Published in final edited form as:

Pancreatology. 2016 ; 16(1): 83–94. doi:10.1016/j.pan.2015.10.015.

Mechanism, Assessment and Management of Pain in Chronic Pancreatitis: Recommendations of a Multidisciplinary Study Group

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Disclosure Statement

The authors have no relevant conflict of interest related to this material.

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Abstract

Description—Pain in patients with chronic pancreatitis (CP) remains the primary clinical complaint and source of poor quality of life. However, clear guidance on evaluation and treatment is lacking.

Methods—Pancreatic Pain working groups reviewed information on pain mechanisms, clinical pain assessment and pain treatment in CP. Levels of evidence were assigned using the Oxford system, and consensus was based on GRADE. A consensus meeting was held during *PancreasFest 2012* with substantial post-meeting discussion, debate, and manuscript refinement.

Results—Twelve discussion questions and proposed guidance statements were presented. Conference participates concluded: *Disease Mechanism*: Pain etiology is multifactorial, but data are lacking to effectively link symptoms with pathologic feature and molecular subtypes. *Assessment of Pain*: Pain should be assessed at each clinical visit, but evidence to support an optimal approach to assessing pain character, frequency and severity is lacking. *Management:* There was general agreement on the roles for endoscopic and surgical therapies, but less agreement on optimal patient selection for medical, psychological, endoscopic, surgical and other therapies.

Conclusions—Progress is occurring in pain biology and treatment options, but pain in patients with CP remains a major problem that is inadequately understood, measured and managed. The growing body of information needs to be translated into more effective clinical care.

Introduction

Chronic pancreatitis (CP) is a chronic inflammatory disorder of the pancreas that is complicated by severe, constant and disabling pain in nearly half of all patients (1) and leads to some of the worst quality of life (QOL) scores for any chronic disease (1–3). Chronic pancreatitis was considered a disease of alcoholism until the discovery that smoking, complex genotypes, and other factors accounted for the underlying etiology in over half of all cases of this disease (4–6). Studies of patients with CP and pain indicate that there are multiple pain patterns, characteristics and severity levels, and that morphology on abdominal imaging may not correlate with pain features (7). The strongest predictor of poor quality of life and disability among complications of CP is constant pain (1). Recent studies have addressed the quality of life (2, 8), and comparative effectiveness of treatment for neuropathic pain (9, 10) and outcomes of both endoscopic and surgical treatments (11, 12). Finally, there is growing use of total pancreatectomy with islet autotransplantation (TPIAT) for control of pain (13–15).

Several recent guidelines for the general management of pain in CP have been published (15–18). In addition, specific guidelines for the endoscopic treatment of pain were published by consensus of a working group supported by the European Society of Gastrointestinal Endoscopy (ESGE) (19). These documents carefully addressed several clinical questions from existing literature and by discussion. The evolving literature on pancreatitis-associated pain, advances in the neuroscience of pain (3), various methods for assessing pain and new treatment options, including total pancreatectomy with TPIAT justify a comprehensive review, identification of knowledge gaps and recommendations for future research.

Guideline Focus

The clinical recommendations guide the evaluation and management of pain in adult patients with recurrent acute pancreatitis (AP) and chronic pancreatitis. Inadequate data on pediatric groups precluded inclusion of this important population in the current review.

The problem of pain in CP is well recognized, and represents a major area of emphasis by the clinical-translational working groups meeting at PancreasFest. In addition to regular working group meetings, a comprehensive, multidisciplinary review of the problem of pain in CP was undertaken over a three-year period at the annual *PancreasFest* meeting, as previously described (15, 20)

The *PancreasFest* working groups were organized by academic physicians and scientists associated with the North American Pancreatitis Study Group (see NAPS2 (4)) and the Center for Pain Research, University of Pittsburgh (www.paincenter.pitt.edu) who had an interest in pancreatic pain. The Pain Working Group was further developed by inviting content experts to participate in the process. *Ad Hoc* sub-groups were organized to develop and frame discussion questions and guiding statements in three areas: 1) mechanisms of pain in CP; 2) the assessment of pain; and 3) the treatment of pain, including TPIAT.

Evidence Review and Grading

Levels of evidence were ranked based on the Oxford Center for Evidence-Based Medicine's system (21). Consensus was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) grid for the clinical guideline statements (22).

Evidence and Discussion

The working group included physicians and scientists who regularly attend PancreasFest, expressed a primary interest in pancreatic pain, and met as a group during break-out sessions. Primary areas of interest and need were identified by discussion and presentations in year one. The *ad hoc* group was encouraged to invite the participation of other experts, and to organize and prioritize the state-of-the-art and state-of-the-science, and present their priorities to the larger group at the subsequent PancreasFest meeting. Dr. Anderson organized the PancreasFest working groups, and the process of developing discussion questions was initiated, with refinement and focus during the third year.

The final discussion questions presented to attendees of *PancreasFest 2012* were followed by one or more guidance statements intended to provide a concise summary and, if indicated, a clinical recommendation or guidance. The initial recommendations were presented to the audience and projected onto a screen on a statement-by-statement basis. The audience, which was approximately 90% MD or MD-PhD, 4% PhD and 6% others, such as study nurses (Appendix), responded to the draft guidance statements for specific clinical questions and then indicated their level of agreement based on a 5-point scale (strong positive, weak positive, uncertain or equivocal, weak negative, strong negative) using digital voting devices. Conference attendees discussed the initial questions and guidance statements of the working group. The responses were tabulated and projected for the entire conference to discuss and revise in real-time. The conference participants then voted again on the level of agreement with each statement that, after discussion, required more information or clarification. The participants sent additional comments to the study members by email to be considered in the final discussion.

The working groups revised and extended the evidence and discussion sections for each question over a two-year period with updated references. The focus was to improve accuracy and specificity in each statement, improve clarity, and re-review controversial areas. In addition, common ground and agreement of experts from different disciplines with different approaches was sought throughout the manuscript writing, review and rewriting process. All working group members reviewed each major version of the document, and all participants who participated in the discussion and reviewed and approved the final document are included as co-authors.

Results

PART 1. MECHANISMS OF PAIN IN CHRONIC PANCREATITIS

Three broad discussion questions were developed. Question 2 was subdivided to address specific issues.

Discussion Question 1: What causes pain in chronic pancreatitis?—Guidance

Statement 1: Pain in CP may arise from mechanical (intraductal pressure/obstruction), inflammatory, malabsorptive or neurogenic/neuropathic changes in the pancreas and/or surrounding organs.

Evidence Level: 2b

Grade of recommendation: B

Level of Agreement: A 89%; B 9%; C 0%; D 0%; E 2%.

Evidence and Discussion: Pancreatic duct obstruction, strictures, and/or peri-pancreatic fibrosis may cause ductal hypertension or ischemia from a stricture or a compartment syndrome leading to pain (23–26). However, when measured, pancreatic duct pressures do not correlate well with pancreatitis pain severity and are not predictive of pain relief in patients undergoing surgical or endoscopic stone removal or stenting (27). The most convincing data that pancreatic duct abnormalities cause pain are studies demonstrating pain

relief in patients undergoing decompressive surgery (e.g. pancreaticojejunostomy) or endoscopic sphincterotomy, pancreatic stone extraction, and/or pancreatic duct stenting (28, 29). Among study patients, 34% had sustained pain relief 5 years after surgery, whereas only 15% of patients were pain-free following endotherapy (29). Neither technique, using the reported patient selection criteria, provides optimal long-term pain relief. Sham-controlled studies of endoscopic or surgical decompressive therapies are lacking.

Alterations in nociception have been associated with both experimental and human CP (30). Sensory nerve excitability is increased in animals with CP and is accompanied by upregulation of calcitonin gene-related peptide (CGRP), substance P and brain-derived neurotrophic factor (BDNF) (31–33), which also signal pain. Pharmacological blockade of these transmitters improves pain. Additionally, release of neuropeptides such as CGRP and substance P, produce classic features of inflammation, including edema, necrosis and neutrophil infiltration (34). Nerve growth factor (NGF), which plays a key role in regulating neuronal activation and receptor expression (e.g., transient receptor potential cation channel subfamily V member 1 [TRPV1]), is ectopically expressed in acinar and ductal tissues in CP (31, 35). Anti-NGF therapy suppresses substance P and CGRP expression and reduces pancreatic pain (33).

Inflammation is a major source of pancreatic pain. Immune cells infiltrating the pancreas with release of cytokines and chemokines, such as IL-8 and fractalkine, have also been linked to pancreatic pain (36, 37). Pain in CP has been associated with increased numbers of mast cells in the pancreas (38). Mast cells produce tryptase, which can activate protease-activated receptor 2 (PAR2) on sensory fibers of the pancreas (38) and increase pain signaling. PAR2 expression is elevated in human CP specimens (39). Tissue resected from patients with severe pancreatitis pain may exhibit leukocytes infiltration of nerves, nerve hyptertrophy and areas of neuritis suggesting both inflammatory and neuropathic changes underlie pain associated with CP (36, 40).

Abdominal pain related to pancreatic disease may originate from outside the pancreas. For example, in a 6-month open label study, patients with proven pancreatic insufficiency taking pancrelipase at an average dose of 187K +/− 75K lipase units/day, had decreased pain severity, with the percent reporting no pain increasing from 37.3% to 66.0% (41). Among all patients, 44% had an improvement in pain score while 10.6% reported worse pain (41). A reduction in flatulence was also reported, raising the possibility that the pain was linked with maldigestion. An older study suggested that PERT reduces pancreatic pain directly in the context of minimal change diseases, but replication studies are needed to confirm or refute these data (42).

Discussion Question 2.A: Are there pathologic features in the pancreas or the peripheral nervous system of patients with chronic pancreatitis that are associated with continuous, neuropathic-type pain?—Guidance Statement: Some patients with CP and constant neuropathic-type pain have changes in peripheral nerve fiber anatomy and physiology. In some patients pain may not be associated with changes in the peripheral nervous system.

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 28%; B 26%; C 33%; D 5%; E 8%

Evidence and Discussion: Pancreatic nerve hypertrophy and intra/perineural inflammation have been described in human CP and correlate with pancreatic pain severity (40). The increased size and excitability of pancreatic nerves appears to be due to the highly neurotrophic environment produced by the inflamed pancreas. There is elevation in growth factors and cytokines that promote growth and/or sensitization of sympathetic and parasympathetic efferents and sensory fibers (3, 31, 40). This environment also increases neuronal expression of genes that cause sensitization including TRPV1, TRPA1, TRPV4 and PAR2 (35, 43–45).

In experimental models the application of antagonists for TRPV1 and TRPA1, channels required for inflammatory hyperalgesia, block pain and prevent recurrent acute pancreatitis (RAP) from developing the hallmarks of CP, including fibrosis and sustained inflammation (46).

Pain associated with CP may result from negative synergistic interactions between the pancreatic parenchyma, immune cells and the PNS. Activated sympathetic fibers can release molecules (e.g. ATP) that sensitize sensory fibers, as well as molecules (e.g. epinephrine) that can activate immune cells. Release of NGF by immune and acinar cells sensitizes sensory fibers and induces sprouting (38). Sensitized primary afferents release CGRP and glutamate, contributing to “neurogenic” inflammation.

Discussion Question 2.B: Are there specific pathologic features in the pancreas or the central nervous system of patients with chronic pancreatitis that are associated with pain?—Guidance Statement: Some patients with CP and pain have changes in the central nervous system. These changes may indicate alterations in central pain processing.

Evidence Level: 3b

Grade of recommendation: C

Level of Agreement: A 57%; B 29%; C 5%; D 0%; E 9%

Evidence and Discussion: Some patients with CP have evidence of alterations in central pain processing. Patients may have hypersensitivity in unaffected organs and an increased incidence in referred pain. For example, CP patients are more sensitive to painful abdominal and rectal stimuli (37). This increased sensitivity may reflect changes in central neuronal pathways of the spinal cord and brain (47, 48). Brain MRI studies show alteration in brain thickness and microstructure in cingulate and prefrontal cortices correlating to CP patients' clinical pain scores (49, 50), reminiscent of changes seen in patients that suffer from other chronic pain states (e.g. lower back pain) (51). Pain from CP may also lead to changes in cortical projections of the nociceptive system (52).

In animal models, changes in the CNS have been reported at the spinal cord level where non-neuronal cells, including microglia and astrocytes, are activated (47, 48). These cells play a pivotal role in central sensitization in a number of models of persistent neuropathic pain.

Discussion Question 3: Are there genetic, environmental, emotional or other factors that contribute to the variability of pain in patients with chronic pancreatitis?—Guidance Statement: Genetic, environmental, including early childhood events (53) and emotional factors (54) have been shown to contribute to the variability of pain in a variety of disease systems. Currently there are insufficient data in humans with CP to define the mechanisms or relative contributions of these factors.

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 82%; B 16%; C 2%; D 0% E 0%

Evidence and Discussion: CP-related pain may have unique mechanisms that are related to genetic background (51). Studies of CP-related pain show no association of pain with genetic markers linked to postsurgical chronic pain (36, 40, 43). However, animal studies as well as human twin and family studies reveal that up to 50% of various chronic pain syndromes can be attributed to heritable factors (36, 56, 57)

Some gene products may predispose an individual to more intense or persistent pain or provide protection from such a pain (56). Having "pain risk alleles" may increase vulnerability to pain (including CP-related pain), through individual and combined effects and interaction with environmental factors (56).

Although the genetic studies of pancreatic pain are still in their infancy compared to studies on somatic pain or migraine, several published reports have shown that certain genetic mechanisms of pain development and/or persistence may be shared between somatic and visceral pain disorders; these include adrenergic and serotoninergic pathways. For example, the serotonin-transporter-linked polymorphic region (5HTTLPR) correlated with pain severity in patients with irritable bowel syndrome (58, 59), and variation in beta-2 adrenergic receptor predicted pain-related quality of life in patients with functional gastrointestinal diagnoses(59).

One reason for slow progress in understanding the genetic aspects of pancreatic pain is lack of comprehensive visceral pain phenotypic assessment in CP patients. Within-case design and association analysis of genetic polymorphisms with specific pain phenotypes (such as constant vs intermittent pain, pain severity/intensity, etc) may be more sensitive for CP-related pain genetics studies and reveal genetic factors that explain inter-individual variability in perception of this pain. Genome-wide association studies in large cohorts of CP patients with pain phenotypes is anticipated to further advance the field (64).

PART 2: ASSESSMENT OF PAIN AND QUALITY OF LIFE (QOL) IN CP

Four discussion questions were developed.

Discussion Question 4: What is the minimum assessment of pain that should be performed in patients with chronic pancreatitis at baseline and at follow-up?—Guidance Statement: Pain should be evaluated at each visit to assess character, frequency and intensity. When possible, validated instruments should be used.

Evidence Level: 2b

Grade of recommendation: B

Level of Agreement: A 80%; B 17%; C 2%; D 0%; E 0%

Evidence and Discussion: The description of pain in patients with CP should include its character, frequency and intensity. Frequency may be one of the most under-appreciated parameters in this field. In a prospective cohort study, 186 patients had constant pain patterns compared to 228 with intermittent pain (1). Regardless of the intensity of the pain, those with constant pain patterns had higher rates of disability (OR 3.2 (95% CI 2.0 to 5.1)), hospitalizations (X^2=8.8, p= 0.00001), pain medications (OR 4.4 (95% CI 2.8 to 6.8)), and lower QOL evaluations (Mental Component Score; MCS 39.9 vs. 47.6, p<0.001) (Physical Component Score; PCS 33.3 vs. 42.2, p< 0.001) than those with intermittent pain (1).

A number of instruments are currently available to evaluate pain severity. The visual analogue scale (VAS) is presented as a 10 cm line anchored by verbal descriptors (no pain-worst pain) (72). Although it is easy to use, it does not measure pain character, frequency, pattern or pain interference. The McGill questionnaire is a 15-item scale (11 sensory, 4 affective) whose score is translated into a sensory score, an affective score and a total score. In addition to the 15 item scale, it also includes a Present Pain Intensity (PPI) scale and a VAS. The NIH Patient-Reported Outcome Measurement Information System (PROMIS) instruments are well validated and can be measured reliably across different conditions (74).

Discussion Question 5: How should the impact of pain be evaluated in patients with chronic pancreatitis?—Guidance Statement: Validated instruments should be used to evaluate quality of life (QOL). This may include evaluation of physical, social, and emotional functions.

Evidence Level: 2b

Grade of recommendation: C

Level of Agreement: A 56%; B 28%; C 9%; D 0%; E 7%

Evidence and Discussion: Chronic pancreatitis strongly impacts a number of functions each of which can reduce a patient's QOL. In a cohort study of 265 CP patients, physical function was impaired in 25% of patients, emotional function in 15%, and the perception of diminished overall health function was present in 19% (75). In the NAPS2 study 443 well-

phenotyped CP subjects and 611 control subjects were assessed for QOL using the Short Form 12 (SF12) questionnaire (4). The QOL in CP subjects was similar or worse than the QOL of many other chronic conditions (2). In another recent study at 4 US pancreatic disease centers, 74% of 111 patients reported that work lives were altered by their disease, 60% reported an effect on social lives and 46% reported an effect on spouse/significant other relationship (76). This study also reported that 80% of CP patients reported that they had not been treated with respect and dignity on at least one visit to the ER being labelled alcoholic or a drug seeker suggesting that self-esteem maybe another domain with an impact on CP patients (76). In a recent smaller study, in addition to pain intensity, BMI and disease duration significantly impacted quality of life (8). Thus, multiple factors associated with CP affect QOL.

Until recently, only generic instruments for the evaluation of QOL have been available to evaluate these patients (77). These include Short-Form 36 (SF-36) and European Organization of Research for the Treatment of Cancer (EORTC) questionairres. Both instruments have undergone extensive psychometric evaluation (75, 78). The SF-12 has been thoroughly studied in CP (2, 79, 80). In an evaluation of 163 consecutive patients with CP, the SF-12 appeared to outperform the EORTC in clinical practice (79). The generic instruments appear to be robust in evalating CP QOL and the SF12 has been follwed sequentially over time in CP (81).

Recently, a new disease-specific instrument was developed for the evaluation of quality of life in this group of patients: Pancreatitis Quality of Life Instrument (PanQOLI) (82). This is an 18 item questionnaire designed to be the first disease-specific instrument to evaluate QOL in CP (82). It includes unique features not found in generic instruments (economic factors, stigma) and consists of 4 domains: physical function (5 items), social function (5 items), emotional function (4 items) and self-esteem (4-items) (83). The presence of a self-esteem component is unique to this disease-specific instrument and is believed by the study group to make it more sensitive for the evaluation of this group of patients.

Given that pain significantly affects QOL, the use of these instruments provides an important measure of pain impact. At least one of the QOL measures should therefore be used in measuring disease progression, impact and treatment success in conjunction with pain measures.

Discussion Question 6: In patients with chronic pancreatitis, should psychosocial assessment be done?—Guidance Statement: Patients should be assessed for psychological co-morbidities (e.g. anxiety, depression, opiate abuse) and functional pain using validated instruments.

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 48%; B38%; C 8%; D 2%; E4%

Evidence and Discussion: Pain behavior is a well-studied phenomenon and is described in patients suffering from chronic pain (84). This behavior can be adaptive and helpful or maladaptive and interfere with coping mechanisms. Examples of maladaptive behaviors include the development of drug abuse/addiction behavior, the development of distress and anxiety disorders that interfere with coping mechanisms, and the development of clinical depression that impairs the ability to deal with pain (85). In a structured, evidencebased review of the literature, 3.27% of chronic pain patients (n=2,507) were found to develop abuse/addiction behavior and 11.5% of patients (n=2,466) developed aberrant drug-related behaviors (86).

There is no single instrument that is currently available to assess these various psychosocial behaviors (68). It is necessary to choose an instrument that is considered to best evaluate the suspected abnormal behaviors (87, 88). Given the complexity of the assessment process, the working group members believe that referral to a pain specialist with skills in behavioral psychology is reasonable, particularly if aberrant pain behavior is suspected and response to therapy has been suboptimal. In addition to administering these assessment instruments to determine the potential presence of aberrant behavior, it is helpful for psychologists to offer interventions in this difficult subset of patients, including the Interdisciplinary Pain Rehabilitation Program (IPRP) (98). Such an approach appears to be cost-effective in this sub-group of patients, as studies demonstrate that approximately 49% of patients can return to work with significantly reduced levels of depression, pain-related catastrophizing and pain intensity, but no change in anxiety levels (99). Furthermore, studies in patients with chronic back pain have demonstrated that an IPRP is 10.6 times more cost-effective than the use of Spinal Cord Stimulators (SCS), 12 times more than standard medical care and 26 times more than surgery (100, 101).

Therefore, it is crucial to evaluate the psychosocial impact of chronic pancreatitis in addition to the pain and quality of life evaluation previously discussed. The suggested instruments for this evaluation would include the Pain-Anxiety Scale (PASS) (89), the Pain Catastrophizing Scale (PCS) (90, 91), the Drug Abuse Screening Test (DAST) (92), the brief Michigan Alcohol Screening Test (bMAST) (88), and/or the Current Opioid Misuse Measure (COMM). If patients are found to have psychosocial dysfunction based on these scales, there is a growing body of literature that is developing to support the use of non-opioid pharmacotherapy (102) and the psychosocial interventions (103), such as cognitive behavioral therapy, mindfulness meditation and hypnotherapy to help address these issues.

Discussion Question 7: Are abdominal imaging studies useful in assessing pain in patients with chronic pancreatitis?—Statement: Abdominal imaging may be useful in identifying pancreatic or biliary duct obstruction, inflammation, pseudocysts or extrapancreatic complications that may direct specific treatments.

Evidence Level: 2b

Grade of recommendation: C

Level of Agreement: A 80%; B 18%; C 2%; D 0%; E 0%

Evidence and Discussion: A number of CP complications can develop that cause or exacerbate pain. These include pseudocysts, pancreatic duct stones and strictures (104) which can be treated with a reasonable expectation of relieving the pain. Therefore, abdominal imaging studies are very important in identifying structural abnormalities that may contribute to pain in some patients, even though images themselves cannot predict the presence, type or pattern of pain (7).

A number of potentially useful imaging modalities are currently available (105). Abdominal imaging with either CT or MRI are widely available and sensitive to detect complications of CP linked to structural or density changes. EUS is also an established modality for evaluation of CP (106). These modalities should be used judiciously and only when the results are expected to change or guide further interventions.

PART 3. MANAGEMENT AND TREATMENT OF PAIN IN CP

Five discussion questions were developed.

Discussion Question 8: What should the initial management be for pain in patients with uncomplicated chronic pancreatitis?—Guidance Statement:

Medical management should be the first line of therapy for pain in uncomplicated CP. If present, psychiatric disorders and maladaptive coping strategies should be addressed in conjunction with pain therapy.

Evidence Level: 1b

Grade of recommendation: B

Level of Agreement: A 65%; B 18%; C 8%; D 3%; E 6%

Evidence and Discussion: All patients with established CP should be offered medical management for pain, when present. Patients who have an inflammatory mass, pancreatic duct obstruction secondary to a stricture and/or main duct stone(s), or peripancreatic complications (e.g., pseudocyst) might require additional treatment(s). Even in patients who appear appropriate for endoscopic or surgical therapy, initial medical management of pain is recommended to give relief, to better understand the pain mechanism, responsiveness to treatment and whether there is a significant sensitization.

A stepwise approach should be used for analgesic medications (17, 108). Non-narcotic analgesic medications (e.g. nonsteroidal anti-inflammatory drugs [NSAIDS]) are the initial choice. Narcotic medications should be considered in a patient who has constant and/or severe pain not controlled with non-narcotic analgesics. The initial choice of narcotic should be a weaker, mixed agonist-antagonist or partial agonist (e.g. tramadol) before using stronger narcotics (e.g. morphine, hydrocodone and hydromorphone). Patients who are expected to require long-term narcotic analgesia for pancreatic pain are most appropriately evaluated and managed in a Pain Clinic. A neuromodulating agent (e.g. pregabalin) should be considered in a patient who requires narcotic analgesics on a regular basis (10).

There is no definitive evidence that pancreatic enzyme replacement therapy (PERT) provide general pain relief in CP (109). However, for initial medical management, oral pancreatic enzyme supplements in adequate doses and with rapid release have been shown to provide some pain relief, possibly by providing negative feedback inhibition of pancreatic secretion in early disease (42). In advanced CP with pancreatic exocrine insufficiency, PERT may provide relief from symptoms of maldigestion (41). Pancreatic enzyme replacement therapy in patients with CP can reduce the extent of steatorrhea and possibly pain, but also other symptoms that impact a patient's QoL (18, 110–112).

The role of antioxidants in management of pain in CP is debatable (113, 114); there is some evidence of a benefit in a subset of patients with idiopathic CP, but not in patients with alcoholic CP (115). Some studies show a trend towards some pain relief, and more so with a combination of antioxidants rather than with single agents (116). Recent meta-analyses also suggest that antioxidants can provide marginal pain relief (117, 118). The challenge with the meta-analysis is that the studies were from different populations, different etiologies, different formulations, and may have other major confounding variables. Thus, antioxidant therapy is not routinely recommended in the management of pain associated with CP, but there may be a role in some cases, such as idiopathic CP (115).

If medical treatment is ineffective within a given, limited time period, or if endoscopic and/or surgical therapy are indicated, these more invasive treatments should not be unduly delayed in hopes of “spontaneous” pain relief over time (119). Patients who have failed or refused endoscopic or surgical therapy should be continued on the most effective medical approaches. In the appropriate setting patients should also undergo evaluation for TPIAT (15), as discussed below.

Discussion Question 9: Does behavior modification (cessation of alcohol consumption and smoking) help in providing pain relief in chronic pancreatitis?—Guidance Statement:

Cessation of alcohol consumption and smoking may help in providing pain relief.

Evidence Level: 2b

Grade of recommendation: C

Level of Agreement. A 49%; B 27%; C 19%; D 5%; E 0%

Evidence and Discussion: There are no data specifically evaluating the role of alcohol abstinence and smoking cessation in improving the severity of CP related pain. However, continued alcohol consumption and smoking increases the risk of recurrent attacks of pancreatitis and disease progression (120–122). A randomized trial in patients with alcoholic acute pancreatitis demonstrated benefit of repeated counseling against alcohol consumption in reducing the risk of recurrent attacks of pancreatitis and hospitalizations (123). It is recommended in several review articles that counseling by certified therapists is indicated for alcohol abstinence and smoking cessation in all patients with CP and irrespective of the presence or severity of pain (124, 125).

Discussion Question 10: What are the indications for endoscopic therapy for pain in chronic pancreatitis?—Guidance Statement: Patients who have symptomatic pancreatic ductal dilatation and/or stricture(s) with/without intraductal stone(s), pseudocysts or leaks are candidates for endoscopic therapy.

Evidence Level: 2b

Grade of recommendation: B

Level of Agreement: A 86%; B 7%; C 3%; D 2%; E 2%

Evidence and Discussion: Endoscopic therapy plays an important role in the treatment of CP associated pain (19). Because the cause of pain is multifactorial not all patients will respond to endoscopic treatment, even when technically successful. It was the opinion of members of the working group that endoscopic treatment should be performed by individuals with specific interest and expertise in this area.

The working group believes that the best candidates for endoscopic treatment are those with significant pain from ductal obstruction identified by cross-sectional abdominal imaging, especially dominant strictures in the head of the pancreas. Endoscopic therapy may also be useful for some patients with biliary obstruction, pancreatic pseudocysts, pancreatic fistula, pancreatic duct strictures and those with pancreatic duct calculi who might respond to extracorporeal shockwave lithotripsy (ESWL).

ESWL has an important role in management of pain in patients with CP. At selected centers with a large experience, ESWL of large (5 mm or greater) pancreatic stones can achieve clearance in approximately 75% of patients undergoing multiple sessions, and treatment was associated with significant pain relief (126). In a randomized trial, ESWL without ERCP for ductal clearance was found to be as effective and more cost effective than the routine combination of ESWL with ERCP and ductal clearance of stones and debris (127).

Pancreatic ductal strictures most amenable to endoscopic therapy are those in the pancreatic head, rather than the body and tail. There is a large literature giving evidence that pancreatic duct stenting is effective for symptomatic ductal obstruction in the setting of CP (128–131), even though there are no randomized, blinded, sham-controlled studies in this setting. Sphincterotomy, stricture dilation, and large caliber plastic stenting with one or more 7–10 French gauge stents for a prolonged period of time (for 3 to 12 months) appears to be most beneficial (132). The use of multiple large plastic stents and expandable metal mesh stents (SEMS) in the pancreatic duct remains experimental and cannot yet be considered standard of care.

The utility of endoscopic versus surgical approaches in treating pain continues to be debated. Two randomized trials (133, 134), including one with long-term follow-up, have compared endoscopic and surgical treatment. The evidence indicates that surgery provides superior pain relief (80 versus 38%) in the short (2 years) and long (6 years) term. Patients assigned to endoscopic treatment had more procedures and approximately half of these eventually had surgical treatment. However, concern has been expressed that this study did

not compare ‘like-with-like’. A highly selected group undergoing surgery was compared to patients were likely to have a poor outcome from endotherapy (e.g. those with disease in the body and tail and those with a heavy ductal stone burden) (135). Thus, the working group believes that additional studies are needed to determine optimal utility of endoscopic and surgical approaches to treating pain in patients with CP.

Analysis of NAPS2 patients who had long-term follow-up at the University of Pittsburgh provides a perspective on current clinical practice in an expert center (11). Patients who were selected for endoscopic therapy if it was considered that the etiology of pain or RAP was obstructive in nature. Endoscopic therapy was clinically successful for 50% of patients with symptomatic CP, defined by cessation of narcotic therapy and resolution of RAP. When endoscopic was not successful, an additional 50% of the remaining patients had long-term relief with surgery (11).

Endoscopic treatment is still used as a first line therapy in many centers and continues to be recommended by endoscopy societies (19). Justification for primary endoscopic treatment is made on the basis of it being less invasive, less expensive and more readily available. In select patients, surgery should be considered the first approach. These include patients who have a heavy stone burden especially in the body/tail of the pancreas with pancreatic ductal dilatation and/or strictures (133, 134), and those with an inflammatory mass (where the primary etiology of pain is not likely to be duct obstruction). However, some patients may decline surgery, are too high risk for surgery or may improve sufficiently following initial endoscopic therapy to not require a definitive surgical approach (11). If patients do not significantly improve following endoscopic therapy and they are surgical candidates, then surgical treatment should not be delayed (119).

Most symptomatic pancreatic pseudocysts can be treated endoscopically. Transmural endoscopic drainage under endoscopic ultrasound guidance with Doppler signal can be attempted where expertise is available. While not more effective than surgery, it is less invasive and expensive (136). Pancreatography at the time of endoscopic cyst drainage may help clarify ductal anatomy, including the location of strictures and leaks (137). In patients with a disconnected duct syndrome, a pseudocyst and proximal duct dilatation, especially when there are intraductal calculi and/or strictures, surgical decompression of the pseudocyst with duct clearance may be indicated to address pain. Pancreatic ductal leaks may cause a pseudocyst and/or fistulae, and can sometimes be treated with transpapillary pancreatic duct stenting (138–140). If the leak is associated with a high-grade proximal strictures and/or calculi then treatment of this obstruction with transpapillary stenting may lead to resolution.

Biliary obstruction from CP may result in abdominal pain but more commonly jaundice or cholestasis. In the short-term, bile duct stenting should be performed particularly to relieve jaundice, cholangitis or severe pruritus. Recent studies suggest that covered expandable metal stents (SEMS) may be a viable management option, although multiple plastic stents can provide better long-term relief (141). However, longer term follow-up data is required. Patients with significant calcifications of the pancreatic head may be those less likely to benefit from stenting in the long-term. Surgical biliary bypass by Roux en Y

hepaticojejunostomy is a definitive treatment, yields excellent durable results and should be considered in the fit patient (142, 143). However, hepatojejunosotomy is not without problems, and rarely can result in an anastomotic stricture and this promote secondary biliary cirrhosis (144). This can be combined with decompressive pancreato-jejunostomy if indicated.

Neurolytic therapies to treat CP can be done using a variety of techniques, including EUS-guided (145), radiology image guided and surgical treatments. At this time, the use of EUS-guided CPB (celiac plexus block) cannot be recommended as routine therapy for pain in CP since only one-half of the patients experience pain reduction and the beneficial effect tends to be short lived (145). A recent randomized controlled trial showed that adding steroids to bupivacaine in celiac plexus block was no more effective than placebo plus bupivacaine and both groups had an overall very poor response (146). Surgical division of the splanchnic nerves in the chest (thoracic splanchnicetomy) yields similar short-term, variable responses and thus cannot be routinely recommended (147).

Discussion Question 11: What are the indications for surgery (resection or drainage procedure) for pain in chronic pancreatitis?—Guidance Statement A:

Surgery by resection or drainage is indicated in patients with persistent chronic pancreatitis pain that fails to respond to medical and/or endoscopic therapy.

Evidence Level: 2b

Grade of recommendation: C

Level of Agreement: A 67%; B 27%; C 6%; D 0%; E 0%

Guidance Statement B: Pancreatic resection or drainage procedures (e.g. lateral pancreatico-jejunostomy) should not be performed in patients who are candidates for total pancreatectomy and islet autotransplantation (TPIAT) in settings where this is available, as this can result in a low yield of islets.

Evidence Level: 2b

Grade of recommendation: C

Level of Agreement: A 100%; B 0%; C 0%; D 0%; E 0%

Evidence and Discussion: Multiple clinical studies provide evidence that surgery is a more effective long-term therapy for pain in patients with CP than endoscopic or other treatments (133, 134). Among patients with pancreatic pain, surgery is the most effective when the etiology of pain is obstructive, typically with significant post-prandial pain exacerbations and a dilated main pancreatic duct (148). Surgery, rather than endoscopic therapy should be considered in patients who have a heavy stone burden, especially in the body/tail of the pancreas with pancreatic ductal dilatation and/or strictures. Endotherapy may be useful as a bridge to surgical treatment for those patients who are candidates for surgery, but who are initially unfit (149).

The timing of surgical intervention is an important factor in clinical outcomes; surgery has been shown to be most successful when performed within three years of symptom onset but the development of central pain is a concern when surgical intervention is deferred (11, 148) The probability of long-term pain relief from surgery can be estimated on the basis of the duration of pain, use of preoperative opioids, and the number of endoscopic interventions (118).

There is a range of surgical options, including resection, decompression and a combination of these (150), as well as TPIAT as reviewed by Bellin et al (15). Among drainage procedures, patients with a dilated main duct and without an inflammatory mass in the head of the pancreas are best managed with decompression of the duct (longtitudinal pancreatico-jejunostomy) and with either coring of the head (Frey procedure) or resection of the head (Beger procedure) (150). Patients with an inflammatory mass in the head of the pancreas, especially if malignancy cannot be excluded, will require pancreatic head resection (Whipple's procedure), with or without pancreatic duct decompression. Patients with obstructive jaundice secondary to a benign distal biliary stricture may benefit from a Roux-en-Y hepatico-jejunostomy at the same time. Patients with non-alcoholic etiologies of CP may do well with TPIAT, but pain relief and outcomes are not as good for patients with an alcohol etiology (15, 151, 152). Recommendations for the evaluation, treatment and follow-up of patients who may be candidates for TPIAT were recently published (15).

There are data suggesting that drainage of a dilated pancreatic duct delays functional deterioration and disease progression in patients with mild-moderate CP and minimal pain (119, 153). This approach has not been widely implemented and patient selection must take into account comorbidities, ongoing substance use and a discussion with the patient by a surgeon about the risks and benefits of surgery.

Prospective randomized trials of pancreatico-duodenectomy (Whipple procedure), the duodenum-preserving pancreatic head resection (Beger procedure), and the local resection of the pancreatic head with longitudinal pancreatico-jejunostomy (Frey procedure) indicate equivalent degrees of pain relief (70–80%) in both the short and long term (28, 154). The Frey procedure has a lower risk of peri-operative and post-operative complications and has become the preferred procedure by many pancreatic surgeons. The principal short-coming of the lateral pancreatico-jejunostomy (Puestow) procedure is the risk of recurrent symptoms due to progressive inflammation localized to the pancreatic head (155). Just draining a dilated duct (lateral pancreatico-jejunostomy) is no longer considered the standard of care for the treatment of pain associated with obstructive pancreatopathy.

TPIAT is a new, and debated approach to management of intractable pain in patients with impaired quality of life due to CP or RAP in whom medical, endoscopic, or prior surgical therapy have failed (15). Because islet isolation requires a special facility and is technically challenging, it is only offered at a limited number of centers, primarily in the United States. Delay in referral of patients for TPIAT that results in progressive fibrosis and loss of islet cells, proceeding with pancreatic resections, or performing some drainage procedures markedly reduce islet yield (151, 158). On the other hand, many CP patients, especially with more advanced disease, may be better served with more traditional approaches.

Discussion Question 12: How should response to therapy for pain be assessed?—Guidance Statement: A combination of objective findings should be used to assess treatment response of therapies over time including use of serial validated pain scores, quality of life (QOL) instruments, pain medication use, frequency of pain episodes, hospitalizations and emergency room visits.

Evidence Level: 2b

Grade of recommendation: B

Level of Agreement: A 93%; B 5%; C: 2%; D 0%; E 0%

Evidence and Discussion: Current tools to predict the response to all forms of therapies (medical, endoscopic, surgery) are inadequate and new ones need to be developed. There are limited data correlating the response to therapies with different pain mechanisms. Pain will not consistently improve with endoscopic or surgical drainage of a dilated pancreatic duct or with resection of inflamed parenchyma. This reinforces that pain mechanisms in CP are complex and may be modulated by multiple and differing pathways during evolution of the disease.

A variety of methods have been used to assess the outcome of intervention for pain and QOL in CP, as reviewed in Discussion Questions 4 to 6. Placebo controlled trials are rare in CP but do suggest a low rate of response of approximately 20% (66). The expectation of spontaneous abatement of pain (burn out) in CP, suggested by some (159) and found to be uncommon by others (102), has resulted in undue patient suffering and been a disincentive to long-term, non-placebo-controlled studies. It appears that the frequency and severity of pain does not correlate with the duration of CP (1), but is affected by multiple disease-modifying factors. Some centers are using a systematic mechanism-oriented approach to pain in CP by applying tools such as quantitative sensory testing, electroencephalography and functional magnetic resonance imaging to address central pain, but this approach has not been proven to be superior to current approaches and requires further study (18). Regardless of method, systematic assessment of pain character, pattern and severity must be monitored for long periods of time so that the effectiveness of interventions can by accurately assessed.

Research Recommendations

Disease Mechanisms

A major research effort is needed to identify sensitive and specific biomarkers that link pain mechanisms with clinical features. The relationship between local and central pain should be clarified in terms of context, timing and clinical features. The development of better techniques to study central pain in humans and experimental models is critical for addressing this issue. Although neuropathology is often evident in human pancreatic tissue samples, the clinical context and associated pain phenotypes have not yet been identified. Thus, neuropathic biology, the clinical context and specific consequences are not easily identified and treated by clinicians. Further studies are needed to determine whether specific neuropathologies, such as neuroinflammation or direct nerve injury, are associated with distinct clinical consequences. The relationship between normal and abnormal responses to

pancreatic stress or injury must also be clarified, especially in relation to genetic and environmental modifiers, including medications. Mechanistic pathways, specific risk factors, other variables and better biomarker linking the syndrome of constant pain to the underlying pathologic processes in individual patients are needed.

Assessment of pain

Although multiple possible mechanisms of pain have been described, there are few, if any, well-validated instruments that discriminate between pain features and mechanisms. Large, well-controlled, long-term trials are needed to define the natural history of pain and to evaluate a range of pain assessment instruments. These studies should include comprehensive evaluation of each patient to determine the relative contribution and potential synergy of active inflammation, obstruction, tissue hypertension or ischemia, neuropathy, centralization, mental health and comorbidities. Specific comorbidities include extra-pancreatic pain, gastroparesis, dysmotility, diabetes mellitus, broader pain syndromes and complications of treatments such as narcotic bowel syndrome. The role of emotional and mental health, including anxiety and depression, must be included in pain evaluations. The effects of perceived symptoms and responses to therapy should be applied to these assessments.

Management and Treatment of Pain

Better methods that specifically target pain mechanisms must be developed along with guidance on which patient types are likely to respond. The indications for the primary use of endoscopic or surgical therapy for specific patient populations must be resolved. Guidance on the individual risk and time window needed to prevent pain sensitization is needed. Pain management should also monitor each active pain mechanism so that the effectiveness of each treatment approach can be monitored, and new problems detected early. The responses to intervention, whether medical, surgical or experimental, should be documented using validated tools in systematic ways for ongoing evaluation. Patients undergoing TPIAT should be studied in a longitudinal and systematic way before and after surgery, and the tissue evaluated to better understand local and central pain mechanisms in specific disease states.

Summary

Pain is the foremost problem in CP, and a major source of morbidity and decreased QOL for affected patients. Future studies to further elucidate the link between clinical signs and symptoms of CP, patient pain phenotypes, neuropathologic features and genetic and environmental influences are critical for the development of new, more effective treatment strategies. New tools for ongoing assessment of pain and pain mechanisms are necessary for understanding the natural history and for effectiveness of treatments in future clinical trials. The complexity of pancreatic pain is clearly one clinical problem that would greatly benefit from a robust dialogue between clinicians and basic science pain researchers. Only by understanding the mechanisms contributing to the various presentations of pancreatic pain will it be possible to identify the most efficacious treatments with the minimum of complications and improvement of the quality of life of the affected patients.

Acknowledgements

This work was supported in part by conference grants from the NIDDK (DK09690; DK100242; DK103527; DK098560), CME programs through the University of Pittsburgh office of Continuing Medical Education and a gift to UPMC from AbbVie to improve patient care.

Appendix

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A. Listed as authors who participated in the guidance conference for pain *and* critically reviewed the paper.

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