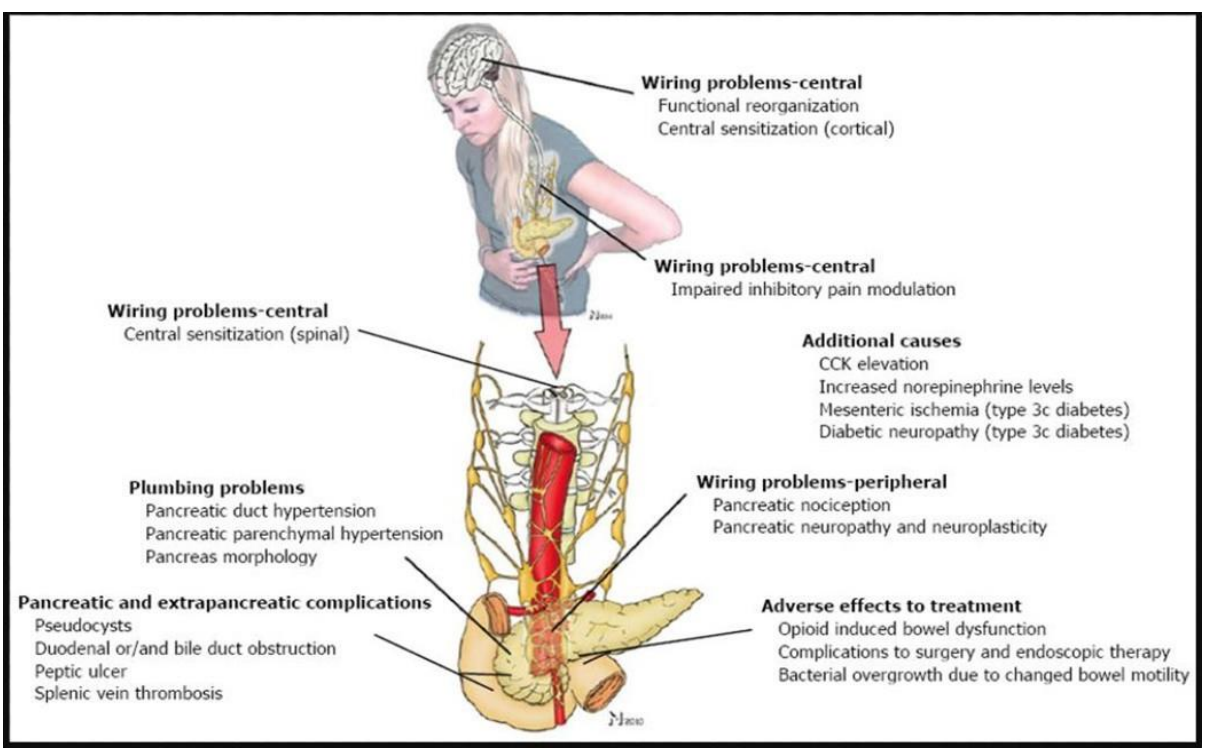


Figure 2. Pain mechanisms in chronic pancreatitis (Poulsen, 2013)

Table 1 - Characteristics of 25 included studies.

| Study title | Author | Year of publication | Country of publication | Type of study | Level of evidence |
|---|---|---|---|---|---|
| Endoscopic versus Surgical Drainage of the Pancreatic Duct in Chronic Pancreatitis | Cahen et al | 2007 | Netherlands | Randomised Trial | IB |
| Endoscopic stenting for pain relief in chronic pancreatitis: Result of a standardized protocol | Ponchon et al | 1995 | France | Prospective study | IIC |
| Stenting in severe chronic pancreatitis: result of medium-term follow up in seventy-six patients | Cremer et al | 1991 | Belgium | Prospective study | IIB |
| A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis | Dite et al | 2003 | Czech Republic | Prospective Randomised Trial | IB |
| Treatment of pancreatic stones with extracorporeal shock wave lithotripsy: results of a multicentre survey | Inui et al | 2005 | Japan | Retrospective Multicentre study | IIB |
| Long-term clinical outcome after endoscopic pancreatic ductal drainage for patients with painful chronic pancreatitis. | Delhaye et al | 2004 | Belgium | Retrospective Study | IIB |
| Long-term results of extracorporeal shockwave lithotripsy and endoscopic therapy for pancreatic stones | Tadenuma et al | 2005 | Japan | Prospective Study | IIB |
| Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi - a large single centre experience | Tandan et al | 2010 | India | Prospective Study | IIB |
| Long Term outcomes associated with pancreatic extracorporeal shock wave lithotripsy for chronic calcific | Seven et al. | 2012 | United States of America | Retrospective Chart Review | IIB |
| Long term follow up of patients with chronic pancreatitis and pancreatic stones treated with extracorporeal shock wave lithotripsy | Adamek et al. | 1999 | Germany | Prospective Study | IIB |
| Prospective evaluation of morphology, function, and quality of life after extracorporeal shockwave lithotripsy and endoscopic treatment of chronic calcific pancreatitis | Brand et al. | 2000 | USA | Prospective Study | IIB |
| Long-term Outcomes of Endoscopic vs Surgical Drainage of the Pancreatic Duct in Patients With Chronic Pancreatitis | Cahen et al | 2011 | Netherlands | Prospective Randomised Trial | IB |
| Endoscopic Stent Therapy in patients with chronic pancreatitis: A five year follow up study | Weber et al | 2013 | Germany | Prospective Study | IIB |
| Endoscopic Treatment of Chronic Pancreatitis: A Multicentre Study of 1000 patients with long term follow up | Rösch et al | 2002 | Germany | Prospective Multicentre study | IIB |
| Ultrasound-guided extracorporeal shock wave lithotripsy of pancreatic ductal stones: six years' experience. | Johanns et al | 1996 | Canada | Prospective Study | IIB |
| Single application extracorporeal shock wave lithotripsy is the first choice for patients with pancreatic duct stones | O'Hara et al | 1996 | USA | Prospective Study | IIB |
| New modalities of treating chronic pancreatitis | Grimm et al | 1989 | Germany | Prospective Study | IIB |
| Endoscopic pancreatic stent drainage in chronic pancreatitis and a dominant stricture: | Binmoeller et al | 1995 | Germany | Retrospective Study | IIB |
| Role of pancreatic duct stenting in the treatment of chronic pancreatitis | Vitale et al | 2004 | USA | Prospective Study | IIB |
| endoscopic treatment of chronic pancreatitis | Bartoli et al | 2005 | France | Retrospective Study | IIB |
| Long-term outcome after pancreatic stenting in severe chronic pancreatitis. | Elefthiriadis et al | 2005 | Belgium | Retrospective Study | IIB |
| Interventional endoscopic therapy in chronic pancreatitis including temporary stenting: a definitive treatment? | Farnbacher et al | 2006 | Germany | Retrospective Study | IIB |

| | | | | | |
|---|---|---|---|---|---|
| Endoscopic treatment of painful chronic pancreatitis: evaluation of a new flexible multi perforated plastic stent. | Boursier et al | 2008 | France | Retrospective Study | IIB |
| Outcome following endoscopic stenting of pancreatic duct strictures in chronic pancreatitis. | Topazian et al | 2005 | USA | Prospective study | IIB |
| Endoscopic treatment of the main pancreatic duct: correlations among morphology, manometry, and clinical follow-up | Renou et al | 2000 | France | Prospective study | IIB |

Table 2 - Outcomes of studies for pain relief of CP via endoscopic therapy, including further forms of treatment

| Author | # of patients | Pain relief achieved | | | | | | | Complications after endoscopic intervention | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Yes | | No | | | | | | |
| | | # of patients | % of patients | # of patients | % of patients | Intervention | # of patients | % of patients | # of patients | % of p atients |
| Cahen et al | 39 | 21 | 53.80 | 19 | 46.10 | Converted to surgery | 4 | 10.30 | 18.00 | 46.20 |
| Ponchon et al | 23 | 7 | 30.40 | 16 | 69.60 | Use of analgesia | 14 | 60.90 | 10.00 | 43.50 |
| Cremer et al | 76 | 72 | 94.00 | 4 | 6.00 | Converted to surgery | 1 | 15.00 | - | - |
| Dite et al | 140 | - | 46.00 | - | 54.00 | - | - | - | - | 39.00 |
| Inui et al | 555 | 428 | 77.10 | 127 | 22.90 | Converted to surgery | 22 | 3.96 | 35.00 | 6.30 |
| Delhaye et al | 56 | 37 | 66.00 | 19 | 34.00 | Converted to surgery | 12 | 63.00 | 14.00 | 25.00 |
| Tadenuma et al | 117 | 49 | 70.00 | 21 | 30.00 | Repeated endoscopic treatment | 21 | 30.00 | - | - |
| Tandan et al | 1006 | 711 | 84.00 | 135 | 16.00 | - | - | - | 71.00 | 7.10 |
| Seven et al | 120 | 60 | 50.00 | 60 | 50.00 | Repeated endoscopic therapy and surgery | - | - | - | - |
| Adamek et al | 80 | 61 | 76.20 | 19 | 23.70 | Converted to surgery | 8 | 10.00 | 6.00 | 7.50 |
| Brand et al | 38 | 17 | 45.00 | 21 | 55.00 | Unknown | - | - | - | - |
| Cahen et al | 31 | 18 | 58.10 | 13 | 41.90 | Converted to surgery | 9 | 47.40 | 13.00 | 68.42 |
| Weber et al | 19 | 17 | 89.40 | 2 | 10.60 | Use of analgesia | 3 | 15.80 | 6.00 | 31.60 |
| Rösch. et al | 1018 | - | 65.00 | - | 35.00 | Converted to surgery | - | 24.00 | - | 40.00 |
| Johanns et al | 35 | 29 | 82.80 | 6 | 17.10 | - | - | - | - | - |
| O'Hara et al | 32 | 25 | 79.00 | 7 | 21.00 | - | - | - | - | - |
| Grimm et al | 61 | 50 | 82.00 | 11 | 18.03 | Repeated endoscopic therapy | - | - | - | - |
| Binmoeller et al | 93 | 69 | 74.00 | 13 | 14.00 | Repeated endoscopic therapy | 11 | 11.80 | 6.00 | 6.45 |
| Vitale et al | 75 | 62 | 83.00 | 13 | 17.00 | Use of analgesia | 55 | 73.30 | - | - |
| Bartoli et al | 39 | 34 | 87.20 | 5 | 12.80 | surgical treatment | 4 | 10.20 | 3.00 | 7.00 |
| Elefthiriadis et al | 100 | 62 | 62.00 | 30 | 30.00 | repeated endoscopic therapy | 34 | 34.00 | 38.00 | 38.00 |
| Farnbacher et al | 98 | 65 | 66.00 | 33 | 34.00 | Repeated endoscopic therapy and surgery | 39 | 39.70 | 31.00 | 31.60 |
| Boursier et al | 13 | 11 | 85.00 | 1 | 7.69 | Repeated endoscopic therapy | 1 | 7.69 | 4.00 | 10.00 |
| Topazian et al | 15 | 13 | 87.00 | 2 | 13.00 | Repeated endoscopic therapy | - | 36.00 | - | - |
| Renou et al | 13 | 10 | 76.90 | 3 | 23.00 | - | - | - | - | - |

Table 3 - Compiled data from all 25 studies

| Criteria | Number of patients (%) |
|---|---|
| Pain relief achieved | 1928 (70.8%) |
| Pain relief not achieved | 580 (28.10%) |
| Complication | 255 (27.00%) |
| Further treatment | 238 (41.00%) |
| Surgery | 60 (25.21%) |
| Additional endoscopic therapy | 106 (44.53%) |
| Use of analgesia | 72 (30.25%) |

In Ireland, most specialists are unaware of any specific guidelines to follow in the management of CP, highlighting the caution that needs to be exercised when selecting patients for endoscopic therapy (Ní Chochubhair et al. 2016).

The National Institute for Healthcare Excellence (NICE) recommends surgical treatment before endotherapy in control of pain in CP (NICE 2010). However, main pancreatic duct strictures are to be treated with "multiple plastic stents". One study showed that strictures were resolved in 95% of patients 24-48 hours following stent removal (Nyguyen-Tang and Dumonceau 2010).

## Future Direction

When looking at future considerations for therapy in pain management of Chronic Pancreatitis, it is difficult for us to make a clinical recommendation on when to use endoscopic therapy, surgery, or pain medication, when the patient cohorts are so ill-defined due to heterogeneous nature of the condition. The aetiologies of chronic intractable pain in CP are still not fully understood, therefore the indications and guidelines for therapy are currently lacking.

Therefore, to expedite and improve our understanding on how to manage pain in CP more efficiently and cost effectively- with lower risks of morbidity and mortality, fewer complications and a higher quality of life- future clinical trials must focus on establishing the causes of pain in chronic pancreatitis. This is partly the reason why Irish gastroenterologists and those around the world are still at odds when it comes to deciding on the correct treatment protocol for each chronic pancreatitis patient. In Ireland, no study has been carried out on the "prevalence, incidence and aetiology of Chronic Pancreatitis" (Duggan 2014).

By understanding how alcohol and other risk factors are involved in the pathogenesis of Chronic Pancreatitis, e.g. by laying down of fibrotic tissue in the parenchyma of the pancreas (which can lead to Main Pancreatic Duct strictures), we will have a better knowledge on how best to manage pain in Chronic Pancreatitis. Much of the ambiguity in the two randomised controlled trials by Cahen et al and Dite et al over the preferred therapy in CP, centres on a lack of understanding of the aetiologies and pathogenesis of both pain in Chronic Pancreatitis and Chronic Pancreatitis as a whole. Taking the Dite study it was concluded that surgery is the preferred method of "long-term pain reduction" in Chronic Pancreatitis. However, it is recommended that endotherapy be offered as a first line therapy, with surgery required in the case of "failure and/or recurrence". In more recent years this method has been widely adopted as the "step-up approach"; with medication being first line, then endotherapy, and in those unresponsive to the latter methods, surgery (Windsor and Reddy 2017). Although Dite acknowledges the shortcomings of this recommendation by stating that patient selection criteria for endotherapy needs to improve in order to"maximize results", no suggestion is given as to how these patients might be appropriately stratified for treatment.

A greater understanding of the aetiologies and pathogenesis of pain in Chronic Pancreatitis would hugely ameliorate the guidelines for therapy. By knowing which procedure is best suited to each patient subgroup (classified based on aetiology and/or pathogenesis), the step-up approach would be avoided in most cases. The results would not only improve patient outcomes, but it would significantly reduce costs associated with therapy and reduce the amount of invasive procedures needed to treat pain in Chronic Pancreatitis.

## Conclusion

In conclusion, by carrying out a systems review with multiple studies, we agree that surgical route of treatment has better long term pain relief compared to endoscopic intervention basing our evidence mainly on two randomised controlled trials. Furthermore, endoscopic therapy has a high failure rate and often necessitates further surgical management. A multidisciplinary approach is best advised when selecting the appropriate patients for endoscopic therapy in pain relief for chronic pancreatitis.

## References


Adamek, H., Jakobs, R., Buttmann, A., Adamek, M., Schneider, A. and Riemann, J. (1999). Long term follow up of patients with chronic pancreatitis and pancreatic stones treated with extracorporeal shock wave lithotripsy. Gut, 45(3), pp.402-405.

Ahmed Ali U, Pahlplatz JM, Nealon WH, van Goor H, Gooszen HG, Boermeester MA. Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. Cochrane Database Syst Rev 2015; 3: CD007884.

Ammann RW, Akovbiantz A, Largiader F, Schueler G: Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. Gastroenterology 1984;86:820–828.

Ammann RW, Muellhaupt B: The natural history of pain in alcoholic chronic pancreatitis. Gastroenterology 1999;116:1132–1140.

Balliet, W., Edwards-Hampton, S., Borckardt, J., Morgan, K., Adams, D., Owczarski, S., Madan, A., Galloway, S., Serber, E. and Malcolm, R. (2012). Depressive Symptoms, Pain, and Quality of Life among Patients with Nonalcohol-Related Chronic Pancreatitis. Pain Research and Treatment, 2012, pp.1-5.

Bartoli E, Delcenserie R, Yzet T, Brazier F, Geslin G, Regimbeau JM, Dupas JL. Endoscopic treatment of chronic pancreatitis. Gastroenterol Clin Biol 2005; 29:515-521.

Binmoeller, K.F., Jue, P., Seifert, H., Nam, W.C., Izbicki, J., Soehendra, N., Endoscopic pancreatic stent drainage in

chronic pancreatitis and a dominant stricture: long-term results. Endoscopy 1995; 27:638-644

Bornman PC, Marks IN, Girdwood AW, et al. Pathogenesis of pain in Chronic Pancreatitis: ongoing enigma. World J Surg. 2003 Nov; 27(11):1175-82.

Boursier, J., Quentin, V., Le Tallec, V., Maurin, A., Person, B., O'Toole, D., Boyer, J., Endoscopic treatment of painful chronic pancreatitis: evaluation of a new flexible multiperforated plastic stent. Gastroenterol Clin Biol 2008; 32:801-805.

Brand, B., Kahl, M., Sidhu, S., Nam, V., Sriram, P., Jaeckle, S., Thonke, F. and Soehendra, N. (2000). Prospective evaluation of morphology, function, and quality of life after extracorporeal shockwave lithotripsy and endoscopic treatment of chronic calcific pancreatitis. The American Journal of Gastroenterology, 95(12), pp.3428-3438

Cahen, D.L., Gouma, D.J., Laramee, P., Nio, Y., Rauws, E.A., Boermeester, M.A., Busch, O.R., Fockens, P., Kuipers, E.J., Pereira, S.P., Wonderling, D., Dijkgraaf, M.G., Bruno, M.J.: Long-term out-comes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology 2011;141: 1690–1695.

Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, Stoker J, Lam- eris JS, Dijkgraaf MG, Huibregtse K, Bruno MJ: Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med 2007;356:676–684.

Cremer, M., Devière, J., Delhaye, M., Baize, M., Vandermeeren, A., Stenting in severe chronic pancreatitis: results of medium-term follow-up in 76 patients. Endoscopy 1991; 23:171-176.

D Freedman, MD, PhD, S. (2017). Overview of the complications of chronic pancreatitis. [online] Uptodate.com. Available at: https://www.uptodate.com/contents/overview-of-the-complications-of-chronic-pancreatitis [Accessed 13 Nov. 2017].

Delhaye, M., Arvanitakis, M., Verset, G., Cremer, M. and Devière, J. (2004). Long-term clinical outcome after endoscopic pancreatic ductal drainage for patients with painful chronic pancreatitis. Clinical Gastroenterology and Hepatology, 2(12), pp.1096-1106.

Diener MK, Hüttner FJ, Kieser M, for the ChroPac Trial Group. Partial pancreatoduodenectomy versus duodenum-preserving pancreatic head resection for chronic pancreatitis: the multicentre, randomised, controlled, double-blind ChroPac trial. Lancet 2017; 390: 1027–37.

Dite P, Ruzicka M, Zboril V, Novotny I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy 2003;35: 553-8.

Duggan, S., Chonchubhair, H., Lawal, O., O'Connor, D. and Conlon, K. (2016). Chronic pancreatitis: A diagnostic dilemma. World Journal of Gastroenterology, 22(7), pp.2304-2313.

Duggan, S., O'Sullivan, M., Hamilton, S., Feehan, S., Ridgway, P. and Conlon, K. (2012). Patients With Chronic Pancreatitis Are at Increased Risk for Osteoporosis. Pancreas, 41(7), pp.1119-1124

Duggan S (2014). Malnutrition, deficiency, and nutritional practice in patients with acute and chronic pancreatitis. [Thesis], Trinity College (Dublin Ireland). School of Medicine. Discipline of Surgery, Pp18 World Health Organisation (2014). Global Status Report on Alcohol and Health: pp 170, 198, 216, 246

Dumonceau JM, Deviere J, Le Moine O, et al. Endoscopic pancreatic drainage in chronic pancreatitis associated with ductal stones: long-term results. Gastrointest Endosc 1996;43:547-55

E. de-Madaria, A. Abad-González , J.R. Aparicio, L. Aparisi, J. Boadas, E. Boix, G. de-las-Heras, E. Domínguez-Muñoz, A. Farr, L. Fernández-Cruz, L. Góme, J. Iglesias-Garcí, K. García-Malpartida, L. Guarner, J. Lariño-Noia, F. L, A. Lópe, X. Molero, O. Moreno-Pérez, S. Navarro, J.M. Palazón, M. Pérez-Mateo, L. Sabater, Y. Sastre, E.C. Vaquero, J. Martinez. (2012) The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: Part 2 (treatment), 13, 1, 18–28

EL, B. (1998). Complications of chronic pancreatitis. The surgical clinics of North Americs, [online] 69(3), pp.481-97. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2658160 [Accessed 13 Nov. 2017].

Eleftherladis, N., Dinu, F., Delhaye, M., Le Moine, O., Baize, M., Vandermeeren A, Hookey L, et al. Long-term outcome after pancreatic stenting in severe chronic pancreatitis. Endoscopy 2005; 37:223-230.

Farnbacher MJ, Mühldorfer S, Wehler M, Fischer B, Hahn EG, Schneider HT. Interventional endoscopic therapy in chronic pancreatitis including temporary stenting. Scand J Gastroenterol 2006; 41:111-117.

Gachago, C. and Draganov, P. (2008). Pain management in chronic pancreatitis. World Journal of Gastroenterology, 14(20), p.3137.

Gabrielli A, Pandolfi M, Mutignani M, Spada C, Perri V, Petruzziello L, Costamagna G (2005). Efficacy of main pancreatic-duct endoscopic drainage in patients with chronic pancreatitis, continuous pain, and dilated duct. Gastrointestinal Endoscopy, 61, 4, pp 576-581

Goulden, M. (2013). The pain of chronic pancreatitis: a persistent clinical challenge. British Journal of Pain, 7(1), pp.8-22.

Grimm, H., Meyer, W.H., Nam, V.C., Soehendra, N., New modalities for treating chronic pancreatitis. Endoscopy 1989; 21:70-74.

Hoogerwerf WA, Zou L, Shenoy M, et al. The proteinase-activated receptor 2 is involved in nociception. J Neurosci 2001; 21: 9036–9042

Inui K, Tazuma S, Yamaguchi T, O'Hara H, Tsuji T, Miyagawa H, Igarashi Y, Nakamura Y, Atomi Y. (2005) Treatment of pancreatic stones with extracorporeal shock wave lithotripsy: results of a multicenter survey. Pancreas, 30(1), pp.26-30

Izbicki JR, Bloechle C, Broering DC, Knoefel WT, Kuechler T, Broelsch CE. Extended drainage versus resection in surgery for chronic pancreatitis: a prospective randomized trial comparing the longitudinal pancreaticojejunostomy combined with local pancreatic head excision with the pylorus-preserving pancreatoduodenectomy. Ann Surg 1998; 228: 771–79

Keck, T., Adam, U., Makowiec, F., Riediger, H., Wellner, U., Tittelbach-Helmrich, D. and Hopt, U. (2012). Short- and long-term results of duodenum preservation versus resection for the management of chronic pancreatitis: A prospective, randomized study. Surgery, 152(3), pp.S95-S102.

LeBlanc JK, DeWitt J, Johnson C, et al. A prospective randomized trial of 1 versus 2 injections during EUS-guided celiac plexus block for chronic pancreatitis pain. Gastrointest Endosc. 2009;69(4):835-842.

Lee, MD, P. and Stevens, MD, T. (2017). Chronic Pancreatitis. [online] Clevelandclinicmeded.com. Available at:http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/gastroenterology/chronic-pancreatitis/

Liu B.N., Zhang T.P, Zhao Y.P, Liao Q., Dai M.H, Zhan H.X. (2010) Pancreatic duct stones in patients with chronic pancreatitis: surgical outcomes. Hepatobiliary Pancreat Dis Int. 2010 Aug; 9 4, 423-427

Löhr, Matthias & Dominguez-Munoz, Enrique & Rosendahl, Jonas & Besselink, Marc & Mayerle, Julia & Lerch, Markus & Haas, Stephan & Akisik, Fatih & Kartalis, Nikolaos & Iglesias-Garcia, Julio & Keller, Jutta & Boermeester, Marja & Werner, Jens & Dumonceau, Jean-Marc & Fockens, Paul & Drewes, Asbjorn & Ceyhan, Güralp & Lindkvist, Björn & Drenth, Joost & Duggan, Sinead. (2017). United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European Gastroenterology Journal, 5, 2, 205064061668469

Mathew, G. and Bhimji, S. (2017). Aneurysm, Pancreatic Pseudoaneurysm. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/books/NBK430937/

Manes G, Büchler M, Pieramico O, Di Sebastiano P, Malfertheiner (1994) Is increased pancreatic pressure related

to pain in chronic pancreatitis? P Int J Pancreatol. Apr; 15(2):113-7.

M. Szary, MD, N. and H. Al-Kawas, MD, F. (2017). 2013. Complications of Endoscopic Retrograde Cholangiopancreatography: How to Avoid and Manage Them, 9(8), pp.496–504.

National Instititute for Healthcare and Excellence (2010). Alcohol-use disorders: diagnosis and management of physical complications, Chapter: Cg 100

Ní Chonchubhair HM., O' Shea B., O Kavanagh D., Ryan BM., Duggan SN., Conlan CK. (2016) Chronic Pancreatitis in Primary and Hospital Based Care in Ireland: The Management of an Orphan Disease. Journal of the Pancreas, 17, 4, 385-393

Nyguyen-Tang T. and Dumonceau JM. 2010. Endoscopic treatment in chronic pancreatitis, timing, duration and type of intervention. Best Practice & Research Clinical Gastroenterology , 24, 3, 281-298

OCEBM Levels of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson, Patel, A., Toyama, M., Alvarez, C., Nguyen, T., Reber, P., Ashley, S. and Reber, H. (1995). Pancreatic interstitial pH in human and feline chronic pancreatitis. Gastroenterology, 109(5), pp.1639-1645.

Pezzilli, R. and Morselli-Labate, A. (2009). Alcoholic Pancreatitis: Pathogenesis, Incidence and Treatment with Special Reference to the Associated Pain. International Journal of Environmental Research and Public Health, 6(11), pp.2763-2782.

Ponchon, T., Bory R.M., Hedelius, F., Roubein, L.D., Paliard, P., Napoleon, B., Chavaillon, A., Endoscopic stent placement for pain relief in chronic pancreatitis: results of a standardized protocol. Gastrointest Endosc 1995;

Poulsen, J. (2013). Pain and chronic pancreatitis: A complex interplay of multiple mechanisms. World Journal of Gastroenterology, 19(42), p.7282.

PubMed Health. (2017). Chronic Pancreatitis - National Library of Medicine - PubMed Health. [online] Available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0022862/ [Accessed 13 Nov. 2017].

Puli SR, Reddy JB, Bechtold ML, et al. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Dig Dis Sci. 2009;54(11):2330-2337.

Rösch, T., Daniel, S., Scholz, M., Huibregtse, K., Smits, M., Schneider, T., Ell, C., et al. Endoscopic treatment of chronic pancreatitis: a multicenter study 1000 patient with long-term follow-up. Endoscopy 2002; 34:765-77

Rutter K., Ferlitsch A., Sautner T., Püspök A., Götzinger P., Gangl A., Schindl M. (2010) Hospitalization, Frequency of Interventions, and Quality of Life after Endoscopic, surgical, or Conservative Treatment in Patients with Chronic Pancreatitis.. World Journal of Surgery 34 11, 2642–2647.

S, L. (1993). Diabetes mellitus secondary to chronic pancreatitis. Danish Medical Bulliten, [online] 40(2), pp.153-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8495594

Santosh, D., Lakhtakia, S., Gupta, R., Reddy, D., Rao, G., Tandan, M., Ramchandani, M. and GudA, N. (2009). Clinical trial: a randomized trial comparing fluoroscopy guided percutaneous technique vs. endoscopic ultrasound guided technique of coeliac plexus block for treatment of pain in chronic pancreatitis. Alimentary Pharmacology & Therapeutics, 29(9), pp.979-984.

Schou Olesen, S., Tieftrunk, E., O. Ceyhan, G. and Mohr Drewes, A. (2015). Pathogenesis and Treatment of Pain in Chronic Pancreatitis. The Pancreapedia: Exocrine Pancreas Knowledge Base.

Seicean A, Vultur S (2014). Endoscopic therapy in chronic pancreatitis: current perspectives. Clinical and Experimental Gastroenterology, 17, 8, pp1-11

Seven, G., Schreiner, M., Ross, A., Lin, O., Gluck, M., Gan, S., Irani, S., Brandabur, J., Patterson, D., Kuhr, C. and Kozarek, R. (2012). Long-term outcomes associated with pancreatic extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. Gastrointestinal Endoscopy, 75(5), pp.997-1004. e1.

Tandan, M., Reddy, D., Santosh, D., Vinod, K., Ramchandani, M., Rajesh, G., Rama, K., Lakhtakia, S., Banerjee, R., Pratap, N. and Venkat Rao, G. (2010). Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi—a large single center experience. Indian Journal of Gastroenterology, 29(4), pp.143-148.

Tandan M., Talukdar R., and Reddy D.N. (2016) Management of Pancreatic Calculi: An Update. Gut and Liver, 10 6, 873-880

Tandan M, DN Reddy, Santosh D, Vinod K, Ramchandani M, Gupta R, Rama K, Lahtakia S, Banerjee R, Pratap N, Rao GV (2010). Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi- a large single centre experience. The Indian Journal of Gastroenterology, 29, 4, 143-148