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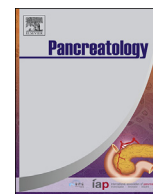
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## Guidelines for the understanding and management of pain in chronic pancreatitis<sup>☆</sup>



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### ABSTRACT

Abdominal pain is the foremost complication of chronic pancreatitis (CP). Pain can be related to recurrent or chronic inflammation, local complications or neurogenic mechanisms with corresponding changes in the nervous systems. Both pain intensity and the frequency of pain attacks have been shown to reduce quality of life in patients with CP. Assessment of pain follows the guidelines for other types of chronic pain, where the multidimensional nature of symptom presentation is taken into consideration. Quantitative sensory testing may be used to characterize pain, but is currently used in a research setting in advanced laboratories.

For pain relief, current guidelines recommend a simple stepwise escalation of analgesic drugs with increasing potency until pain relief is obtained. Abstinence from alcohol and smoking should be strongly advised. Pancreatic enzyme therapy and antioxidants may be helpful as initial treatment. Endoscopic treatment can be used in patients with evidence of ductal obstruction and may be combined with extracorporeal shock wave lithotripsy. The best candidates are those with distal obstruction of the main pancreatic duct and in early stage of disease. Behavioral interventions should be part of the multidisciplinary approach to chronic pain management particularly when psychological impact is experienced. Surgery should be considered early and after a maximum of five endoscopic interventions. The type of

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surgery depends on morphological changes of the pancreas. Long-term effects are variable, but high success rates have been reported in open studies and when compared with endoscopic treatment. Finally, neurolytical interventions and neuromodulation can be considered in difficult patients. © 2017 IAP and EPC. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

In 2016, John P Neoptolemos, David C Whitcomb and Tooru Shimosegawa embarked on a joint venture to produce the first truly International Guidelines on chronic pancreatitis (CP) with endorsement from the four International Societies and support from their respective Presidents and members in general. Although different guidelines exist such as the recent European consensus [1], the aim was to create a fresh clinical approach to the most important complications of CP; not only to assist a more pragmatic basis for patient diagnosis and management, but also to help accelerate the assessment and hence the development of newer therapies. The guidelines follow a new mechanistic definition of chronic pancreatitis and conceptual model of disease initiation and progression [2], which has been adopted by major international societies. Producing guidelines on CP is unquestionably a considerable task. Therefore the core committee for the working group decided to divide the work into more manageable sections. Each section focused on the key topics of CP, which were felt would benefit from consensus statements. The core committee identified International experts to ensure multidisciplinary representation from most regions of the world, and they were invited to contribute work to their respective areas. Calls for volunteers to participate in the process were also circulated around the four International Societies.

Prior to the process starting, the core committees were asked to vote on their preferred system for rating the quality evidence, which would be used as the basis for the International CP guideline recommendations. The consensus was in favor of adopting a GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach for topics lending themselves to evidence based statements. The guideline development process evolved over several milestone meetings at subsequent society conferences hosted throughout 2016.

The members of the Pain Management Working Group were appointed to represent worldwide specialists in treatment of pancreatic pain with representatives from gastroenterology, endoscopy, surgery and psychiatry/psychology. This was done to ensure an appropriate balance between the different regions and specialties in order to achieve the most comprehensive evaluation and recommendations. AMD was appointed as chairman of the group. First the following questions (Q) thought to be the most urgent and clinical relevant were made and authors assigned to answer them. These were (author initials in brackets):

- Q1. What is the natural history and burden of pain in CP (in relation to treatment)? (DY, CMC)
- Q2. Are there different types of pain in CP? (PJP, SSO, ES)
- Q3. Which methods are available to assess pancreatic pain and its response to treatment? (CMC, PJP)
- Q4. What is the role of smoking and alcohol on pain treatment in CP? (ES, PKG)
- Q5. Do enzymes and antioxidants influence pain in CP? (PKG, ES)
- Q6. How can analgesics be used to treat pain in CP? (SSO, AMD, ES)

- Q7. Is endoscopic therapy effective for pain treatment in CP? (MD, SI, SAWB)
- Q8. Is ESWL effective for pain treatment in CP? (CH, MD)
- Q9. Are other treatments (psychological, neurolytical etc.) of value for pain treatment in CP? (HvG, ES, TP)
- Q10. What is the optimal surgical approach to release pain in CP? (GOC, HvG, SAWB)
- Q11. When is the optimal time for surgery in painful CP? (GOC, IED)
- Q12. How to manage pain "relapse" after surgery or endoscopy? (IED, SI)
- Q13. What are the indications for referral to a specialist center for further investigation of pain (CH, DY)

The working group then provided a structured format for systematic reviews for the different questions, and included instructions on how to evaluate the level of evidence and clinical implications according to the GRADE guidelines, as adapted for "UpToDate" (<http://www.uptodate.com/home/grading-tutorial>). In the absence or limited availability of literature, the Pain Management Working Group decided if a recommendation would be included in the consensus report. The quality of evidence supporting the different statements was graded as (i) "high" if there was very low probability of further research completely changing the presented conclusions, (ii) "moderate" if further research may completely change the conclusions, (iii) "low" if further research is likely to change the presented conclusions completely. The term "very low" (iv) could be used if new research will most probably change the presented conclusions completely; however, the term was not used in the present work.

The strength of the recommendation was classed as "weak/conditional", "strong" or "not applicable". This took into account the quality of evidence, the translation of evidence into clinical practice, and any relevant uncertainties relating to population risk.

Finally, to gauge the level of objective support from the participating international expert panel, the members of the Pain Management Working Group voted using a nine-point Likert scale on their level of agreement with the recommendations and their GRADE score. Voting results were classified under "agreement" as either; strong ( $\geq 80\%$  of votes were 7 or above), conditional ( $\geq 65\%$  of votes were 7 or above), and weak ( $< 65\%$  of votes were 7 or above).

All authors reviewed the final manuscript to ensure the general relevance and applicability of the conclusions. The European Pancreatic Club conference in July 2016 hosted the first milestone meeting for the process of developing the International CP guidelines. AMD presented the outcomes of "the Pain Management Working Group" to the meeting and the work is summarized in this manuscript.

In the present document, the recommendations are listed with a summary of the most relevant information and references. However, due to word limits *most* information could not be included and the reader is encouraged to see the [Appendix](#) where the full text and references are found.

## Q1. What is the natural history and burden of pain in chronic pancreatitis?

*Abdominal pain is the most frequent symptom of CP. However, the severity, temporal nature, and natural history of pain is highly variable (Quality assessment: moderate; Recommendation: strong; Agreement: strong)*

While variation in disease estimates exist, the prevalence of CP has been approximated at ~50/100,000 population [3]. Abdominal pain, alone or during episode(s) of acute exacerbation of pancreatitis, is the most common symptom. Patients typically describe their pain as a dull, sharp or nagging sensation in the upper abdomen, which can radiate to the back, and often presents after or worsened by food intake. In natural history studies, pain was observed as the initial presentation in ~75% of patients [4], and present during the clinical course in 85–97% [4–7]. Patients with early onset-disease and those with alcohol etiology are more likely to have pain [4,5]. According to the *burn-out* hypothesis, a majority of patients with chronic pancreatitis achieve lasting pain-free status during the clinical course [5,8]. This claim, however, has not been substantiated by others, mainly due to persistence of pain symptoms in a significant fraction of patients with ongoing pain even after 10 or more years of disease [9]. Naturally, CP is a major burden for patients and both pain intensity and the frequency of pain attacks have been shown to reduce quality of life substantially [10,11].

## Q2. Are there different types of pain in CP and what does it mean for treatment?

*Pain in CP remains poorly understood and inadequately correlated with neurobiological mechanisms. By definition, CP is characterized by inflammation but unlike other inflammatory disorders, there is a paucity of therapeutic attempts targeting this particular aspect of pathophysiology. On the other hand, there are striking changes in structure and function in both the peripheral and central nervous system in this condition, lending plausibility to a maladaptive state that includes both neuropathic and dysfunctional pain. In the absence of effective anti-inflammatory approaches, it is clearly important to focus on the alteration of function that accompanies these changes in the nociceptive system as a potential therapeutic target. (Quality assessment: low; Recommendation: strong; Agreement: strong)*

An early approach to classifying pain in CP was made by Amman et al. [8] “A-type pain” pattern was seen in patients with one or more discrete episodes of pain interspersed with pain-free intervals. Slightly less than half (44%) of patients also had “B-type pain” described as persistent (i.e. daily) pain over prolonged periods of time and/or closely clustered exacerbations of severe pain. A later study demonstrated that clinical outcomes were best predicted when “intermittent” (about 45% of patients) versus “constant” pain were compared, thus echoing the earlier binary classification [10].

## Putative neurobiological causes of pain

**Inflammation:** It is intuitively appealing to suggest that a significant, if not major, type of pain in CP is inflammatory in nature. Animal models have also shown that inflammatory pain in CP is mechanistically generally similar to other chronic inflammatory conditions. The expression of numerous algogenic factors is altered

in experimental models as well as in human pancreatic specimens. Some but not all of these factors and molecules have been shown to correlate with pain severity, although causation is not proven [12–14]. On the other hand, “intermittent” episodes of pain observed in patients correspond not always to a “flare” of inflammation. Correspondingly, in a large prospective cohort study, there was no correlation between temporal pattern and the presence or absence of radiological evidence of inflammation or obstructive pathology [10,15].

**Neuropathy:** Animal models have provided convincing evidence that CP results in hypersensitivity of pain responses to pancreatic stimulation, associated with impressive sensitization of the primary nociceptive neurons with specific electrophysiological and molecular changes. The models also suggest a component of central sensitization including potential roles for spinal glial activation and descending inhibitory pathways [16–18]. Correspondingly, patients with severe CP have lower pain thresholds and expanded pain referral areas than patients with moderate CP or healthy volunteers, which many be a reflection of spinal sensitization [19,20]. Alterations in descending inhibitory influences on spinal nociceptive neurons have also been shown in humans [19–22]. Finally, electroencephalographic and imaging findings in patients with CP similarly show functional changes suggesting a maladaptive pain response [20,23–26].

## Q3. Which methods are available to assess pancreatic pain and its response to treatment?

*Assessment of pain in CP follows the guidelines for other types of chronic pain, where the multidimensional nature of symptom presentation is taken into consideration. Only a few instruments have been validated for subjective pain assessment in CP; however, several appropriate measures exist despite not being rigorously validated in this population. (Quality assessment: moderate; Recommendation: strong; Agreement: strong)*

### Subjective verbal reports

#### One-dimensional scales (usually pain intensity)

One-dimension scales assess a single element of pain, and allow for a simple and fast method for patients to self-report the subjectively experienced intensity of their pain, but can oversimplify the pain experience [27]. These scales use numeric (often 0–10), verbal or visual descriptors to quantify pain or the degree of pain relief. Numerical scales, such as the visual analogue scale (VAS), are commonly applied to assess the intensity of pain in CP patients, but should be combined with a standardized registration of the pain pattern in time [10].

#### Multidimensional scales

Multidimensional scales measure several of the above over-viewed aspects of pain, including its intensity, nature and location, and in some cases, pain's impact on mood or activity level. A commonly used measure in CP, the Izbicki pain score was developed to capture some of the aforementioned dimensions of pain and provide a surrogate score [28]. It has, however, never been strictly validated in patients with CP. The Brief Pain Inventory (BPI) is commonly used with chronic pain patients and validated in CP. It quantifies intensity as well as pain's interference in mood, ability to work etc., and correlates with quality of life in CP patients [11]. The McGill Pain Questionnaire is another commonly used survey that assesses three aspects of the pain experience, including sensory, affective, and evaluative dimensions and likely a more appropriate pain assessment measure in CP patients than unidimensional

numeric scales alone [29].

#### Quantitative sensory testing (QST)

Pain sensitivity can be reliably assessed and quantified in the laboratory using quantitative sensory testing (QST) [30]. These calibrated and standardized methods for delivering noxious stimuli under controlled conditions [31] are reflective of clinical conditions, as subjects who rate QST stimuli as most painful [32,33], or show heightened central sensitization [34,35] report the most frequent, disabling clinical pain. Dynamic QST techniques have the potential to more directly assess CNS pain-modulatory processes [36]. QST is frequently employed to evaluate treatment responses among CP patients. For example, pregabalin inhibited central sensitization [37], and oxycodone was found to be more effective than morphine on visceral pain in patients with CP [38].

#### Q4. What is the role of smoking and alcohol on pain treatment in CP

*Abstinence from alcohol and smoking, in addition to adequate treatment, should be strongly advised in patients with CP (Quality assessment: moderate (alcohol) to weak (smoking); Recommendation: strong; Agreement: strong)*

**Alcohol:** High alcohol intake is a risk factor for acute and chronic pancreatitis [39], and abstinence from alcohol is associated with reduction in frequency of recurrence of pancreatitis [40,41]. Pharmacological treatment is often necessary to ensure that the patients refrain from alcohol intake. Benzodiazepines and mood stabilizers such as carbamazepine are safe and efficacious in treating moderate symptoms of alcohol withdrawal [42]. Only three medications are used for treatment of alcohol dependence; naltrexone, acamprosate and disulfiram. Naltrexone has strong support in reducing relapse in alcoholics [43], while acamprosate has shown efficacy in some [44] but not all trials [45]. While disulfiram has been widely used, there is no clear clinical trial data supporting positive outcomes [46].

**Non-pharmacological treatments** have also been widely used. Several psychosocial interventions have shown significant behavioral change in patients with alcohol dependence including cognitive behavioral therapy [47,48]. Self-help organizations such as Alcoholics Anonymous can also be helpful [49].

**Tobacco:** Several studies have shown that smoking tobacco, particularly cigarettes increased the risk for developing both acute [50,51] and chronic pancreatitis [52,53] and this relative risk is dose-dependent. More than 80% of patients with alcoholic chronic pancreatitis are smokers and smoking potentiates alcohol toxicity in dose-dependent way [53]. While cigarette smoking is often present in alcohol abuse, studies showing smoking as an independent predictive factor are emerging [50,54]. However, no study has evaluated the effect of smoking cessation on pain in patients with CP.

**Pharmacological treatment:** Logically, smoking cessation should be a strong recommendation. In a recent Cochrane review nicotine replacement, bupropion, varenicline, and cytosine, another partial nicotine receptor agonist, had the greatest evidence for improving the chances of quitting [55].

**Non-pharmacological treatment:** Cognitive behavioral therapy combined with smoking cessation medications can be effective in smokers who are motivated to quit [56]. Mindfulness-based therapy may also help with recovery from smoking relapse [57].

#### Q5. Do enzymes and antioxidants influence pain in CP?

*Pancreatic enzyme therapy with high protease content may be tried as an initial treatment for pain relief in patients with CP. Furthermore; combination of antioxidants in sufficient dosages should be included in the armamentarium of pain treatments (Quality assessment: moderate; Recommendation: strong; Agreement: weak)*

The pathophysiological basis of using pancreatic enzymes for pain in CP is related to the hypothesis that nutrients stimulate the release of cholecystokinin releasing factor (CRF) from the duodenum [58]. The CRF then releases cholecystokinin, which stimulates pancreatic secretion and this may increase intraductal pressure in patients who have ductal obstruction. Theoretically, the pancreatic enzymes degrade CRF thus limiting the release of cholecystokinin and subsequently decrease pancreatic secretion. Six randomized clinical trials have been reported on the effect of pancreatic enzymes in pain relief. In a review of these [59], pain relief using pancreatic enzymes as tablets was noted in two trials [60,61] and no benefit was noted in 4 trials that used acid-protected capsule form of enzymes [62–65]. The reason could be that pancreatic enzymes were not released in the duodenum in the acid-protected form. If enzyme therapy is tried for pain relief, the preparations should be uncoated, contain large amounts of proteases (>25,000 USP units per tablet) and be given in a dosage of four to eight tablets four times a day.

**Antioxidants** may also be helpful in pain treatment. Oxidative stress as a mechanism of inflammation in CP has been shown for the past 30 years [66–70]. Consequently, antioxidant supplementation has been used to ameliorate oxidative stress and relieve pain in patients with CP. Recent meta-analyses of randomized controlled trials have shown beneficial effect of antioxidants in patients with CP [71–73]. A combination of antioxidants ( $\beta$ -carotene, vitamin C, vitamin E, selenium, and methionine) has shown significant pain relief while studies with single antioxidant therapy showed no significant pain relief. A recent study has shown that a combination of pregabalin and antioxidants resulted in benefit in those who had recurrence of pain after surgical and/or endoscopic therapy [74].

#### Q6. Which analgesics are recommended for pain in chronic pancreatitis?

*Currently the standard guideline for analgesic therapy in CP follows the principles of the “pain relief ladder” provided by the World Health Organization (WHO) adjusted to the pain characteristics of this condition (Quality assessment: moderate; Recommendation: strong; Agreement: strong)*

The standard guidelines for analgesic therapy in CP follow the principles of the “pain relief ladder” provided by the World Health Organization (WHO). This approach enables a simple stepwise escalation of drugs with increasing analgesic potency (level I-III) until pain relief is obtained, with simultaneous monitoring and handling of side effects [75].

**Simple analgesics** are used as a cornerstone in pain treatment and paracetamol is the preferred level I drug due to its limited side effects. The non-steroidal anti-inflammatory drugs (NSAIDs) should in general be avoided due to their gastrointestinal toxicity [76]. This may especially be relevant in CP as patients are already predisposed to peptic ulcers [77].

*Adjuvant analgesics* are a heterogeneous group of drugs initially developed for indications other than pain and include antidepressants, anticonvulsants as well as anxiolytics (and spasmolytics in the gut). Although adjuvant analgesics have been widely used in the clinic to treat pain in CP, only pregabalin has been investigated in this patient group and was found to induce a moderate pain relief [78].

*Anti-depressive drugs* are widely used pain treatment in functional visceral pain disorders and although no data exist in CP, their positive effects in patients with neuropathic pain (thought to be prevalent in CP) makes them attractive [79]. It is, however, unclear if their effect is mediated through direct analgesic effects or indirectly by reducing anxiety and depression [80].

*Opioid analgesics* seem to be a necessary step to dampen pain in many patients with CP, and it is mandatory that pancreatologists understand the complexity of opioids [81]. Opioid based treatments are often associated with many severe adverse effects such as constipation or opioid induced hyperalgesia [82,83]. Patients on long-term opioid therapy must be kept under close clinical surveillance and it shall be stressed that only about 25% of patients benefit from treatment. Some drugs such as tramadol possesses both a weak opioid agonist activity along with an effect on noradrenaline and serotonin uptake [84]. Tramadol is often the preferred level II analgesia and was shown to be superior to morphine in patients with CP, with fewer gastrointestinal side effects for the same level of analgesia [85]. Transdermal administration of opioids should be reserved to patients having trouble with tablet ingestion. There is marked inter-individual variability in responsiveness to different opioids, and often a trial of an alternative opioid is indicated [81,86].

In some patients *unconventional treatment* with drugs such as ketamine is beneficial, but only in the hands of pain specialists. Somatostatin-analogue inhibits pancreatic secretion and may theoretically alleviate pain through reduction of pancreatic ductal pressure. However, there are conflicting data about the efficacy. Other drugs including clonidine, benzodiazepines, anti-psychotics or cannabinoids may also be beneficial in difficult cases.

In *clinical practice* pain treatment is mainly guided by evidence from somatic pain studies together with individual experience and traditions. In Fig. 1 the pain treatment algorithm used at Centre for Pancreatic Diseases, Aalborg University Hospital, Denmark is shown. This includes neurophysiological and psychological testing. For example segmental hyperalgesia of the epigastric skin area (pancreatic viscerotome) may predict the response to gabapentinoids [87].

#### Q7. Is endoscopic therapy effective for pain treatment in CP?

*The best candidates for successful treatment of painful CP with first-line endoscopic therapy are patients with distal obstruction of the main pancreatic duct (single stone and/or single stricture in the head of the pancreas) and in the early stage of the disease. Endoscopic therapy can be combined with Extracorporeal Shock Wave Lithotripsy (ESWL) in the presence of large (>4 mm) obstructive stone(s) located in the pancreatic head, and with ductal stenting in the presence of a dominant main pancreatic duct stricture that induces a markedly dilated duct. (Quality assessment: moderate; Recommendation: strong; Agreement: conditional)*

Endoscopic therapy (ET) in painful CP is based on the rationale that pain is related to an outflow obstruction of the main pancreatic duct (MPD) due to stricture(s) or pancreatic intraductal stone(s).

Endoscopic retrograde cholangio-pancreatography (ERCP) can achieve MPD drainage by sphincterotomy of the major and/or

minor papilla, by short-term stent placement or by pancreatic stone extraction, usually after fragmentation with ESWL.

The effectiveness of ET is usually the result of these combined procedures; all of these are aimed to restore drainage of the MPD. With this approach about 60% experience complete or partial pain relief both in the short (<2 years) and long-term (>5 years) follow-up. However, the quality of evidence of reported results remains low in most of these retrospective observational non-randomized studies (see *Tables and studies in Appendix*). Only two randomized controlled trial (RCT) compared ET and surgery, and both favored surgery [88,89]. There were, however, several shortcomings. Among them was the low technical success rate [88] and suboptimal procedures [89] compared with previous studies (*Tables in Appendix*). Contrary to surgery, ET is possible in patients with risk factors such as older age and co-morbidities. Factors predicting favorable clinical outcome after ET ± ESWL have been identified and are shown in Fig. 2 [90,91] (see also *Tables in Appendix*), and if clinical success can be obtained with ≤ 5 endoscopic interventions, the patient will probably achieve long-term favorable outcome.

#### Q8. Is ESWL effective for pain treatment in CP?

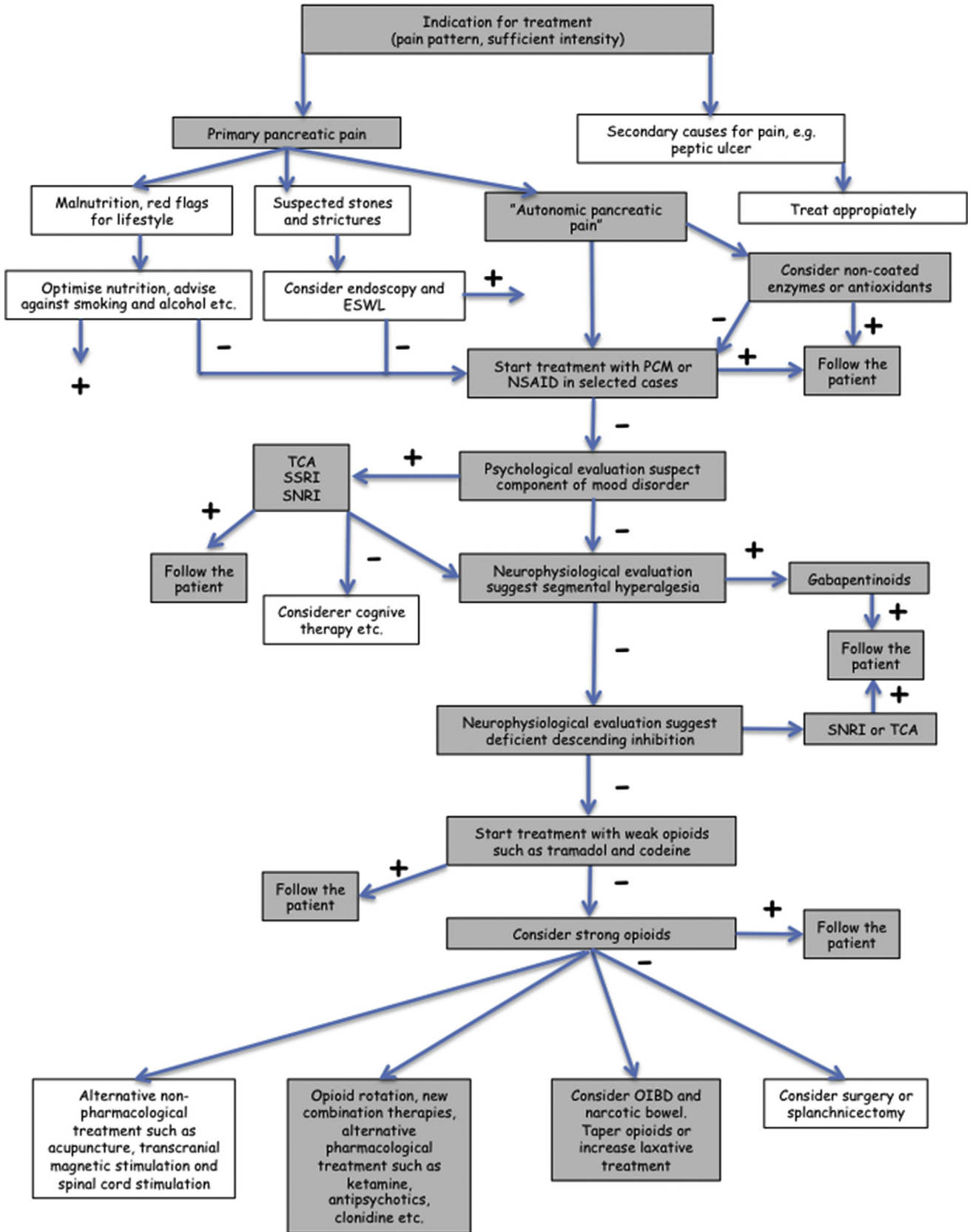
*In patients with uncomplicated painful calcified CP, ESWL alone is a safe and effective treatment. Best candidates for benefiting from initial first-line ESWL are patients with obstructive calcifications, > 4 mm confined to the head of pancreas. Combining systematic endoscopic therapy with ESWL adds to the cost of patient care, at the same time not probably improving the outcome of pancreatic pain (Quality assessment: moderate, Recommendation strong; Agreement: conditional).*

ESWL for pancreatic stones is indicated for patients with all of the following:

1. recurrent attacks of pancreatic pain
2. moderate to marked changes in the pancreatic ductal system
3. obstructing ductal stones (minimal diameter: 2–5 mm, calcified or radiolucent) [92].

Regardless of the method of shock waves generation ESWL provides high rates of stones fragmentation (average of 91% ranging from 54 to 100%) [92]. ESWL was proven useful for treating CP related pain in several meta-analyses [93,94] where the pooled proportion of patients with absence of pain at follow-up was about 50% and narcotic use was decreased in 80%. In a prospective randomized study that compared ESWL alone with ESWL combined with endoscopy [95], there was no evidence that the combination of endoscopy and ESWL was better than ESWL alone for pain treatment. Data regarding duct clearance have been somewhat conflicting ranging between similar for the procedures alone [96] to a better outcome for the combined procedures [97]. Factors associated with complete stone clearance included the presence of a single stone vs. multiple stones [98,99], the absence of a MPD stricture [98] and a lower density of stones (<820 Hounsfield units) [100].

After treatment with ESWL (alone or combined with endoscopic drainage), most of the patients who experienced pain relapses developed them during the first two years following treatment [90,95,101]. Pain relapse occurred significantly more frequently in patients with incomplete removal of stones after the initial therapy and in those with a MPD stricture [98]. Other factors associated with long-term pain relief are short disease duration, low frequency of pain attacks before treatment, complete ductal stone clearance, absence of MPD stricture and discontinuation of alcohol



**Fig. 1.** Suggested algorithm for pharmacological treatment (grey boxes) of pain in chronic pancreatitis. In most cases, combination therapies are necessary. Treatment with antidepressives is guided by psychological evaluation including assessment of catastrophizing, depression etc. In case gabapentinoids are considered we use evaluation of the ratio between segmental and generalised hyperalgesia (see text). Of note, treatment with gabapentinoids, TCA, SNRI (or SSRI in selected cases) should be titrated slowly until sufficient effect or intolerable adverse effects occur. Treatment shall be individualised due to major differences in receptor properties and analgesic mechanisms between patients. NSAIDs are normally not indicated and should be used carefully. Opioids shall be avoided if possible due to the major side effects on the gastrointestinal tract etc., but in severe pain they may be

and tobacco [90,98,101,102].

#### **Q9. Are other treatments (neurolytical, psychological, etc.) effective for pain management in CP?**

*Neurolytical interventions can be used in selected patients with painful CP who have failed endoscopic and surgical treatment. Thoracoscopic splanchnic denervation is more effective regarding long-term pain relief in patients who are not on chronic opioid treatment. Behavioral interventions should be part of the multidisciplinary approach in CP pain particularly when patients experience psychological impact of pain and quality of life has decreased. Early intervention in children may be particularly important. (Quality assessment: low; Recommendation: strong; Agreement: conditional)*

*Neurolytic interventions:* Celiac plexus blocks and splanchnic nerve ablation of patients with CP are generally advised when other medical treatments for pain have failed. Several techniques for percutaneous celiac plexus blockade have been described [103], but pain relief only lasts for short term with a risk for side effects such as postural hypotension and diarrhea. Therefore celiac plexus block is nowadays rarely applied in CP. Thoracoscopic splanchnicectomy was first described as a minimally invasive therapy for pain in 1994 [104]; however, to date no RCT has been done. Preoperative opioid use, duration of disease and pain seem to impair long term results probably due to central sensitization [105].

There are only a few studies of spinal cord stimulation and transcranial magnetic stimulation in chronic pancreatitis [106,107]. Pain relief by spinal cord stimulation was achieved in 66% of patients, but a drawback of the procedure is its invasiveness. Repetitive TMS holds promise for treating depression in chronic pancreatitis patients with a possible concurrent pain relieving effect.

*Psychological/psychiatric interventions:* There is a paucity of studies in CP, but in other chronic pain conditions psychological interventions have been shown to be efficacious [108,109]. Interventions include cognitive behavioral therapy, mindfulness approaches, hypnosis etc. [110–113].

Children with CP represent an important subgroup who experiences frequent pancreatitis-related abdominal pain [114], but there are no studies conducted to date. However, psychological treatments for other forms of pediatric chronic pain have promising effects.

#### **Q10. What is the optimal surgical approach to relieve pain in CP?**

*Depending on the morphological changes of the pancreas and pain processing status a (partially) resection, decompression of the pancreatic duct or combined interventions can be performed to reduce pain. Long-term effects are variable, but success rates up to 80% have been reported. The emerging role of total pancreatectomy*

*as initial surgical treatment looks promising but needs further investigation (Quality assessment: moderate; Recommendation: strong; Agreement: conditional)*

Surgical options for pain are classified into three categories: a) decompression (focusing on ductal hypertension), b) resection (focusing on inflammatory masses and stones in the pancreatic head) and c) combined procedures. Although long-term results of surgery are promising, most of studies to date are observational or only compare different invasive procedures. There are several procedures available dependent of the indication (see Appendix). In randomized controlled trials, tailored organ-sparing procedures have been found to be superior to Whipple or the pylorus-preserving Whipple procedure in regard to pain relief (75%) and morbidity (20%) [115,116]. An indication for total pancreatectomy (with/without islet autotransplantation) is to palliate pain especially before diabetes mellitus has developed [117,118]. When central sensitization is present endoscopic and/or surgical therapy has a higher risk of failure. Factors that are relevant in developing sensitization are duration of the disease, age, pain history and previous invasive treatment [119]. Surgery has to be tailored to the needs of patients and should be organ sparing in a high-volume center with expertise in pancreatic surgery.

#### **Q11. When is the optimal time for surgery in painful CP?**

*Current evidence on the timing of surgery for painful CP suggests a beneficial role for early surgery, i.e. 1) within the first 2–3 years after diagnosis or symptom onset, 2) for patients who had equal to or fewer than 5 endoscopic procedures, and 3) for patients who have not yet required opioid analgesics for medical pain treatment (Quality assessment: low; Recommendation: weak; Agreement: strong).*

Although there are no prospective controlled studies that specifically addressed the timing of surgery for painful CP, increasing amount of evidence suggests that surgery should be considered early for better pain outcomes. In a systematic review that analyzed the role of timing, it was found that early surgery was associated with a greater probability to attain postoperative pain relief [120]. The optimal cutoff point for was found 26.5 months or less [121]. Preoperative opioid use and 5 or more endoscopic interventions also seems to have negative influence [122,123]. In patients with obstruction of the duct system timing can be decisive for the outcome.

#### **Q 12. How to manage pain "relapse" after surgery or endoscopy for painful CP?**

*Current evidence suggests that the first step for the management of pain relapse should be exclusion of obstructing stones or strictured anastomosis via imaging, followed by a limited number endoscopic interventions, and early consideration of re-surgery to achieve pain*

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prescribed for limited periods and the physician shall always be aware of opioid induced bowel dysfunction and hyperalgesia (narcotic bowel).

"Plus sign" indicate sufficient/satisfactory effect.

"Minus sign" indicate insufficient effect

ESWL: extracorporeal shock wave lithotripsy

PCM: paracetamol

NSAID: non-steroidal anti-inflammatory drugs

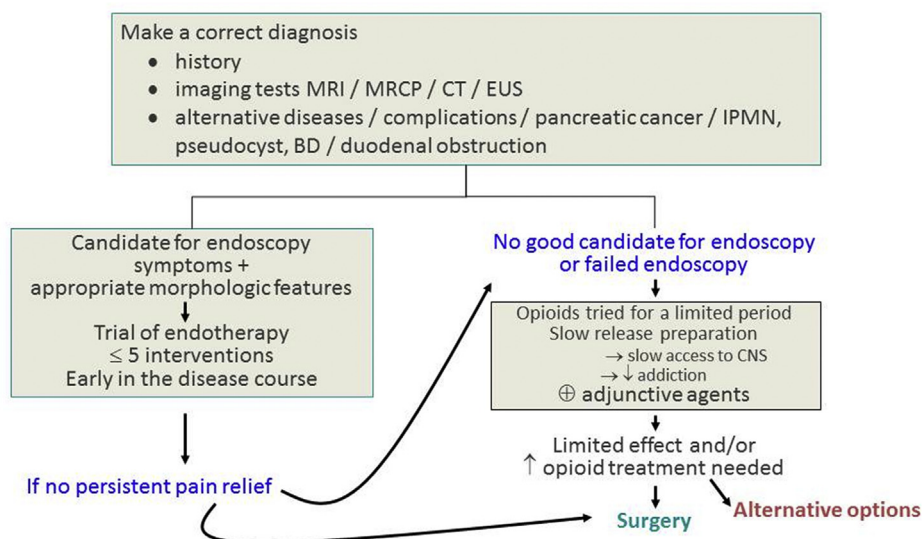
TCA: tricyclic antidepressives

SNRI: serotonin-noradrenalin reuptake inhibitors

SSRI: selective serotonin reuptake inhibitors

OIBD: opioid induced bowel dysfunction.





**Fig. 2.** The first step for the management of pain in patients with chronic pancreatitis should be to make a correct diagnosis based on clinical history and imaging procedures, and to exclude alternative diseases or complications that could induce pain not related to pancreatic ductal obstruction by stones and/or strictures. The second step should be to select the appropriate candidates for endoscopy (see the text for the definition of best candidates for endoscopic treatment with or without ESWL) and to treat such good candidates early in the disease course (within the first 2–3 years after symptom onset), with a limited number ( $< \text{or} = 5$ ) of endoscopic interventions. If no persistent pain relief was obtained after a limited trial of endoscopic treatments  $\pm$  ESWL, that means that other factors than increased pancreatic ductal pressure could be involved in the pain syndrome and for these patients no further attempts at drainage should be proposed. In these patients or if the patient is not a candidate for endoscopy or in case of technical failure of endoscopy, medical treatment could be tried see e.g. Fig. 1. Surgery and alternative options could also be proposed if no persistent pain relief was obtained after endoscopy, in case of limited effect of medical treatment.

control (Quality assessment: weak; Recommendation: strong; Agreement: weak).

After both surgery [124–126] and endoscopy [127], the long-term (5-year) pain free status is around 50–60%. Patients with pain relapse after endoscopic treatment may benefit of combined antioxidant-pregabalin therapy [74]. There is lack of sufficient evidence for concrete recommendations for managing pain relapse after surgery, but surgeons should consider that any kind of subsequent treatment may be subject to failure due to irreversible neuropathic alterations [79,128]. In all cases, it is crucial to first exclude more simple reasons for therapy failure such as obvious stricture of anastomosis, or obstructing stones in the pancreatic or bile duct [129]. Furthermore, it should be considered that a salvage operation for pain relapse may end up in a total pancreatectomy.

### Q13. What are the indications for referral to a specialist center for further investigation of pain?

All patients with presumed or established diagnosis of CP should be routinely referred to specialist pancreatic centers for investigation and treatment of their disease (Quality assessment: moderate; Recommendation: strong; Agreement: strong).

Referral should be considered when non-specialist management is failing, chronic pain is poorly controlled, there is significant distress, and/or where specific specialist intervention or assessment is considered. A systematic review of observational studies (although not in CP) concluded that a longer delay between specialist referral and specialist consultation resulted in poorer health and pain management [130].

### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://>

[dx.doi.org/10.1016/j.pan.2017.07.006](http://dx.doi.org/10.1016/j.pan.2017.07.006).

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