SMART APPROACH

Medical Management of Pancreatitis Pain

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Overview

Chronic pain is the most distressing feature of recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP). Pain can arise from injury, inflammation, obstruction of ducts, neuritis, and/or inherent problems with pain processing and tolerance in the brain and nervous system. A summary of current data related to pancreatic pain include:

- Pain experiences in individuals with RAP and CP differ in pattern, frequency, severity, character, and chronicity, with 10-15% having no pain.
- There is typically no relation between pancreatic morphology and pain.
- Neuropathic changes within the pancreas and central nervous system more strongly correlate with pain of CP than pancreatic obstruction.
- Timing of intervention in relation to pain onset impacts pain outcomes.
- The absence of sham arms in prior trials of endoscopic or surgical interventions for painful CP is a major limitation in drawing conclusions regarding their efficacy. (New trial do include a sham arm)
- Long-term differences in pain outcomes between endoscopy and surgery have only been shown in one trial where 20% of patients were lost to follow up.
- There are no differences in pain outcomes between endoscopy and surgery in the short-term when complete ductal stone clearance is achieved using extracorporeal shock wave lithotripsy (ESWL).
- Newer modalities such as pancreatoscopy-guided electrohydraulic/laser lithotripsy (EHL/LL) are further augmenting ductal clearance rates.
- Pregabalin has an incremental pain benefit over opioid analgesics and endoscopic ductal clearance.
- Pancreatic surgery fails to relieve pain in 2 out of 5 patients.

Basic Pain Management

Acute versus chronic pain. The etiology and treatment of pain in acute pancreatitis and chronic pancreatitis differ. For example, a component of acute pancreatitis pain may come from innate response to factors associated with tissue injury or to visceral ischemia. The focus here is pain in chronic pancreatitis.

Pain algorithm. An international consensus algorithm for the management of pain in chronic pancreatitis has been published.[1] Once pain is confirmed to be of pancreatic origin then attention to confounding lifestyle practices such as smoking and alcohol use should be addressed. Anatomic causes of obstruction such as pancreatic stones or strictures should be confirmed and treated by endoscopy or surgery. The addition of antioxidants has been helpful in patients without duct obstruction but these are rarely used in the United States to treat pain.[2] For chronic pain lasting over 3 months, gabapentinoids are also useful.

Opioid ladder. In 1986 the World Health Organization (WHO) developed an analgesic ladder for treatment of cancer pain beginning with nonopioid medications. With persistent pain they recommended administering weak opioids, and, if needed, progressing to the use of stronger opioids. This model has been widely adopted for noncancer pain conditions, including pancreatitis. However, the limited efficacy of opioids in many patients with RAP and CP pain and the risk of opioid side effects, dependence, and addiction indicates that other approaches are needed.

Pharmacogenetic analysis. If RAP or CP patients have chronic pain that cannot be controlled by acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or short-term opioid treatment then pharmacogenetic analysis of pain medicine activation and clearance is indicated (see Table 1).[3] This analysis should include pain medicines such as NSAIDs (e.g., *CYP2C9*), opiates (e.g., *CYP2D6*

Abbreviations used in this paper.; CP, chronic pancreatitis; EHL/LL, electrohydraulic/laser lithotripsy ; ESWAL, extracorporeal shock wave lithotripsy; EUS, endoscopic ultrasound; GAD, general anxiety Disorder; MDD, major depressive disorders; PTSD, post-traumatic stress disorder; QST, quantitative sensory testing. RAP, recurrent acute pancreatitis; SNRI, selective norepinephrine reuptake inhibitor TCA. Tricyclic antidepressant; WHO, World Health Organization.

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mutations plus copy number variants), and neurology/psychiatric medications including anxiolytic and antidepressants (e.g., *CYP2C19, CYP2D6, NAT2, HLA-A*). Recommendations on genotype-based dosing of tricyclic antidepressants (TCA; e.g., nortriptyline), tertiary amines (clomipramine, doxepin, imipramine, and trimipramine) and complex metabolism of amitriptyline have been published.[4] Based on these data the current medical regimen should be tailored to optimize treatment of medications in each class and in anticipation of future medical treatment.

How I Manage Persistent Chronic Pancreatitis Pain

Chronic pain is generally defined as pain lasting for more than 3 months. For chronic painful CP or persistently painful AP, I typically use pregabalin (start at 75 mg po bid with ramp up to maximum dose of 300 mg po bid). This is consistent with the dosing regimen in the only placebo-controlled randomized controlled trial assessing the efficacy of pregabalin in CP.[5] If insurance does not cover pregabalin, then use gabapentin (starting dose for pain is 300 mg po tid, up-titrating by 300 mg increments at each dosing time point with max at 1200 mg po tid). Anything lower than 300 mg po tid does not generally work for pain. Response is best with proper starting dose and aggressive up-titration every 3 days as tolerated. There is data among older adults showing that gabapentinoid drugs have a greater impact on chronic pain than opioids.[6] In addition, data from pancreatic cancer suggests less requirement of opioids when gabapentinoid drugs are used in combination with opioids

Tricyclic antidepressants (TCA). TCAs are important pain modulators. I use nortriptyline and duloxetine (a selective norepinephrine reuptake inhibitor [SNRI]) although there have been no studies specifically evaluating these drugs in patients with pancreatitis pain. They can be used to augment the effect of a gabapentinoid drug if there is an incomplete pain response and/or if increasing the gabapentinoid drug to a higher dose results in side effects.

Nortriptyline, as a TCA (for metabolism see Hicks, Table 2)[4], is effective for pain but can result in anticholinergic side effects such as dry eyes, dry mouth, esophageal reflux, constipation, and fatigue. These anticholinergic side effects can often be avoided with liberal oral water intake and administration of the medication at night just before bedtime. I start at 25 mg but generally need to up-titrate the dose to somewhere between 75 mg to 150 mg (with the latter being the maximum daily dose). Following serum nortriptyline levels can be helpful as the therapeutic window is typically between 100-150 ng/mL.

Duloxetine is an SNRI with relatively few side effects (metabolized by *CYP2D6*), but most patients require 90-120 mg before an impact is seen on pain. I will typically start patients on 30 mg at night before bedtime and increase the dose by 30 mg every 3 nights until I reach a dose of 120 mg or the patient experiences pain relief.

Other Considerations and Non-pharmacological Approaches.

Co-occurring psychiatric disorders. New research is demonstrating that genetic loci associated with major depressive disorders (MDD), general anxiety disorder (GAD) and post-traumatic stress disorder (PTSD) are associated with a worse pain experience and quality of life.[7, 8] Clinical studies also demonstrate that depression is strongly associated with pain in chronic pancreatitis.[9] These data highlight the importance of central processing and experiences associated with pain signals and provide a target for complementary treatment strategies as part of a holistic approach.

Cognitive Behavioral Therapy (CBT) is proving to be an effective adjunct therapy for pain management in various chronic inflammatory diseases. Online tools are also available, but are not covered here.

Quantitative Sensory Testing (QST). QST is a technique to measure a subject's innate response to different types of pain stimuli. These tests demonstrate changes in central processing that may best respond to neuromodulators.[10, 11] Studies on patients with painful CP demonstrate that 28% had segmental hyperalgesia and 21% had widespread hyperalgesia (i.e., chronic widespread pain syndrome with pain in more than one anatomic location), again demonstrating the importance of central processing rather than pancreatic pathology alone in pain experience.[12] Defects in central processing of pain may have a genetic basis.[13] QST is one of many tools that are being developed to phenotype pancreatitis pain and determine if they can predict the pain response to various pharmacologic and invasive therapies.

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