ClinicalEvidence

Chronic pancreatitis

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ABSTRACT

INTRODUCTION: Chronic pancreatitis affects 3–9 people in 100,000; 70% of cases are alcohol-induced. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of lifestyle interventions in people with chronic pancreatitis? What are the effects of dietary supplements in people with chronic pancreatitis? What are the effects of drug interventions in people with chronic pancreatitis? What are the effects of nerve blocks for pain relief in people with chronic pancreatitis? What are the effects of different invasive treatments for specific complications of chronic pancreatitis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2011 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 27 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: avoiding alcohol consumption, biliary decompression, calcium supplements, ductal decompression (endoscopic or surgical), low-fat diet, nerve blocks, opioid analgesics, pancreatic enzyme supplements, pseudocyst decompression (endoscopic or surgical), resection using distal pancreatectomy, resection using pancreaticoduodenectomy (Kausch–Whipple or pylorus-preserving), and vitamin/antioxidant supplements.

QUESTIONS

INTERVENTIONS

LIFESTYLE INTERVENTIONS

Likely to be beneficial

Unknown effectiveness

DIETARY SUPPLEMENTS

Likely to be beneficial

Unknown effectiveness

DRUG INTERVENTIONS

Trade off between benefits and harms

LOCAL INJECTIONS

Unknown effectiveness

INVASIVE TREATMENTS

Trade off between benefits and harms

To be covered in future updates

Lateral pancreaticojejunostomy

Footnote

*Based on consensus.

Key points

- Chronic pancreatitis is characterised by long-standing inflammation of the pancreas due to a wide variety of causes, including recurrent acute attacks of pancreatitis.

Chronic pancreatitis affects between 3 and 9 people in 100,000; 70% of cases are alcohol-induced.

- Pancreatic enzyme supplements reduce steatorrhoea in people with chronic pancreatitis, but they may have no effect on pain.

  We don't know whether consuming a low-fat diet or avoiding alcohol consumption improves symptoms of chronic pancreatitis. We also don't know whether calcium or vitamin/antioxidant supplements are effective.

- There is consensus that tramadol is the most effective oral opioid analgesic for reducing pain in people with chronic pancreatitis, but it is associated with gastrointestinal adverse effects.

  We don't know whether nerve blocks are effective.

- There is consensus that endoscopic and surgical pseudocyst decompression and ductal decompression have both benefits and harms; it is unclear which technique is best, and choice often depends on local expertise.

  There is consensus that, despite complications, biliary decompression is essential in people with chronic pancreatitis who have biliary obstruction.

- Resection using pancreaticoduodenectomy may be equivalent to localised excision of the pancreatic head in improving symptoms, but it reduces quality of life and increases intraoperative and postoperative complications. In clinical practice, resection using pancreaticoduodenectomy is usually reserved for when other surgical options, such as pseudocyst or duct decompression, are not feasible because of severity of disease.

  There is consensus that distal pancreatectomy may be a viable option in people with chronic pancreatitis limited to the tail of the pancreas, with most efficacy when multiple pseudocysts are present. It is associated with complications in 15% to 50% of people.

Clinical context

DEFINITION

Pancreatitis is inflammation of the pancreas. The inflammation may be sudden (acute) or ongoing (chronic). Acute pancreatitis usually involves a single "attack", after which the pancreas returns to normal. Chronic pancreatitis is characterised by long-standing inflammation of the pancreas owing to a wide variety of causes, including recurrent acute attacks of pancreatitis. Symptoms of chronic pancreatitis include recurring or persistent abdominal pain and impaired exocrine function. The most reliable test of exocrine function is the demonstration of increased faecal fat — although this test is frequently not performed if imaging is consistent (particularly calcification of the pancreatic gland on computerised tomography scan). **Diagnosis:** There is no consensus on the diagnostic criteria for chronic pancreatitis. [1] [2] [3] [4] Typical symptoms include pain radiating to the back, and people may present with malabsorption, malnutrition, and pancreatic endocrine insufficiency. However, these symptoms may be seen in people with more common disorders such as reflux disease and peptic ulcers (also more common in heavy drinkers), and also in people with more serious diseases such as pancreatic or periampullary cancers. Diagnostic tests for chronic pancreatitis include faecal elastase measurement (to prove pancreatic insufficiency) and imaging. [1] [2] [3] [4] Biopsy may be required to resolve diagnostic uncertainty.

INCIDENCE/ PREVALENCE

The annual incidence of chronic pancreatitis has been estimated in one prospective study and several retrospective studies to be between 3 and 9 cases/100,000 population. Prevalence is estimated at between 0.04% and 5%. [5] [6] [7] Alcoholic chronic pancreatitis is usually diagnosed after a long history of alcohol abuse, and is the most common cause.

AETIOLOGY/ RISK FACTORS

The TIGAR-O system describes the main predisposing factors for chronic pancreatitis as: **T**oxic-metabolic (which includes alcohol-induced [70% of all cases], smoking, hypercalcaemia, hyperlipidaemia, and chronic renal failure); **I**diopathic (which includes tropical pancreatitis and may form up to 20% of all cases); **G**enetic (which includes cationic trypsinogen, CFTR, and SPINK1 mutation); **A**utoimmune (which includes solitary and syndromic); **R**ecurrent and severe acute pancreatitis (which includes postnecrotic and radiation-induced); and **O**bstructive (which includes pancreatic divisum and duct obstruction owing to various causes). [1] Although 70% of people with chronic pancreatitis report excessive consumption of alcohol (>150 g/day) over a long period (>20 years), [5] [8] only 1 in 10 heavy drinkers develop chronic pancreatitis, [9] suggesting underlying genetic predisposition or polymorphism, although a link has not been established conclusively. [1]

PROGNOSIS

Mortality in people with chronic pancreatitis is higher than in the general population, with mortality at 10 years after diagnosis estimated at 70% to 80%. Diagnosis is usually made between 40 and 48 years of age. Reported causes of mortality in people with chronic pancreatitis are: complications of disease as well as treatment; development of pancreatic cancer or diabetes; and continual exposure to risk factors for mortality, such as smoking and alcohol. [10] [11]

AIMS OF INTERVENTION To minimise pain of chronic pancreatitis, alleviate symptoms and sequelae of pancreatic exocrine insufficiency, improve quality of life, and reduce complications, with minimal adverse effects of treatment.

OUTCOMES **Mortality**, **pain relief**, reduction of **steatorrhoea** (includes alleviation of nutritional insufficiency), **global symptom improvement**, **weight gain/maintenance**, **quality of life**, **development of complications** (includes incidence of diabetes and incidence of pancreatic cancer), **adverse effects** (includes intraoperative and postoperative complications).

METHODS *Clinical Evidence* search and appraisal August 2011. The following databases were used to identify studies for this systematic review: Medline 1966 to August 2011, Embase 1980 to August 2011, and The Cochrane Database of Systematic Reviews, Issue 2, 2011 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blind for non-drug studies, double blind for drug studies, and open label for surgery studies, containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. For surgical interventions we also searched for: retrospective and prospective cohort studies; case-control studies and case series studies, the criteria for inclusion as for RCTs as applicable. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 30). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of lifestyle interventions in people with chronic pancreatitis?

OPTION AVOIDING ALCOHOL CONSUMPTION

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- We don't know whether avoiding alcohol consumption improves symptoms of chronic pancreatitis.
- There is consensus that alcohol abstinence may be beneficial, as it prevents further injury to the pancreas and other organs.

Benefits and harms

Avoiding alcohol consumption:

We found no systematic review, RCTs, or observational studies of sufficient quality.

Further information on studies

Comment: **Clinical guide:**
Avoiding alcohol consumption may be beneficial in people with alcoholic chronic pancreatitis (where there is usually prolonged exposure to large amounts of alcohol) by preventing further injury to the pancreas and other organs (such as the liver, heart, and nervous system). Randomising people with chronic pancreatitis to continuing alcohol consumption would be unethical. [12]

OPTION LOW-FAT DIET

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- We don't know whether consuming a low-fat diet improves symptoms of chronic pancreatitis.
- Low-fat diets decrease the amount of overall fat presented to the intestine for digestion and absorption, and may be helpful in alleviating steatorrhoea.

Benefits and harms

Low-fat diet:

We found no systematic review, RCTs, or observational studies of sufficient quality.

Further information on studies

Comment: **Clinical guide:**
Low-fat diets may help symptom control in alleviating steatorrhoea (where this is a major presenting symptom of chronic pancreatitis) by decreasing the amount of overall fat presented to the intestine for digestion and absorption. If people are given pancreatic enzyme supplements, they are usually advised to maintain a normal diet, as there is no need to lower fat intake alongside enzyme supplementation.

QUESTION What are the effects of dietary supplements in people with chronic pancreatitis?

OPTION PANCREATIC ENZYME SUPPLEMENTS

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- Pancreatic enzyme supplements reduces steatorrhoea in people with chronic pancreatitis, but they seem to have no effect on pain.

Benefits and harms

Pancreatic enzyme supplements versus placebo:

We found one systematic review (search date 2009). [13] The review included in its reporting two RCTs already reported here in detail, which we continue to report for some outcomes not covered by the review. [14] [15] See further information on studies for data on protein absorption.

Pain relief

Pancreatic enzyme supplements compared with placebo We don't know whether pancreatin is more effective at reducing pain in people with chronic pancreatitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[13] Systematic review	Number of people and characteristics not reported 4 RCTs in this analysis	**Analgesic use** with pancreatic enzyme with placebo	Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported The review did not perform a meta-analysis owing to heterogeneity (data description, presentation, and different pain scales) The review reported that most included RCTs had inadequate allocation concealment, and that none of the trials adequately reported withdrawals and loss to follow-up. In addition, it was unclear for most trials whether intention-to-treat (ITT) analyses had been used			
[13] Systematic review	Number of people and characteristics not reported 5 RCTs in this analysis	**Pain intensity** with pancreatic enzyme with placebo Absolute numbers not reported The review did not perform a meta-analysis because of heterogeneity (data description, presentation, and different pain scales). It reported that 3 of 4 RCTs that reported on pain intensity found that pancreatic enzymes significantly reduced pain compared with placebo The review reported that most included RCTs had inadequate allocation concealment, and that none of the trials adequately reported withdrawals and loss to follow-up. In addition, it was unclear for most trials whether ITT analyses had been used	Significance not assessed		

No data from the following reference on this outcome. [14] [15]

Steatorrhoea

Pancreatic enzyme supplements compared with placebo Pancreatin may be more effective at increasing faecal fat absorption at 2 weeks, reducing faecal fat at 2 weeks, and decreasing stool frequency at 2 weeks in people with chronic pancreatitis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Faecal fat					
[13] Systematic review	55 people 2 RCTs in this analysis	**Amount of faecal fat , 2 weeks** with pancreatic enzyme with placebo Absolute numbers not reported The review reported that most included RCTs had inadequate allocation concealment, and that none of the trials adequately reported withdrawals and loss to follow-up. In addition, it was unclear for most trials whether intention-to-treat analyses had been used	SMD –1.03 95% CI –1.60 to –0.46	○○○	pancreatic enzyme

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fat absorption					
[15] RCT **Crossover design**	29 people with chronic pancreatitis, 27 (93%) alcohol-induced, 28 men, mean age 53 years, with faecal fat >10 g/day In review [13]	**Fat absorption , at 15 days** 81% with pancreatin for 2 weeks (4 capsules at meal times and 2 with snack) 54% with placebo Absolute numbers not reported There was a 1-week pre-treatment washout	P = 0.002	○○○	pancreatin
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [13]	**Fat absorption increase from baseline , 2 weeks** 37% with pancreatin (4 capsules at meal times and 2 with snacks) 12% with placebo Absolute numbers not reported There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days	P = 0.02	○○○	pancreatin
Stool frequency					
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [13]	**Stool frequency reduction from baseline , 2 weeks** 5 stools/day with pancreatin (4 capsules at meal times and 2 with snacks) 11 stools/day with placebo There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days	P = 0.0015	○○○	pancreatin

Global symptom improvement

Pancreatic enzyme supplements compared with placebo We don't know whether pancreatin is more effective at improving investigator-assessed global symptom scores (measured by the Clinical Global Impression Disease Symptom Scale) in people with chronic pancreatitis, or at improving patient-assessed global symptom scores (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptom improvement					
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [13]	**Mean difference in patient-scored Clinical Global Impression Disease Symptoms Scale (CGIDS) from baseline , 2 weeks** –0.3 with pancreatin (4 capsules at meal times and 2 with snacks) +0.4 with placebo There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days CGIDS scored from 1 (very much improved) to 7 (very much worse)	P = 0.06	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [13]	**Improvement in investigator-scored CGIDS from baseline , 2 weeks** –0.3 with pancreatin (4 capsules at meal times and 2 with snacks) +0.4 with placebo There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days CGIDS scored from 1 (very much improved) to 7 (very much worse)	P = 0.04	○○○	pancreatin

No data from the following reference on this outcome. [15]

Mortality

No data from the following reference on this outcome. [13] [14] [15]

Weight gain/maintenance

No data from the following reference on this outcome. [13] [14] [15]

Development of complications

No data from the following reference on this outcome. [13] [14] [15]

Quality of life

No data from the following reference on this outcome. [13] [14] [15]

Adverse effects

Pancreatic enzyme supplements compared with placebo Pancreatin may be associated with major changes in fasting glucose levels over 4 weeks in people with chronic pancreatitis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT **Crossover design**	29 people with chronic pancreatitis, 27 (93%) alcohol-induced, 28 men, mean age 53 years, with faecal fat >10 g/day In review [13]	**Blood glucose control , 4 weeks** with pancreatin (4 capsules at meal times and 2 with snack) with placebo There was a 1-week pre-treatment washout	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		28/29 (97%) people had major changes in fasting glucose levels on crossover; 1 person developed diabetic ketoacidosis after commencing pancreatin			
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [13]	**Non-serious adverse effects (include nausea, mild tremor, mild weakness, and abdominal pain) , 2 weeks** 6/13 (46%) with pancreatin (4 capsules at meal times and 2 with snacks) 11/14 (79%) with placebo There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days	P = 0.5	⟷	Not significant
[14] RCT	27 people with chronic pancreatitis, 9 men, mean age 51 years, faecal fat values greater than or equal to 10 g/day and/or a fat absorption <80% In review [13]	**Serious adverse effects , 2 weeks** 0/13 (0%) with pancreatin (4 capsules at meal times and 2 with snacks) 0/14 (0%) with placebo There was a 2-week placebo run-in A high-fat diet was followed on 6 of the treatment days	Significance not assessed		

Further information on studies

[15] The RCT found a significant increase in protein absorption with pancreatin compared with placebo at 15 days (86% with pancreatin *v* 81% with placebo; P = 0.004).

Comment:

Clinical guide:
Pancreatic enzyme supplementation is the most commonly used treatment for steatorrhoea as there is consensus that pancreatic enzymes ameliorate exocrine insufficiency. However, change in pancreatic enzyme levels can exacerbate pancreatic endocrine dysfunction, and supplementation may need monitoring if introduced suddenly. Fat absorption seems best if pancreatic enzyme supplements are taken during or after meals. [16] Besides reiterating the beneficial effects of pancreatic enzyme supplements on fat absorption, the most recent systematic review does not add any further information. [13]

OPTION CALCIUM SUPPLEMENTS

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- We don't know whether calcium is effective.
- Reduction in calcium intake is advised for people with hyperparathyroidism or renal failure associated with chronic pancreatitis (to manage the underlying disease).

Benefits and harms

Calcium supplements:

We found no systematic review, RCTs, or observational studies of sufficient quality.

Further information on studies

Comment: **Clinical guide:**
In current clinical practice, calcium supplements are no longer considered as useful treatment for most people with chronic pancreatitis. Reduction in calcium intake is advised for people with hyperparathyroidism or renal failure associated with chronic pancreatitis (to manage the underlying disease).

OPTION VITAMIN/ANTIOXIDANT SUPPLEMENTS

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- We don't know whether vitamin/antioxidant supplements are effective in people with chronic pancreatitis.

Benefits and harms

Oral citrate versus placebo:

We found one RCT comparing oral citrate (20–40 g/day) versus placebo. [17] See further information on studies for data on calcification.

Pain relief

Vitamin/antioxidant supplements compared with placebo We don't know whether oral citrates are more effective at reducing pain at 18 months in people with chronic pancreatitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[17] RCT **Crossover design**	44 people aged 36 to 64 years with symptoms of chronic pancreatitis for a median 11 years, 37 of whom consumed >80 g alcohol/day, 17 with diabetes, steatorrhoea, or both	**Proportion of people pain-free , 18 months** 14/19 (74%) with oral citrate (20–40 g/day) 13/17 (76%) with placebo/no treatment Pre-crossover results 36 people in analysis; 20/36 (55%) were pain free before trial	Significance not assessed		

Mortality

No data from the following reference on this outcome. [17]

Steatorrhoea

No data from the following reference on this outcome. [17]

Global symptom improvement

No data from the following reference on this outcome. [17]

Weight gain/maintenance

No data from the following reference on this outcome. [17]

Development of complications

No data from the following reference on this outcome. [17]

Quality of life

No data from the following reference on this outcome. [17]

Adverse effects

No data from the following reference on this outcome. [17]

Further information on studies

[17] The RCT found that oral citrate significantly reduced calcification at 18 months compared with placebo (proportion of people with reductions in calcification: 7/19 [37%] with oral citrate 40 g/day *v* 1/17 [6%] with placebo; P <0.05).

Comment: **Clinical guide:**
Vitamin supplements may benefit people with chronic pancreatitis independent of altering the clinical course of the disease, because of underlying nutritional deficiency, especially in people with pancreatitis associated with heavy alcohol consumption.

QUESTION What are the effects of drug interventions in people with chronic pancreatitis?

OPTION OPIOID ANALGESICS

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- There is consensus that tramadol is the most effective oral opioid analgesic for reducing pain in people with chronic pancreatitis, but is associated with gastrointestinal adverse effects.

Benefits and harms

Opioid analgesics versus each other:
We found one RCT. [18]

Pain relief

Opioid analgesics compared with each other Tramadol may be more effective than morphine at increasing the proportion of people who rate their pain relief as excellent at 4 days in people with chronic pancreatitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[18] RCT	25 people with chronic pancreatitis, 80% alcohol-induced	**Proportion of people who rated pain relief as "excellent" , at day 4** 67% with tramadol 20% with morphine Absolute numbers not reported People rated treatment as excellent, satisfactory, or unsatisfactory	P <0.001	○○○	tramadol

Mortality

No data from the following reference on this outcome. [18]

Steatorrhoea

No data from the following reference on this outcome. [18]

Global symptom improvement

No data from the following reference on this outcome. [18]

Weight gain/maintenance

No data from the following reference on this outcome. [18]

Development of complications

No data from the following reference on this outcome. [18]

Quality of life

No data from the following reference on this outcome. [18]

Adverse effects

Opioid analgesics compared with each other Morphine may be associated with more adverse effects (such as increasing gastrointestinal transit times, headaches, drowsiness, dizziness) than tramadol in people with chronic pancreatitis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT	25 people with chronic pancreatitis, 80% alcohol-induced	**Orocaecal and colonic transit times** with tramadol with morphine Absolute results reported graphically Transit times longer with morphine compared with tramadol	P <0.05	○○○	tramadol
[18] RCT	25 people with chronic pancreatitis, 80% alcohol-induced	**Headache** 33% with tramadol 60% with morphine Absolute numbers not reported	P <0.001	○○○	tramadol
[18] RCT	25 people with chronic pancreatitis, 80% alcohol-induced	**Dizziness** 13% with tramadol 40% with morphine Absolute numbers not reported	P <0.001	○○○	tramadol
[18] RCT	25 people with chronic pancreatitis, 80% alcohol-induced	**Drowsiness** 13% with tramadol 40% with morphine Absolute numbers not reported	P <0.001	○○○	tramadol

Further information on studies

Comment: **Clinical guide:**
Pain is a major symptom in most people with chronic pancreatitis, which may be continuous or intermittent. Non-opioid analgesics rarely alleviate visceral pain (as in chronic pancreatitis). Clinical consensus suggests that tramadol may be the most effective oral opioid analgesic, but is associated with gastrointestinal adverse effects.

QUESTION What are the effects of nerve blocks for pain relief in people with chronic pancreatitis?

OPTION NERVE BLOCKS

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- We don't know whether nerve blocks are effective.

Benefits and harms

Nerve block versus placebo or other non-drug treatments:

We found no clinically important results from RCTs or observational studies about the effects of nerve blocks compared with placebo or other non-drug treatments in people with chronic pancreatitis.

Endoscopic ultrasound-guided nerve block versus computerised tomography-guided nerve block:

We found one RCT comparing endoscopic ultrasound-guided nerve block versus computerised tomography-guided nerve block. [19]

Pain relief

Endoscopic ultrasound-guided nerve block compared with computerised tomography-guided nerve block Endoscopic ultrasound-guided nerve block may be more effective at improving median pain scores at 4 weeks in people with chronic pancreatitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[19] RCT	22 people with chronic pancreatitis (10 alcohol-induced, mean age 45 years, 45% male, duration of pancreatitis not reported)	**Median pain score (visual analogue scale 0–10 where 0 = no pain) , 4 weeks** 1 with endoscopic ultrasound (EUS)-guided nerve block (bupivacaine 10 mL 0.75% plus 3 mL triamcinolone 40 mg) 9 with computerised tomography (CT)-guided nerve block (bupivacaine 10 mL 0.75% plus 3 mL triamcinolone 40 mg) 18 people in analysis See further information on studies for details on pain relief in the longer term	P <0.02	◌◌◌	EUS-guided nerve block

Mortality

No data from the following reference on this outcome. [19]

Steatorrhoea

No data from the following reference on this outcome. [19]

Global symptom improvement

No data from the following reference on this outcome. [19]

Weight gain/maintenance

No data from the following reference on this outcome. [19]

Development of complications

No data from the following reference on this outcome. [19]

Quality of life

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT	22 people with chronic pancreatitis (10 alcohol-induced, mean age 45 years, 45% male, duration of pancreatitis not reported)	**Diarrhoea** 1/10 (10%) with EUS-guided nerve block (bupivacaine 10 mL 0.75% plus 3 mL triamcinolone 40 mg) 2/8 (25%) with CT-guided nerve block (bupivacaine 10 mL 0.75% plus 3 mL triamcinolone 40 mg)	Significance not assessed		
[19] RCT	22 people with chronic pancreatitis (10 alcohol-induced, mean age 45 years, 45% male, duration of pancreatitis not reported)	**Postural hypotension** 0/10 (0%) with EUS-guided nerve block (bupivacaine 10 mL 0.75% plus 3 mL triamcinolone 40 mg) 1/8 (13%) with CT-guided nerve block (bupivacaine 10 mL 0.75% plus 3 mL triamcinolone 40 mg)	Significance not assessed		

Further information on studies

[19] 30% of people receiving EUS-guided nerve block had pain relief at 24 weeks; 12% receiving CT-guided nerve block had pain relief at 12 weeks, with 75% returning to pretreatment pain scores by 18 weeks.

Comment: **Clinical guide:**
Coeliac plexus block is technically demanding and tends to be reserved for people with pain that is refractory to opioid analgesics — usually those with small-duct chronic pancreatitis and without large-duct obstruction. In people with large-duct obstruction, endoscopic or surgical drainage is usually performed instead. The need for technical expertise with either ultrasound- or CT-guided nerve block must be weighed against the relatively short-term pain relief offered.

QUESTION What are the effects of different invasive treatments for specific complications of chronic pancreatitis?

OPTION BILIARY DECOMPRESSION

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- Biliary decompression may prevent jaundice and biliary cirrhosis, and there is consensus that despite complications, it is essential in people with obstruction to the biliary tree.

Benefits and harms

Endoscopic versus surgical biliary decompression:

We found no systematic review, RCTs, or observational studies of sufficient quality assessing endoscopic or surgical biliary decompression (see comment).

Further information on studies

Comment: **Clinical guide:**
Biliary obstruction secondary to chronic pancreatitis may occur in 3% to 10% of people admitted to hospital with chronic pancreatitis, and in 6% to 46% of people having surgery for chronic pancreatitis, resulting in a lifetime risk of 5% to 10% in all people with chronic pancreatitis. [20] Biliary decompression may prevent the effects of jaundice, such as cholangitis, which may happen in 9% of people (27/288 in a collection of case reports from 1976 to 1988), and long-term biliary cirrhosis, in 7% (21/288 in a collection of case series from 1976 to 1988). [20] While endoscopic decompression may offer relief in the short term, surgical decompression will be required when chronic pancreatitis causes biliary obstruction (and this may be combined with operation for the pancreatic disease). Rarely, when cancer cannot be ruled out, a surgical resection (pancreaticoduodenectomy) may be carried out (see option on resection using pancreaticoduodenectomy (Kausch–Whipple or pylorus-preserving) in people with more severe disease limited to the head of the pancreas, p 22).

OPTION DUCTAL DECOMPRESSION

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- There is consensus that endoscopic and surgical pseudocyst decompression and ductal decompression have both benefits and harms; it is unclear which technique is best, and choice often depends on local expertise.
- Surgery has attendant morbidity, mortality, and slow recovery rates.

Benefits and harms

Endoscopic versus surgical ductal decompression:

We found two RCTs [21] [22] and one cohort study. [23]

Mortality

Endoscopic compared with surgical ductal decompression We don't know how endoscopic ductal decompression and surgical ductal decompression compare at reducing mortality (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[21] RCT	39 patients with pancreatic duct obstruction associated with chronic pancreatitis and severe recurrent pancreatic pain, 54% alcohol-induced, mean age 49 years, 67% male	**Mortality , 2 years** 1/19 (5%) with endoscopic treatment 0/20 (0%) with surgical treatment 1 patient in endoscopy group died of a perforated duodenal ulcer 4 days after receiving shock-wave lithotripsy	Significance not assessed		
[22] RCT	72 people with pancreatic duct obstruction associated with chronic pancreatitis, 88%	**Mortality** 0% with endoscopic treatment 0% with surgical treatment	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	alcohol-induced, mean age 41.7 years, 85% male	140 people initially included; 68/140 (49%) refused to participate in trial			

No data from the following reference on this outcome. [23]

Pain relief

Endoscopic compared with surgical ductal decompression Surgical ductal decompression may be more effective at reducing pain at 2 and 5 years (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[21] RCT	39 patients with pancreatic duct obstruction associated with chronic pancreatitis and severe recurrent pancreatic pain, 54% alcohol-induced, mean age 49 years, 67% male	**Mean Izbicki scores , 2 years** 51 with endoscopic treatment 25 with surgical treatment	Mean difference 24 95% CI 11 to 36 P <0.001	○○○	surgical ductal decompression
[21] RCT	39 patients with pancreatic duct obstruction associated with chronic pancreatitis and severe recurrent pancreatic pain, 54% alcohol-induced, mean age 49 years, 67% male	**Proportion of people with complete or partial pain relief , at 2 years** 6/19 (32%) with endoscopy 15/20 (75%) with surgery	P = 0.007	○○○	surgical ductal decompression
[22] RCT	72 people with pancreatic duct obstruction associated with chronic pancreatitis, 88% alcohol-induced, mean age 41.7 years, 85% male	**People pain-free , at 5 years** 15% with endoscopic decompression 34% with surgical decompression Absolute numbers not reported 140 people initially included; 68/140 (49%) refused to participate in trial	P <0.05	○○○	surgical ductal decompression
[22] RCT	72 people with pancreatic duct obstruction associated with chronic pancreatitis, 88% alcohol-induced, mean age 41.7 years, 85% male	**People pain-free , 1 year and 3 years** with endoscopic decompression with surgical decompression Absolute results reported graphically 140 people initially included; 68/140 (49%) refused to participate in trial The RCT reported similar results for surgical and endoscopic ductal decompression at 1 and 3 years	Significance not assessed		
[23]	1018 people with pancreatic duct obstruction associat-	**Proportion who had no pain or weak pain , at mean 4.9 years**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retrospective case series	ed with chronic pancreatitis, 72% alcohol-induced, mean age 50 years, 71% male Study carried out over 7 years (1989–1995) with mean follow-up of 4.9 (range 2–12) years	87% (of 758 people) with endoscopic treatment only 79% (of 238 people) with surgical intervention after failed endoscopic treatment Absolute numbers not reported Initial success of endoscopic treatment: 69%			

Weight gain/maintenance

Endoscopic compared with surgical ductal decompression Surgical ductal decompression may be more effective at increasing the proportion of people with increased body weight at 5 years, but we don't know about at 1 and 3 years (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Weight gain/maintenance					
[22] RCT	72 people with pancreatic duct obstruction associated with chronic pancreatitis, 88% alcohol-induced, mean age 41.7 years, 85% male	**People with increased body weight , 5 years** 29% with endoscopic decompression 47% with surgical decompression Absolute numbers not reported 140 people initially included; 68/140 (49%) refused to participate in trial	P <0.05	○○○	surgical ductal decompression
[22] RCT	72 people with pancreatic duct obstruction associated with chronic pancreatitis, 88% alcohol-induced, mean age 41.7 years, 85% male	**People with increased body weight , 1 year and 3 years** with endoscopic decompression with surgical decompression Absolute results reported graphically 140 people initially included; 68/140 (49%) refused to participate in trial The RCT reported similar results for surgical and endoscopic ductal decompression at 1 and 3 years	Significance not assessed		

No data from the following reference on this outcome. [21] [23]

Steatorrhoea

No data from the following reference on this outcome. [21] [22] [23]

Global symptom improvement

No data from the following reference on this outcome. [21] [22] [23]

Development of complications

No data from the following reference on this outcome. [21] [22] [23]

Quality of life

No data from the following reference on this outcome. [21] [22] [23]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] RCT	72 people with pancreatic duct obstruction associated with chronic pancreatitis, 88% alcohol-induced, mean age 41.7 years, 85% male	**Complications after procedure** 8% with endoscopic decompression 8% with surgical decompression Absolute numbers not reported 140 people initially included; 68/140 (49%) refused to participate in trial Similar complications in each group, including bleeding, acute pancreatitis, and fistula	Significance not assessed		
[21] RCT	39 patients with pancreatic duct obstruction associated with chronic pancreatitis and severe recurrent pancreatic pain, 54% alcohol-induced, mean age 49 years, 67% male	**Complications** 11/19 (58%) with endoscopic treatment 7/20 (35%) with surgical treatment Adverse effects associated with endoscopy included a skin wound, stent complications, pancreatitis, cholecystitis Adverse effects associated with surgery included anastomotic leakage, bleeding, pneumonia, and wound infections 4 people with endoscopy had surgical drainage due to intractable pain. There was 1 post-endoscopy death, which may be unrelated to the procedure	P = 0.15	⟷	Not significant

No data from the following reference on this outcome. [23]

Different types of surgical ductal decompression versus each other:

We found one RCT comparing Beger ductal decompression and Frey ductal decompression. [24] For further information on the outcomes of exocrine or endocrine insufficiency, see further information on studies.

Mortality

Different types of surgical ductal decompression compared with each other We don't know how Beger ductal decompression and Frey ductal decompression compare at reducing mortality at 8.6 years (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[24] RCT	74 people with chronic pancreatitis with an inflammatory mass limited to the pancreatic head, 51 evaluated, alcohol intake and age not reported	**Late mortality , median 8.6 years** 8/26 (31%) with Beger ductal decompression 8/25 (32%) with Frey ductal decompression	Reported as not significant P value not reported	⟷	Not significant

Pain relief

Different types of surgical ductal decompression compared with each other We don't know how Beger ductal decompression and Frey ductal decompression compare at reducing pain at 8.6 years (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[24] RCT	74 people with chronic pancreatitis with an inflammatory mass limited to the pancreatic head, 51 evaluated, alcohol intake and age not reported	**Pain score on visual analogue scale (0–100) , median 8.6 years** 20 with Beger ductal decompression 20 with Frey ductal decompression	P = 0.499	⟷	Not significant

Quality of life

Different types of surgical ductal decompression compared with each other We don't know how Beger ductal decompression and Frey ductal decompression compare at improving global quality-of-life scores at 8.6 years (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[24] RCT	74 people with chronic pancreatitis with an inflammatory mass limited to the pancreatic head, 51 evaluated, alcohol intake and age not reported	**Global quality-of-life score (range 0–100 where 100 = higher function) , median 8.6 years** 66.7 with Beger ductal decompression 58.4 with Frey ductal decompression	P = 0.48	⟷	Not significant

Steatorrhoea

No data from the following reference on this outcome. [24]

Global symptom improvement

No data from the following reference on this outcome. [24]

Weight gain/maintenance

No data from the following reference on this outcome. [24]

Development of complications

No data from the following reference on this outcome. [24]

Adverse effects

Different types of surgical ductal decompression compared with each other We don't know how Beger ductal decompression and Frey ductal decompression compare at reducing postoperative complications (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] RCT	74 people with chronic pancreatitis with an inflammatory mass limited to the pancreatic head, 51 evaluated, alcohol intake and age not reported	**Postoperative complications , median 8.6 years** 32% with Beger ductal decompression 22% with Frey ductal decompression Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant

Further information on studies

[24] The RCT found no significant difference between Beger and Frey ductal decompression in exocrine or endocrine insufficiency at median 104 months (exocrine insufficiency: 22/25 [88%] with Beger *v* 18/25 [72%] with Frey; P = 0.16; endocrine insufficiency: 14/25 [56%] with Beger *v* 15/25 [60%] with Frey; P = 0.16).

Comment: **Clinical guide:**
Endoscopic ductal decompression may be the preferred treatment because of its relatively quick recovery rates. Surgery may have better long-term results, but has attendant morbidity and mortality. In clinical practice, the choice between Beger or Frey ductal decompression depends on local expertise. Other more extensive surgical procedures, such as resection, may have higher attendant risks, and may be used based on the extent of disease.

OPTION PSEUDOCYST DECOMPRESSION

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- We found no direct results from RCTs or observational studies comparing the effects of endoscopic or percutaneous pseudocyst decompression versus surgical pseudocyst decompression in people with chronic pancreatitis, or different types of surgical pseudocyst decompression versus each other in people with chronic pancreatitis.
- Pseudocysts are drained if they are complicated or long-standing, to reduce the risk of life-threatening complications, such as haemorrhage, infection, or rupture. Both procedures are associated with serious postoperative complications.

Benefits and harms

Endoscopic or percutaneous versus surgical pseudocyst decompression:

We found no systematic review, RCTs, or observational studies directly comparing endoscopic versus surgical pseudocyst decompression (see comment).

Different types of surgical pseudocyst decompression versus each other:

We found no systematic review or RCTs directly comparing different surgical pseudocyst decompression techniques (see comment).

Further information on studies

Comment:

Endoscopic or percutaneous versus surgical pseudocyst decompression:
Retrospective data suggest that endoscopic drainage is successful in 62% to 84% of people in the long term. [25] [26] [27] [28] Recurrence was seen in up to 20% of people. [26] [27] [28] Two retrospective studies assessed surgical drainage performed after failure of conservative management or endoscopic drainage (see clinical guide). [25] [27] One study suggested that recurrence after surgery may occur in up to one third of people, [25] but another study reported no recurrence. [27] Retrospective data suggest that complications (infection and bleeding) are seen in up to 34% of people receiving endoscopic or percutaneous drainage, and up to 10% of procedures may require emergency surgery. [26] [29] Surgical drainage has a complication rate of 8% to 20% (infection, bleeding, perforation, and fistula; see table 1, p 28). [25] [27] In one large retrospective study, [30] endoscopic and minimally invasive procedures were found to be superior to open surgical techniques with respect to success rates, morbidity, and mortality. Of 1126 patients, endoscopic treatment had a mean success rate of 79%, recurrence of 7.6%, and complications of 12.8% and was comparable to laparoscopic procedures.

Different types of surgical pseudocyst decompression versus each other:
One comparative case series suggested that cystogastrostomy had a shorter operative time than cystojejunostomy. There was no significant difference between procedures in length of hospital stay or recurrence rates (see table 1, p 28). [31] The case series also suggested that cystogastrostomy had a shorter operative time and caused less intraoperative blood loss than cystojejunostomy, but caused more postoperative haemorrhage. [31] There was no significant difference between procedures in overall complications or perioperative mortality (see table 1, p 28).

Clinical guide:
Clinical experience suggests that in people with chronic pancreatitis, most pseudocysts >6 cm in diameter or present for >6 weeks will not regress spontaneously. However, reported case series assessing initial conservative management of pseudocysts are in mixed populations (people with acute and chronic pancreatitis) and it is therefore difficult to draw conclusions about whether conservative management is possible. [25] [27] About 40% to 60% of people with chronic pancreatitis will require surgical intervention for failed conservative management, with up to 10% requiring emergency surgery for life-threatening complications such as haemorrhage or infection. [25] [27] Need for intensive care is greater with emergency surgery compared with planned surgery (46% with emergency surgery *v* 1% with planned surgery), and the length of intensive care stay is longer. [32] Endoscopic, percutaneous, and surgical drainage have attendant morbidity and failure rate.

OPTION RESECTION USING DISTAL PANCREATECTOMY IN PEOPLE WITH DISEASE LIMITED TO THE TAIL OF THE PANCREAS

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- We found no direct information from RCTs about the effects of distal pancreatectomy in people with chronic pancreatitis whose disease is limited to the tail of the pancreas, compared with no treatment or other treatments.

- There is consensus that distal pancreatic resection may be a viable option in people with chronic pancreatitis limited to the tail of the pancreas, with most efficacy when multiple pseudocysts are present.

Benefits and harms

Resection using distal pancreatectomy in people with disease limited to tail of the pancreas:

We found no systematic review, RCTs, or observational studies comparing surgical resection versus endoscopic decompression, or different surgery techniques versus each other. We found 4 case series in people with chronic pancreatitis (see comment for further information from these case series).

Further information on studies

Comment:

Three case series found that distal pancreatectomy was associated with reduction in pain in up to three-quarters of people. [33] [34] [35] Results concerning improvements in endocrine function were inconclusive (see table 2, p 29). [33] [34] [35] Case series suggested that distal pancreatectomy was associated with low perioperative mortality (0–0.9%). [33] [34] [35] [36] Postoperative complications occurred in 15% to 46% of people. [33] [34] [35] [36] There may be new-onset or worsening diabetes mellitus in 25% to 45% of people (see table 2, p 29). [33] [35]

Clinical guide:
Distal pancreatic resection may be a viable option in people with chronic pancreatitis limited to the tail of the pancreas, with most efficacy when multiple pseudocysts are present.

OPTION RESECTION USING PANCREATICODUODENECTOMY (KAUSCH–WHIPPLE OR PYLORUS-PRESERVING) IN PEOPLE WITH MORE SEVERE DISEASE LIMITED TO THE HEAD OF THE PANCREAS

- For GRADE evaluation of interventions for Chronic pancreatitis, see table, p 30 .
- Resection using pancreaticoduodenectomy may be equivalent to localised excision of the pancreatic head in improving symptoms, but it reduces quality of life and increases intraoperative and postoperative complications. In clinical practice, resection using pancreaticoduodenectomy is usually reserved for when other surgical options, such as pseudocyst or duct decompression, are not feasible because of severity of disease.

Benefits and harms

Resection using pancreaticoduodenectomy versus other surgical techniques:

We found one systematic review (search date 2006) [37] comparing pancreaticoduodenectomy versus duodenum-preserving pancreatic head resection (Frey and Beger procedures), and one subsequent RCT [38] presenting long-term follow-up results of one of the RCTs reported in the review. [39]

Mortality

Resection using pancreaticoduodenectomy compared with other surgical techniques We don't know how pylorus-preserving pancreaticoduodenectomy and duodenum-preserving pancreatic head resection compare at reducing mortality (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[37] Systematic review	184 people (150 men, 34 women), mean age range 43 to 47 years 4 RCTs in this analysis	**Mortality** 0/91 (0%) with pancreaticoduodenectomy 2/93 (2%) with duodenum-preserving pancreatic head resection	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		1 of the deaths was with Frey procedure, and 1 with Beger procedure The review reported methodological weaknesses with all RCTs, including inadequate randomisation description and allocation concealment, and lack of blinded outcome assessment and predetermined follow-up periods			

No data from the following reference on this outcome. [38]

Pain relief

Resection using pancreaticoduodenectomy compared with other surgical techniques We don't know how pylorus-preserving pancreaticoduodenectomy and duodenum-preserving pancreatic head resection compare at reducing composite pain scores at 24 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[37] Systematic review	173 people, approximately 80% men, mean age range 43 to 47 years 4 RCTs in this analysis	**Proportion of people pain free , 24 months** 62/86 (72%) with pancreaticoduodenectomy 71/87 (82%) with duodenum-preserving pancreatic head resection The review reported methodological weaknesses with all RCTs, including inadequate randomisation description and allocation concealment, and lack of blinded outcome assessment and predetermined follow-up periods	RR 1.08 95% CI 0.88 to 1.33 P = 0.46	⟷	Not significant
[38] RCT	46 people Further report of reference [39]	**Pain measured by visual analogue scale , 7 years** with pylorus-preserving pancreaticoduodenectomy with limited pancreatic head excision with extended drainage (Frey procedure) Absolute numbers not reported The RCT was a long-term follow up of a previously published RCT. 46/60 (77%) people were followed up after 7 years	P = 0.67	⟷	Not significant

Weight gain/maintenance

Resection using pancreaticoduodenectomy compared with other surgical techniques Pancreaticoduodenectomy may be less effective than duodenum-preserving pancreatic head resection at increasing weight gain (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Weight gain					
[37] Systematic review	173 people, approximately 80% men, mean age range 43 to 47 years 4 RCTs in this analysis	**Proportion of people with postoperative weight gain** 34/86 (40%) with pancreaticoduodenectomy 70/87 (80%) with duodenum-preserving pancreatic head resection The review reported methodological weaknesses with all RCTs, including inadequate randomisation description and allocation concealment, and lack of blinded outcome assessment and predetermined follow-up periods	RR 1.93 95% CI 1.33 to 2.81 P <0.01	●●○	duodenum-preserving pancreatic head resection

No data from the following reference on this outcome. [38]

Quality of life

Resection using pancreaticoduodenectomy compared with other surgical techniques Pylorus-preserving pancreaticoduodenectomy may be less effective than duodenum-preserving pancreatic head resection at increasing global quality-of-life scores in the shorter term, but not in the longer term (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[37] Systematic review	101 people, approximately 80% men, mean age range 43 to 47 years 2 RCTs in this analysis	**Global quality-of-life score (EORTC questionnaire)** with pancreaticoduodenectomy with duodenum-preserving pancreatic head resection Absolute numbers not reported The review reported methodological weaknesses with all RCTs, including inadequate randomisation description and allocation concealment, and lack of blinded outcome assessment and predetermined follow-up periods	WMD 25.07 95% CI 18.93 to 31.31 P <0.0001	○○○	duodenum-preserving pancreatic head resection
[38] RCT	46 people Further report of reference [39]	**Global quality-of-life score (EORTC questionnaire) , 7 years** with pylorus-preserving pancreaticoduodenectomy with limited pancreatic head excision with extended drainage (Frey procedure) Absolute numbers not reported The RCT was a long-term follow up of a previously published RCT. 46/60 (77%) people were followed up after 7 years	P = 0.974	⟷	Not significant

Steatorrhoea

No data from the following reference on this outcome. [37] [38]

Global symptom improvement

No data from the following reference on this outcome. [37] [38]

Development of complications

No data from the following reference on this outcome. [37] [38]

Adverse effects

Resection using pancreaticoduodenectomy compared with other surgical techniques Pylorus-preserving pancreaticoduodenectomy may be associated with increased rates of postoperative complications and requirement for blood transfusion compared with duodenum-preserving pancreatic head resection (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] Systematic review	184 people, approximately (150 men, 34 women), mean age range 43 to 47 years 4 RCTs in this analysis	**Proportion of people with postoperative morbidity** 40/91 (44%) with pancreaticoduodenectomy 23/93 (25%) with duodenum-preserving pancreatic head resection The review reported methodological weaknesses with all RCTs, including inadequate randomisation description and allocation concealment, and lack of blinded outcome assessment and predetermined follow-up periods	RR 0.54 95% CI 0.20 to 1.46 P = 0.22	⟷	Not significant
[37] Systematic review	184 people, approximately (150 men, 34 women), mean age range 43 to 47 years 4 RCTs in this analysis	**Intraoperative blood replacement** with pancreaticoduodenectomy with duodenum-preserving pancreatic head resection Absolute numbers not reported The review reported methodological weaknesses with all RCTs, including inadequate randomisation description and allocation concealment, and lack of blinded outcome assessment and predetermined follow-up periods	WMD –1.28 units 95% CI –2.32 units to –0.25 units P = 0.02	●●○	duodenum-preserving pancreatic head resection

No data from the following reference on this outcome. [38]

Further information on studies

Comment: **Clinical guide:**
In clinical practice, resection using pancreaticoduodenectomy is usually reserved for when other surgical options, such as pseudocyst or duct decompression, are not feasible. It is required for disease limited to gland (typically in absence of dilated pancreatic duct).

GLOSSARY

Biliary decompression Procedure to relieve bile duct obstruction (either surgical or endoscopic or percutaneous).

Cystogastrostomy A communication between (pancreatic) pseudocyst and stomach, which can be performed endoscopically (stent) or surgically.

Cystojejunostomy An anastomosis between (pancreatic) cyst and jejunum.

Distal pancreatectomy Resection of the tail of the pancreas, usually to the left of the portal vein/superior mesenteric vein confluence. This may take place with or without splenectomy.

Frey procedure Localised pancreatic head resection with pancreaticojejunostomy (anastomosis between pancreatic duct and jejunum).

Beger procedure Localised pancreatic head resection with pancreatic neck transection and requiring reconstruction to pancreatic neck as well as tissue covering bile duct. Also called duodenum-preserving pancreatic head resection.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Pancreaticoduodenectomy Removal of the head of the pancreas, lower end of the bile duct, and duodenum. It may include surgical resection of the distal end of the stomach (antrum). Also called Kausch–Whipple or Whipple procedure.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Pancreatic enzyme supplements New evidence added. [13] Categorisation unchanged (Likely to be beneficial).

Resection using pancreaticoduodenectomy (Kausch–Whipple or pylorus-preserving) in people with more severe disease limited to the head of the pancreas New evidence added. [37] [38] Categorisation unchanged (Trade-off between benefits and harms).

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Disclaimer

TABLE 1 **Pseudocyst decompression (see text, p 20).** [25] [26] [27] [28] [29] [31]

Ref	Study design	Participants	Intervention	Results
Endoscopic drainage, surgical drainage, or conservative management of pseudocysts				
[25]	Retrospective case series over 16 years (1980–1995), single centre	114 people with pseudocysts, 60% with chronic pancreatitis, 37% alcohol-induced, mean age 48 years, 63% male	Conservative management (68 people, 28% with chronic pancreatitis) *v* surgery (46 people, 41% with chronic pancreatitis). Types of surgery performed: percutaneous drainage (13%), surgical drainage (57%), resection (17%). 13% had aspiration only	*Conservative management:* **Success rates:** 43/68 (63%) at median 51 months **Resolution of cyst in people successfully managed conservatively:** 13/43 (30%) at mean 46 months **Emergency surgery:** 5/68 (8%) at median 51 months **Elective surgery:** 19/68 (28%) at median 51 months **Mortality:** 0% at median 51 months *Surgery (percutaneous or surgical drainage):* **Postoperative complications:** 67% with percutaneous drainage (fistula/abscess), 20% with surgical drainage (bleeding, infection) **Recurrence/persistent pseudocyst:** 32% (11% with symptomatic pseudocysts) after median follow-up of 40 months. Results not calculable for each type of surgery **Mortality:** 0% at median 40 months
[26]	Retrospective case series over 6 years (1993–1999), multicentre	38 people with pseudocysts, 12 (31%) with alcohol-related chronic pancreatitis, 65% male	Endoscopic drainage	**Disappearance of cyst at 3 months:** 100% **Recurrence over mean 44 months:** 16% (all in people with alcohol-related chronic pancreatitis) **Postoperative complications:** 13% **Mortality over mean 44 months:** 0%
[27]	Retrospective case series over 11 years (dates not reported), single centre	36 people with pseudocysts, 12 (33%) with chronic pancreatitis, 3 alcohol-induced, median age 55 years, 52% male	Conservative management *v* endoscopic drainage *v* surgical drainage	*Conservative management:* **Success rates:** 14/36 (39%), 9 with chronic pancreatitis over mean 37.6 months **Recurrence:** 1/14 (7%) *Endoscopic drainage:* Carried out for 12/36 (33%) people **Success rates:** 10/36 (28%) **Recurrence:** 2/36 (5%) **Complications:** 0/36 (0%) *Surgical drainage:* Carried out for 10/36 (28%) people **Success rates:** 10/36 (28%) **Recurrence:** 0/36 (0%) **Complications:** 3/36 (8%), 2 developed abscesses, 1 developed pulmonary embolism
[28]	Retrospective case series over 2 years (dates not reported), single centre	34 people with pseudocysts (27 evaluated), median age 38 years, 79% male, 59% with chronic pancreatitis over 2 years, 56% alcohol-induced	Endoscopic drainage	**Initial success:** 24/34 (71%) **Recurrence:** 3/34 (9%). Factors associated with failure: >1 cm wall thickness, location of pseudocysts in tail of pancreas **Success at median 46 months:** 21/34 (62%)
[29]	Retrospective case series over 17 years (1983–2000), single centre	92 people with pseudocysts, median age 49 years, 72% male, 70% with chronic pancreatitis with a median 9 months of disease, 50% with alcohol-induced pancreatitis	Endoscopic drainage	**Absence of cyst at a median 43 months (success rates):** 71% Multivariate analysis suggested higher success rates if pseudocysts were located in the pancreatic head as compared with body/tail (OR 0.17, 95% CI 0.05 to 0.60), drainage duration of >6 weeks' duration (OR 0.19, 95% CI 0.06 to 0.60), and drainage with multiple rather than single stents (OR 0.08, 95% CI 0.01 to 0.79) **Postoperative complications:** 34% (common complications included bleeding and infection) **Mortality at 60 days (procedure-related):** 1%

Ref	Study design	Participants	Intervention	Results
Different types of surgical pseudocyst decompression versus each other				
[31]	Retrospective case series over 15 years (1975–89), single centre	98 people with pseudocysts, 67 with alcohol-induced pancreatitis, mean age 45–49 years, 82% male	CG (39 people) *v* CJ (59 people). Short-term follow-up (postoperative, not specified, up to 116 days, longest duration in range) and long-term follow-up (up to 4 years after surgery)	**Note:** People having CG had significantly larger cysts than those having CJ: 11.1 cm with CG *v* 6.7 cm with CJ; P <0.005 **Length of operation:** Significantly shorter with CG compared with CJ: 148 minutes with CG *v* 265 minutes with CJ; P <0.05 **Intraoperative blood loss:** Significantly lower with CG compared with CJ: 397 mL with CG *v* 703 mL with CJ; P <0.05 **Postoperative haemorrhage:** Higher with CG than CJ: 8% with CG *v* 2% with CJ; significance not assessed **Overall complications:** 10% with CG *v* 12% with CJ; significance not assessed **Length of hospital stay:** 11.3 days with CG *v* 18.9 days with CJ; P value reported as not significant **Perioperative mortality:** Similar rates: 5% with CG *v* 3% with CJ; significance not assessed **Recurrence:** 10% with CG *v* 7% with CJ at 4–6 years; significance not assessed

CG, cystogastrostomy; CJ, cystojejunostomy; Ref, reference.

TABLE 2 **Resection using distal pancreatectomy in people with disease limited to the tail of the pancreas (see text, p 21).** [33] [34] [35] [36]

Ref	Study design	Participants	Results
[33]	Retrospective case series over 20 years (1980–2000), single centre	90 people with chronic pancreatitis (84 evaluated), 58% alcohol-induced, median age 40 years, 69% male	**Pain relief:** 57% at median 34 months' follow-up. People whose pain recurred reported pain relief for a median 12 months **Postoperative complications:** 32% **Perioperative mortality:** 0.9% **Long-term mortality:** 10% at a median 34 months **Endocrine dysfunction:** Increase from 10% to 33% over a median 34 months
[34]	Retrospective case series over 22 years (1976–1997), single centre	40 people with chronic pancreatitis (32 evaluated), 25% alcohol-induced, median age 47 years, 55% male	**Pain relief:** 81% (49% complete pain relief, 32% partial pain relief) at mean 6.7 years **Postoperative complications:** 15% **Perioperative mortality:** 0% **Long-term mortality:** 5% at mean 6.7 years **Endocrine dysfunction:** Increased by 47% at mean 6.7 years **Diabetes:** New-onset diabetes at mean 2.8 years: 45%
[35]	Prospective case series over 14 years (1982–1995), single centre	74 people with chronic pancreatitis, alcohol intake not reported, median age 47 years, 55% male	**Pain relief:** 80% at median 58 months **Postoperative complications:** 46% **Perioperative mortality:** 0% **Long-term mortality:** 12% at median 58 months **Diabetes:** New-onset diabetes: 25% at median 58 months
[36]	Retrospective case series over 14 years (1984–1997), single centre	235 people, 24% with chronic pancreatitis, alcohol intake not reported, median age 50 years, 43% male	**Pain relief:** Not assessed **Postoperative complications:** 31% **Mortality:** 0.9 in postoperative period (median 10 days) **Median hospital stay:** 10 days

Ref, reference.

GRADE **Evaluation of interventions for Chronic pancreatitis.**

Important outcomes	Adverse effects, Development of complications, Global symptom improvement, Mortality, Pain relief, Quality of life, Steatorrhoea, Weight gain/maintenance								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of dietary supplements in people with chronic pancreatitis?									
4 (not reported) [13]	Pain relief	Pancreatic enzyme supplements versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, inclusion of poor-quality RCTs, and no significance assessment between groups
3 (55) [13] [14] [15]	Steatorrhoea	Pancreatic enzyme supplements versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (27) [13] [14]	Global symptom improvement	Pancreatic enzyme supplements versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and short follow-up. Directness point deducted for use of subjective outcome
2 (56) [13] [14] [15]	Adverse effects	Pancreatic enzyme supplements versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (36) [17]	Pain relief	Oral citrate versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted as only 16 people had pain before trial started
What are the effects of drug interventions in people with chronic pancreatitis?									
1 (25) [18]	Pain relief	Opioid analgesics versus each other	4	–3	0	0	0	Very low	Quality points deducted for sparse data, short follow-up, and incomplete reporting of results
1 (25) [18]	Adverse effects	Opioid analgesics versus each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of nerve blocks for pain relief in people with chronic pancreatitis?									
1 (18) [19]	Pain relief	Endoscopic ultrasound-guided nerve block versus computerised tomography-guided nerve block	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no between-group analysis for 1 outcome
What are the effects of different invasive treatments for specific complications of chronic pancreatitis?									
2 (111) [21] [22]	Mortality	Endoscopic versus surgical ductal decompression	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and for quasi-randomisation in 1 RCT. Directness point deducted for small number of events
3 (1129) [21] [22] [23]	Pain relief	Endoscopic versus surgical ductal decompression	4	–3	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, quasi-randomisation in 1 RCT, and inclusion of observational data. Directness point deducted for no direct comparison between groups in 1 study
1 (72) [22]	Weight gain/maintenance	Endoscopic versus surgical ductal decompression	4	–3	0	0	0	Very low	Quality points deducted for sparse data, quasi-randomisation, and incomplete reporting of results

Important outcomes	Adverse effects, Development of complications, Global symptom improvement, Mortality, Pain relief, Quality of life, Steatorrhoea, Weight gain/maintenance								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (51) [24]	Mortality	Different types of surgical ductal decompression versus each other	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results
1 (51) [24]	Pain relief	Different types of surgical ductal decompression versus each other	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results
1 (51) [24]	Quality of life	Different types of surgical ductal decompression versus each other	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results
1 (51) [24]	Adverse effects	Different types of surgical ductal decompression versus each other	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results
4 (184) [37]	Mortality	Resection using pancreaticoduodenectomy versus other surgical techniques	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and inclusion of RCTs with extensive methodological weaknesses. Directness points deducted for no statistical comparison between groups and for small number of events
4 (173) [37] [38]	Pain relief	Resection using pancreaticoduodenectomy versus other surgical techniques	4	–3	0	0	0	Very low	Quality points deducted for sparse data, low follow-up, and inclusion of RCTs with extensive methodological weaknesses
4 (173) [37]	Weight gain/maintenance	Resection using pancreaticoduodenectomy versus other surgical techniques	4	–2	0	0	0	Low	Quality points deducted for sparse data and inclusion of RCTs with extensive methodological weaknesses
2 (101) [37] [38]	Quality of life	Resection using pancreaticoduodenectomy versus other surgical techniques	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
4 (184) [37]	Adverse effects	Resection using pancreaticoduodenectomy versus other surgical techniques	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.