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Pancreatic Pain – Knowledge Gaps and Research Opportunities in Children and Adults: Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop

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Abstract

A workshop was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to focus on research gaps and opportunities in pancreatic pain. The event was held on July 21, 2021, and structured into four sessions: (1) pathophysiology; (2) biomarkers, mediators, pharmacology of pain; (3) pain assessment; and (4) pain treatment-challenges and opportunities. The current state of knowledge was reviewed; many knowledge gaps and research needs were identified that require further investigation. Common themes included the need to better understand the underlying mechanisms of pain in pancreatic diseases, the relationship of visceral neural pathways and central pain centers, the role of behavioral factors and disorders on the perception of pain, and differences in pain perception and processes in children when compared with adults. In addition, the role of genetic risk factors for pain, and the mechanisms and role of placebos in pain treatment were discussed. Methods of pain assessment including quantitative sensory testing were examined, as well the process of central sensitization of pain. Finally, newer approaches to pain management including cognitive behavioral therapy, nerve stimulation, experimental (non-opioid) drugs, and cannabinoid compounds were covered.

Keywords

Pancreatitis; pancreatic cancer; peripheral sensitization; central sensitization; placebo; quantitative sensory testing

INTRODUCTION

Although a common manifestation of both benign and malignant pancreatic diseases,[1–3] pain is an unreliable indicator of the extent of pancreatic damage, the underlying mechanisms are not well understood and the assessment remains challenging.[4] Pain in chronic pancreatitis (CP) can be variable in intensity and location, can have a heterogenous pattern, and can often be refractory to therapy.[5] Chronic pain can be disabling for both adults and children with pancreatitis, impacting their quality of life and predispose to opioid addiction[5–8], whereas in patients with pancreatic ductal adenocarcinoma, chronic pain[9, 10] and opioid use[11, 12] are indicators of poor survival.

Pancreatic pain, as with all other pain, has four determinants that include nociception, perception, suffering and pain behaviors. The regions of the brain that process nociception, emotion and cognition overlap. It is possible that, over time, suffering has a larger impact on pancreatic pain intensity than nociception. This may explain why a large proportion of patients with painful CP have overt clinical manifestations[13] and/or susceptibility to psychologic conditions, such as depression and anxiety.

Visceral pain is poorly localized because of viscerosomatic sensory convergence at the level of the spinal cord and can be associated with autonomic symptoms (e.g. diaphoresis, tachycardia) due to “cross-talk” between sensory afferent nerves, sympathetic and parasympathetic nervous systems.[13] Chronic pancreatitis pain can be difficult to distinguish from other visceral diseases, such as functional bowel disorders. There are no diagnostic tests to accurately differentiate early CP from functional bowel disorders,[14, 15] but it is well established that the latter are far more prevalent,[16, 17] Although no correlation has been demonstrated between CP symptoms and imaging findings,[4] a recent study found a positive correlation between opioid dose requirements and morphologic severity of acute pancreatitis,[18] This further supports the general concept that acute pain is a reflection of nociception due to direct tissue injury whereas chronic pain reflects central mechanisms.

There are several challenges in the diagnosis and treatment of pain in pancreatic diseases. *First,* there are no validated multidimensional pain assessment tools for pancreatic pain. Although pain is a subscale of the Pancreatitis Activity Scoring System (PASS) in acute pancreatitis[19] and in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QOQ) – Core 30 and PAN26 in pancreatic ductal adenocarcinoma,[20] these systems were designed to evaluate disease prognosis and health related quality of life, respectively, rather than pain. The recent development of Comprehensive Pain Assessment Tool - Short-Form (COMPAT-SF) offers clinicians a validated and clinically feasible pain assessment tool for CP but requires further study in different patient populations.[21] Functional brain magnetic resonance imaging (MRI), electroencephalography (EEG) and pancreatic quantitative sensory testing (P-QST) have

been studied as biomarkers for pancreatic pain, but are not ready for clinical use. *Second,* there are no evidence-based data that point to specific treatments for pancreatic pain syndromes. Invasive treatments are commonly pursued for pain in CP and ductal obstruction but have unpredictable and variable response rates. Two randomized controlled trials (RCTs) showed benefit of surgery over endoscopy for pain in CP,[22, 23] but in a more recent study, endoscopy with complete clearance of obstructing stones was as effective as surgery.[24] Some endoscopic interventions report high initial success rates, but this drops off after a few months.[25] Endoscopic ultrasound-guided celiac neurolysis yields ~70% response[26, 27] that lasts less than 1 month with no improvement in pain in patients already on opioids[28] and is associated with shorter survival.[29] Opioids continue to be the cornerstone of the pancreatic pain management[30–32] despite their well-known side effects and risks associated with long-term use.[11, 33]

The National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored Workshop titled: *Pancreatic Pain: Knowledge Gaps and Research Opportunities in Children and Adults,* which was designed to explore the most recent developments in understanding the origins and mechanisms of pain in pancreatic disease, evaluate risk factors, methods for diagnosis and treatment, including the role of placebo and novel approaches. Speakers addressed gaps in the current understanding of pain in pancreatic diseases and proposed research topics for future studies.

The pathophysiology of pancreatic pain

Peripheral pain processes—A key to understanding chronic pain is the concept of nociceptive sensitization, which is broadly classified into two types. The first is peripheral sensitization which involves changes in the excitability of primary nociceptors. The second is central sensitization which can occur at the spinal cord or higher levels, including the brain. It is important to note that central sensitization inevitably accompanies ongoing peripheral input (the so-called “afferent barrage”).[34] Thus, in response to electrical stimulation of the viscera, projected brain signals in patients with CP resemble those of patients with neuropathic pain as they have altered referred pain patterns elsewhere such as chest and abdomen.[35] In a chronically inflamed organ with constant abnormal input to the central nervous system (CNS), it is difficult to determine the importance of central sensitization as an *independent* factor in the pathogenesis of pain as in most cases it will subside if the peripheral barrage of signals dies down.[36]

Peripheral nociceptive afferents, the first order neurons housed in the dorsal root ganglia, transmit pain sensation from the pancreas to the second order neurons located in the spinal cord. The second order neuron then conveys this impulse to the thalamus and beyond to the various regions in the brain that together form the pain suffering complex. The receipt of these signals then invokes counter regulatory signals that descend to the spinal cord. Some of these signals are facilitatory in that they can amplify the pain in certain conditions, but most are inhibitory and serve to dampen down the signals.[37]

Pancreatic pain is both inflammatory and neuropathic. Inflammatory or neuropathic pain leads to sensitization of the peripheral nervous system, which can cause hyperalgesia (exaggerated response to painful stimuli) and/or allodynia (perception of pain even with

physiologic stimuli). Inflammation directly and indirectly causes nerve fibers to start firing signals that are then conveyed to the brain and perceived as pain. Due to the intimate relationship of nerves with the pancreatic parenchyma, the tissue structures break down and the nerves are exposed to toxic chemicals and mediators during inflammation. Pancreatic nerves may show hypertrophy, increase in density, inflammation within and around the nerves, and an increase in the number of nerve endings. These changes correlate with the severity of pain in CP.[38]

There are multiple potential molecular factors for peripheral sensitization.[39] The first factor is signal transduction, which translates a transduced injury in the organ into an electrical signal by the expression of various specialized chemicals and receptors. This signal is then conducted back to the spinal cord through propagation of action potentials. Finally, after reaching the spinal cord, the signal is handed over to the second order neuron by conversion of the electrical signal to a chemical signal. This is achieved by the entry of calcium and release of specific neurotransmitters, which then act on corresponding receptors on the second order neurons. There is extensive preclinical evidence to support involvement of these factors in the pathogenesis of chronic pain in CP.

Pancreatic nociception appears to be significantly affected in CP with increased excitability, associated with downregulation of potassium currents. Specific molecules implicated in this process include the vanilloid receptor transient receptor potential cation channel subfamily V member 1 (TRPV1), nerve growth factor (NGF), the protease activated receptor (PAR2), transforming growth factor beta (TGF-beta), calcitonin gene related peptide (CGRP), and they may be readily amenable as targets for currently available drugs.[40–44] A number of these neurotransmitters and growth factors have been demonstrated to be increased within the pancreas driving sensitization.[38]

An example of peripheral sensitization in CP in humans has been the efficacy of pregabalin for the treatment of pain in a RCT.[45] Pregabalin exerts its effect by blocking the A2-delta component of the calcium channel that is required for exocytosis of the neurotransmitters which relay the message from the central end of the peripheral nerves to the second order neurons,[45] suggesting that peripheral afferents play a role in maintaining the pain in CP.

Central pain processes: CNS pathways and mediators—There is now good evidence that a substantial part of the risk of developing chronic pain is based on brain anatomy. This knowledge remains limited mainly to chronic back pain, although consistent evidence is also now coming from other types of chronic pain.

Chronic pain can be conceptualized along four different stages of temporal evolution – predisposition, injury, transition and maintenance. The traditional view is that all of these stages are explained by nociceptive circuitry, i.e. primary afferents and their effects on the spinal cord. However, emerging data especially for chronic neuropathic pain conditions suggests an important role of limbic emotional circuitry clustering with the emotional learning processes to put the subject in different transitional states, and that development of chronic pain leads to distinct anatomical and functional properties in the brain. This framework allows consideration of relevant biomarkers – prognostic to predict

predisposition, nociceptive biomarkers and stress-related events that associate with injury, and diagnostic biomarkers that associate with maintenance state when chronic pain has developed. The transition state is important, as depending on the peripheral and central mechanisms and their interaction, the subject can have recovery or develop chronic pain. The transitional state may provide a time window where there is an opportunity for intervention to alter the development of chronic pain.[46–48]

Certain brain parameters can predict long term development of chronic from acute pain. The mesolimbic system with interaction between the prefrontal cortex, nucleus accumbens and hippocampus, can make the transition into or away from chronic pain. Once chronic pain is established, there are functional regional brain activity changes in relation to chronic pain, information processing disruption in the brain, as well as anatomic reorganization of the brain that accompany the chronic state, making the chronic pain brain as an uniquely novel brain state itself. [49, 50]

Nociception occurs all the time invading the cortex and the limbic system. Once there is injury, this information is enhanced, and the way the brain processes this information becomes a transitional state. If there is adequate control of the limbic circuitry with healing, pain goes away. Otherwise, an emotional learning system is activated and this in turn gives rise to reorganization that changes synaptic and circuit properties, both in the cortex and the emotional learning system involving the limbic system creating predisposition to chronic pain.[47]

As an illustrative example, the predictive ability of the connections between the prefrontal cortex and the nucleus accumbens for persistent back pain was demonstrated in human subjects who underwent imaging at baseline, 3, 6 and 12 months after onset of symptoms reflecting the acute, subacute and chronic stages. It was noted that the development of persistent pain at 12 months was predicted by the strength of the connection between these two areas of the brain at baseline (area under the curve, AUC 0.80). Interestingly, the strength of the association did not change at 3, 6 and 12 months, suggesting a nonvariant nature of this connection.[51] These findings have been replicated in a validation cohort. This concept suggests that at least in part the brain is becoming addicted to the nociceptive inputs, not necessarily the subject making a conscious decision.

In terms of diagnostic markers of chronic pain, global disruption of information sharing in the brain has been demonstrated to be a useful single marker in cross-sectional studies of healthy subjects when compared with those who have other painful conditions, such as chronic back pain, chronic complex regional pain syndromes and osteoarthritis.[52] On functional MRIs, chronic pain was noted to be associated with an overall decrease in the connectivity of brain areas with large connections, and an increase in the local connectivity. The disruption was directly proportional to the pain intensity and was similar across the different pain conditions. This observation was also reproducible in rodent studies of neuropathic pain where changes were not seen in short (5 days) but only in a longer time frame (1 month) after injury, implying that these changes were related to the chronic pain state. This parameter can also be used as an unbiased estimate for the amount of pain a subject is experiencing with an accuracy of 60–70%.

Rodent models of neuropathic pain, spared nerve injury (SNI), show strong parallels to human chronic pain regarding limbic circuitry in transition to chronic pain in terms of functional reorganization and medial shell nac neurons. In patch clamp recordings from nucleus accumbens looking at D1 and D2 dopamine containing neurons known for their emotional and motivational role in various conditions, within days of a peripheral nerve injury, there are excitability and morphology changes of the neurons, modification of synaptic inputs and reduction in the amount of dopamine by about 50%. Moreover, with chemogenetic manipulation of the neurons in neuropathic conditions, there is an increase or decrease in sensitivity to peripheral injury related to tactile allodynia establishing neuropathic pain behavior in these animals suggesting a causal link to the amount of excitability of this small number of neurons in nucleus accumbens.[53, 54]

In a recent RCT, the combination of l-dopamine and a non-steroidal agent for 12 weeks was tested in the transitional state (subacute pain) among subjects considered to be at high-risk for transition to chronic pain based on functional MRI imaging. Although the primary outcome was not significant between the groups, an approximately 50% reduction from baseline was noted in subjects from three groups (both medications, l-dopamine, and a non-steroidal agent); there was a differential response based on gender (females had greater response), and a suggestion of the role of brain circuitry in treatment response.[55]

Chronic pancreatic pain, as any other chronic pain, should be conceptualized primarily as a neurologically-predetermined pathology. Many critical questions however remain unanswered. The contribution of nociceptive signaling from the injury site relative to the central risk factors is the main issue that remains unknown. Knowledge about these two factors' interaction and how that interaction induces the spectrum of chronic pain would critically advance the field scientifically and open the horizon for future therapies.

Biomarkers, Mediators, and Pharmacology of Pain

Nociception occurs through a highly complex and regulated system of sensory and autonomic nerve activity converging on the CNS including the cortical areas that enable perception and shape the pain experience.[39] In multicenter studies evaluating CP pain in children and adults, the pain experience ranges from mild to severe and intermittent to constant, but interestingly about 10–15% of patients have no pain at all.[4, 56, 57] Because there is often no correlation between pain severity and end organ morphology,[4] understanding biomarkers and mediators of pain is important for developing treatments that provide adequate pain relief.

Activation of the stress axis and the sympathetic nervous system as well as mood disorders such as depression and anxiety are linked with chronic pain. Several mechanisms are involved in amplification and chronification of pain, including peripheral sensitization, neuropathic pain, deafferentation pain, sympathetically maintained pain, and central sensitization.[58] Further, a variety of inflammatory and immune transmitters enhance pain signaling.

Emotional and Psychiatric Contributors to Pain—A comprehensive psychiatric evaluation is critical. Factors that exacerbate chronic pain include those that can directly

cause pain amplification as well as factors that make people more vulnerable to the disabling and distressing elements of chronic pain, such as temperament, behavioral conditioning, and life circumstances.[59] Major depression increases pain signaling and interferes with pain-gating mechanisms. Anxiety activates the autonomic sympathetic system and results in increased pain sensitivity. Both of these decrease the ability of patients to distract themselves from chronic pain and increase the sense of distress associated with pain. Treatment with neuromodulators that have antidepressant properties may be useful for chronic pain.[58]

Patients with particular temperaments are more aware of their sensations, may be less able to tolerate discomfort, or may be more impatient with the process of recovery in a way that amplifies pain.[60] Patients may be conditioned to be more sensitive to pain by a variety of unintentional rewards for experiencing pain. The most common problem is opiate pain medications directed at short-term relief of intense pain, then may become “rewarding” in a way that worsens pain over time through the process of opiate-induced hyperalgesia. Additionally, rewards related to pain, such as attention, relief from responsibilities, financial support, and sympathy, can sometimes amplify the pain experience. Lastly, pain amplification can occur in the setting of addictions, such that the pain becomes integral to obtaining addictive medication and plays a role in increasing drug-seeking behavior that disrupts function.[61]

Genetic Factors in Pain—Clinical evaluation may identify anxiety, depression, or other patient factors known to amplify or exacerbate pain.[62] Emerging research suggests that genetic biomarkers may be useful for identifying those individuals at higher risk for chronic pain. Several candidate genes associated with depression, anxiety, and post-traumatic stress disorder risk loci were found to be associated with constant or severe pain in participants with CP in the multi-center North American Pancreatitis Study.[63, 64] However, much remains unknown in the field of genetic biomarkers for pain. Other possible candidate genes to evaluate include those associated with nociceptive activation markers or other pain disorders. Large cohorts of pancreatitis patients with and without pain as well as different pain experiences are needed to identify the role of genetic biomarkers in pancreatitis pain pathogenesis and whether they can be useful for patient care.[65]

The Role of Placebo Effects in Pain—The placebo effect is among the most intriguing phenomena which modulate clinical outcomes.[66] Placebo (and nocebo) effects are the result of the patient’s, proxy’s, and provider’s expectations, conditioning, prior therapeutic experience and depend upon psychoneurobiological mechanisms, distinguishing them from confounders (e.g. regression to the mean, spontaneous remission, and fluctuations in symptoms).[67, 68] In RCTs, the inclusion of a no-treatment arm and possibly a measurement of patient’s, proxy’s, and provider’s expectations are critical elements that can help separate placebo effects from these potential confounders.[69]

As more rigorous and systematic research on the mechanisms of the placebo effect has continued, placebo effects began to be differentiated from confounding variables, as well as other individual and disease factors influencing symptom variability. New evidence continues to suggest that placebo effects influence physiological mechanisms of pain and related outcomes.[70] While pharmacological approaches for pain therapeutics have

mainly focused on the ascending neurotransmission and opioid receptor–mediated therapies, placebo effects provide an opportunity for scientists to focus on the descending modulatory systems as a target for improvement of clinical pain outcomes. Also, the investigation of placebo effects is emerging as a line of research to elucidate why some patients are mildly affected while others suffer debilitating pain-induced dysfunctions. Endogenous modulatory mechanisms and therefore placebo effects can in part account for patients' variability in pain experience, pain severity, adherence to treatment, distinct coping strategies, and chronicity development. Different systems and mechanisms trigger placebo effects that influence pain processing, clinical outcomes, and sense of well-being. Recognition of the placebo effect is important in considering patients with CP in clinical and research settings.

Pancreatic Pain in Children—Children represent a unique subset of patients with CP, with considerations that are different from those of adults. Children with CP experience substantial pain. In the large multicenter INSPPIRE (INternational Study group of Pediatric Pancreatitis: In search for a cuRE) study, children with CP had a median of two emergency department visits in the past year and four hospitalizations during their lifetime; they missed a median of 2 days of school per month.[71] This loss of school time and social interaction comes at a cost to their school achievement and productivity as young adults.

The development of chronic pain in childhood is associated with a decline in grades during adolescence for more than 40% of children. They require increased school accommodations for success.[72] As young adults, their educational outcomes are diminished compared to those of adolescents who had no chronic pain; they also have lower rates of high school and college graduation. Young adults who experienced chronic pain as children have a 31% increased likelihood of receiving public assistance.[73] Children with CP have significantly lower health-related quality of life and more fatigue than healthy children.[74] Of great concern, children with CP have a high rate of opioid use, increasing their risk of future opioid use in adulthood.[8]

Adults experiencing chronic pain from many causes have been shown to have structural and functional changes in the brain.[75] While data are lacking in children with CP, newborns and infants born prematurely who are exposed to untreated recurrent or chronic pain during neonatal care show changes in pain sensitivity and response, brain development, cognitive function and behavioral changes that may be long lasting.[76] Developmental age and degree of neuroplasticity may have a profound impact on long-term outcomes of pain. We know little about the outcomes of chronic pain in adolescents, much less that of toddlers or elementary school–age children. Increased neuroplasticity in young children may exacerbate the impact of pain but may also allow for more neural recovery. Cognitive difficulties, long recognized as a complication of chronic pain, should be investigated in children with CP.[77] In addition, because chronic pain is a toxic stress, examining the impact of early chronic pain on non-CP diseases (i.e. obesity, heart disease, cancer) in adulthood would be of value.

Pain assessment

The assessment of pain is crucial to convert a subjective experience into more objective metrics. In the clinical setting, this will improve diagnosis, communication, monitoring,

clinical decision making, and selection of the most appropriate treatment. In the research setting, an assessment of pain will improve the accuracy of patient allocation and outcome reporting.[78]

Assessment Tools for Pancreatic Pain—Important outcome domains have been determined for the assessment of chronic pain[79] and refined to six core domains for clinical trials[80]: pain description, physical functioning, emotional functioning, rating of global improvement, adverse effects, and participant disposition. Published pain assessment tools specifically for CP have been reviewed, and there is predominance of unidimensional scores, poor coverage, and little evidence of reliability and validity.[81] A comprehensive approach to pain assessment in patients with CP is required and one that takes into account the important outcome and supplementary pain domains.[80] Such a pain assessment tool (COMPAT) was developed (with expert and patient input) and piloted in CP patients.[82] COMPAT was then used to compare patients with CP and chronic pain of other causes and this highlighted two pain patterns: intermittent versus constant (± exacerbations). Pain in CP patients with constant pain was very similar to chronic pain from other causes, reflecting that pain chronification and central sensitization are common features across disorders dominated by pain (unpublished data). To improve usability in the clinical setting, a short form of COMPAT (SFCOMPAT) was developed with 5 pain dimensions (pain pattern, pain provocation, pain spreading, pain description and pain severity) (Table 1) which are individually scored and a total weighted score derived. SF-COMPAT has been shown to be reliable and valid when tested in 3 referral centers[21]. Most recently, an international consensus study was conducted on the assessment of pain associated with CP, based on 27 systematic reviews to provide an evidence base for a series of curated questions.[83]

Quantitative Sensory Testing—Pain is a subjective experience of actual or impending harm and cannot be measured objectively. Nociception—the neural encoding of impending or actual tissue damage has potential to be measured indirectly via standardized methods. In CP, altered nociception can occur due to changes in peripheral or central nerve sensitization. Peripheral nociceptive changes can occur secondary to repeated episodes of inflammation, formation of scar tissue, or local release of neuroinflammatory regulators. Central nervous system changes can occur due to repeated or persistent stimulation from peripheral nerves, release of systemic neuroinflammatory cytokines, or changes in the state of central neuron hyperexcitability. Central sensitization is a phenomenon of neuroplastic remodeling and reorganization of pain pathways, resulting from persistent pain stimuli, leading to phenomena such as hyperalgesia or allodynia. Quantitative sensory testing (QST) is an indirect systematic evaluation of nociceptive responses by administration of standardized external stimuli and recording of the evoked responses.[84] This technique has previously been used in other chronic pain disorders to identify patients with patterns of widespread hyperalgesia or allodynia—suggestive of central sensitization—and to predict outcomes to intervention.[85] In CP, sensitization can be restricted to the spinal cord segments innervated by pancreatic afferents (known as segmental sensitization) or be more widespread, suggestive of central sensitization. Central sensitization is thought to play a role in the difficulty of predicting response.

A QST technique called the Nijmegen Aalborg Screening QST (NASQ) paradigm that incorporates electric tetanical testing, pressure testing, and conditioned pain modulation testing has been used in research settings to show the ability of QST to phenotype sensory patterns in CP patients and associate them with clinical characteristics. Increasing nociceptive impairment has been found to correlate with increasing severity of underlying CP, and evidence of widespread altered nociception has been shown to decrease efficacy of thoracoscopic splanchnic denervation and medical treatment.[86] Dissemination of the NASQ technique, however, has been limited by cumbersome methods, and a new Pancreatic QST (P-QST) protocol[87] involving simple bedside tests has evolved from this (Figure 1). Pancreatic-QST has been able to successfully phenotype patients based on pain pattern, independent of psychiatric comorbidity, and correlate increasingly widespread hypersensitivity with both pain severity and interference, as well as poor quality of life. It is hypothesized that the presence of widespread hyperalgesia may render patients less likely to respond to successful local therapies (as seen with attempts to relieve pancreatic ductal obstruction) for pancreatic pain. Quantitative sensory testing has yet to be incorporated into the mainstream assessment and treatment algorithm for painful CP; however, new bedside techniques, such as P-QST, make this increasingly possible and this approach recommended for use in recent guidelines.[88] The ability of this set of tools to predict outcome to therapy or be used for monitoring of treatment efficacy remain promising possibilities for future exploration.

Central Sensitization of Pain and Addiction—Pain assessment has many confounders, where addiction to opioids and hyperalgesia associated with their use is of major concern. As opioid use is common in patients with CP, measurements of pain must account for this. Conceptualizing addiction from a heuristic framework that comprises a binge/intoxication stage, a withdrawal/negative affect stage, and a preoccupation/anticipation (craving) stage (representing the domains of incentive salience, negative emotional states, and executive function) has allowed the identification of key neurocircuits that underlie pain that are associated with addiction.[89] Such compulsive drug seeking is hypothesized to derive from multiple sources of motivational dysregulation, one of which is negative reinforcement that is driven by the emotional pain of drug or alcohol withdrawal and protracted abstinence.[90] Negative reinforcement is defined as opioid taking that alleviates a negative emotional state or “hyperkatifeia” (i.e., hypohedonia, dysphoria, anxiety, pain, hyperalgesia, irritability, and sleep disturbances) that is created by drug abstinence.[91] There is evidence that both hyperalgesia and hyperkatifeia contribute to pain that is associated with opioid addiction and perpetuate further compulsive opioid seeking. Hyperkatifeia can be defined as a greater sensitivity and an extreme response to a negative emotional state during drug withdrawal. Compelling evidence argues that hyperkatifeia is triggered by acute excessive drug intake, sensitized during compulsive opioid taking followed by repeated withdrawal, persists into protracted abstinence, and contributes to the development and persistence of compulsive drug seeking.[92] Similar to opioid-induced hyperalgesia, opioid-induced hyperkatifeia has been observed in animal models following chronic opioid administration, in opioid-dependent individuals, and in patients who are treated therapeutically with chronic opioids. Neurobiological mechanisms for both hyperalgesia and hyperkatifeia involve both within- and between-system neuroadaptations

and include the dysregulation of key neurochemical circuits within the brain reward systems (dopamine and opioid peptides) in the basal ganglia and brain stress systems (corticotropin-releasing factor, dynorphin, norepinephrine, hypocretin, vasopressin, glucocorticoids, and neuroimmune factors), in the extended amygdala.[93] Neural substrates for hyperalgesia and hyperkatifeia overlap in the extended amygdala and involve not only the loss of reward system function but also the gain of brain stress system function. Understanding the intersection between hyperalgesia and hyperkatifeia may be key to understanding the development of compulsive opioid seeking with chronic opioid treatment in some pain patients. The intersection between hyperalgesia and hyperkatifeia also may be hypothesized to explain the role of alcohol and opioids in “deaths of despair” and the effects of social isolation that is caused by the COVID-19 pandemic.

Pain treatment – Challenges and Opportunities

Neurolysis and Neural Blockade—The common goal for pain treatment in CP is to interrupt or modify the neural (pain) conduction pathways. Blocks of the splanchnic nerves and celiac plexus, the most common targets, are accomplished percutaneously under the guidance of fluoroscopy. While decreases in pain scores appear similar among patients suffering from chronic nonmalignant abdominal pain from CP, dysmotility and intraabdominal adhesions receiving either a celiac plexus block or a splanchnic block, recent studies suggest that fluoroscopically guided T11 bilateral splanchnic blocks afford significantly longer pain relief.[94] Following successful splanchnic nerve block (>50% pain relief), a radiofrequency denervation can be considered. Advantages of splanchnic radiofrequency ablation include long-term pain relief with rare complications. Spinal cord stimulation may also be an effective long-term therapeutic solution for patients suffering from chronic abdominal pain including CP.[95, 96] In a subgroup of patients with CP, pain scores were reduced by approximately half with concomitant long-term opioid use reduction by more than 60%.[96] Future needs include a RCT to determine the efficacy of radio frequency ablation and spinal cord stimulation for mitigation of chronic abdominal pain in pancreatitis patients.

Cognitive Behavioral Therapy—Pain in CP is commonly associated with psychological comorbidities including depression and anxiety symptoms, low physical functioning, sleep problems and low quality of life, as well as high economic and societal burden. A recent study found that 40% of CP patients had clinically significant levels of anxiety and depressive symptoms which were associated with high pain severity and pain interference.[97] Pain self-management programs using cognitive behavioral therapy (CBT) approaches equip patients with coping skills to minimize the impact of painful conditions on activity participation and psychosocial well-being. However, there has been limited study of psychological interventions to manage painful CP across the lifespan. In a recently completed RCT, Palermo et al[98] demonstrated the feasibility and acceptability of an internet CBT program in 30 adults with painful CP. Patients randomized to Internet-CBT versus control demonstrated moderate to large effects in reducing pain intensity and pain interference from baseline to 3-months. A RCT evaluating internet-CBT vs. education control to reduce pain and pain-related disability, and to enhance health-related quality of life in adolescents with CP is currently under way.[99] Research priorities in this area

are to understand psychosocial risk and protective factors that influence pain severity and interference; to develop and implement screening tools to identify patients at risk for low health-related quality of life who would benefit from psychosocial intervention; and to conduct large definitive trials of psychosocial interventions in painful CP. Longitudinal study designs will be particularly useful in examining behavioral and psychosocial factors that predict trajectories of pain and disability over time.

Endocannabinoid Signaling and Treatments—Pain perception can be effectively controlled by neurotransmitters that operate within the CNS and at terminals of afferent nerve fibers outside the CNS. Endocannabinoid signals are thought to play important roles in both the central and peripheral control of pain processing. Anandamidemediated signaling at cannabinoid receptors-1 (CB1) in dorsal root ganglia (DRG) may act as a ‘gate’ that limits entrance of incoming pain-related information into the spinal cord. An analogous function has been ascribed to paracannabinoid messengers that do not interact with cannabinoid receptors.[100] One such lipid, palmitoylethanolamide (PEA), exerts profound anti-inflammatory and antinociceptive effects in animal models,[101] and clinical evidence suggests that PEA may also have analgesic properties.[102] Anandamide and PEA appear to modulate acute and chronic nociception by acting at peripheral sites, and it is likely that these antinociceptive actions can be amplified pharmacologically for therapeutic benefit. A current research focus is on small-molecule inhibitors of the enzymes fatty-acid amide hydrolase (FAAH) and N-acylethanolamine acid amidase (NAAA), which are responsible for the intracellular deactivation of anandamide and PEA, respectively. NAAA-regulated PEA signaling at peroxisome proliferator-activated receptor (PPAR)-alpha may serve as a critical checkpoint for the transition from acute to chronic pain; and NAAA inhibitors may mitigate chronic pain following physical injury. Adequately powered RCTs are urgently needed to test the safety and efficacy of cannabis and inhibitors of endocannabinoid deactivation in patients with chronic pain.

The Role of Ketamine—Originally classified by the Food and Drug Administration as an anesthetic induction agent, ketamine has been employed in a variety of settings. The ‘dissociative anesthesia’ observed with ketamine administration can be a useful alternative or adjunct to more commonly utilized anesthetic and analgesic agents. Ketamine is also used by pain specialists and palliative medicine clinicians for complex, often treatment-refractory cancer pain and chronic pain syndromes.[103] Ketamine’s potent pharmacologic antagonism of the NMDA (n-methyl d-aspartate) receptor may account for its analgesic action. Ketamine is often used when conventional opioid analgesics are ineffective, or when they are believed to be paradoxically worsening the pain (opioid tachyphylaxis). In this circumstance, it is hypothesized that ketamine’s NMDA receptor effect may interrupt a malignant cellular cycle (excitotoxicity). When effective, this interruption can improve pain control, significantly reduce opioid requirements, and/or may appear to help ‘recapture’ opioid responsiveness. Of particular interest is that short-term intensive in hospital treatments may lead to several months of pain relief. As with the other pain management opportunities discussed here, the use of ketamine in patients with intractable pain requires further study in patients with chronic pancreatitis pain.

The NIH HEAL Initiative—Successful programs have been launched to address other painful conditions and better understand multiple factors associated with the experience and treatment of chronic pain. The NIH HEAL Initiative – Helping to End Addiction Long-term – was established to address this challenge through supporting insight into the science as well as the various stakeholders resulting in programs promising actionable solutions with engaged partners.[104] The research program includes clinical research as well as pre-clinical and translational research aimed at enhancing pain management. Novel medication options, new prevention and treatment strategies and translation of research into clinical practice aim to improve treatment for opioid misuse and addiction. Because many individuals with opioid use disorder do not receive appropriate treatment, HEAL research aims to develop new interventions and test integration into real world community, justice and emergency settings. Although pain control is important in clinical care, this must be balanced with the risks of long-term opioid treatment and long-term recovery. Hence, HEAL research is testing non-addictive medications, longer lasting treatments, and new models of care for pain management. The clinical conundrum facing clinicians caring for patients with chronic pain is being addressed by HEAL research aimed at better characterizing patients with chronic pain. Because of the multi-factorial nature of chronic pain, a one-sized-fits-all treatment approach cannot be effective. Instead, barriers to achieving pain control and functional improvement must be addressed along with the painful condition to prevent negative consequences of treatment. HEAL programs such as the Early Phase Pain Investigation Clinical Network (EPPIC Net)[105] and the Back Pain Consortium (BACPAC) Research Program[106] are evaluating appropriately targeted treatments for some of these populations. Similarly, optimal strategies are being explored through the Pain Management Effectiveness Research Network (ERN)[107] and Pragmatic and Implementation Studies for the Management of Pain (PRISM).[108] Through precision medicine approaches to determine the right treatment for the right patient at the right time, it is hoped that these research programs will decrease the morbidity and even mortality associated with failed treatments for chronic pain.

Conclusions

The workshop examined the pathophysiology of pancreatic pain, including the concept of peripheral vs. central sensitization, the contributions of inflammation, signaling molecules, genetic and placebo-related factors. The impact of emotional and psychosocial factors, perception, pain modulation and pain-related suffering were discussed. Speakers raised the importance of age-related factors as well as challenges to objectively assess and treat pancreatitis pain. The participants identified multiple gaps in our understanding of pain in pancreatitis and repeatedly emphasized that without addressing these gaps, it would not be possible to advance the field and offer diagnostic and therapeutic alternatives to children and adults with pancreatic pain. Critical areas for further research identified are outlined below.

Research Gaps and Opportunities

Future research should be directed to better understand the pathophysiology of pain in pancreatic diseases, define diagnostic biomarkers and mediators of pain, develop effective pain assessment tools and robust end-points for clinical studies and finally efficient

therapies. Specific priorities for research to improve our understanding of the pain in pancreatic diseases include:

- Development of patient-related outcomes (PROs) and quality of life measures in patients with recurrent acute or chronic pancreatitis acceptable to regulatory agencies (e.g. Food and Drug Administration).
- Development and validation of multi-dimensional assessment tools to predict and measure response to treatments for pancreatic pain and other future treatments.
- Development of biomarkers specific for pancreatic pain using genetic, proteomic and metabolomic analysis, including pancreatic fluid and/or clinical parameters.
- Define pain phenotypes based on biological and psychosocial paramenters.
- Define mechanisms of pain processing both peripherally and centrally to help develop targeted treatments.
- Characterize anatomical and functional distortions in the brain specific to pancreatic pain in comparison to healthy controls and other visceral and somatic (e.g. back) pain conditions.
- Discover objective biomarkers of pancreatic pain from clinical parameters and liquid biopsies using multi-omic platforms.
- Advancement of research related to placebo effects across pain disorders, including chronic pancreatitis.
- Investigation of the molecular and genetic mechanisms underlying placebo and nocebo effects (e.g. omics, animal studies).
- Design of accurate (e.g. assessment of patients' expectations) and large studies that allow cluster and machine learning approaches to better understand the driving factors for individual placebo and nocebo responsiveness.
- Determine the influence of language and culture on pancreatic pain assessment.
- Investigation of the differences in the long-term outcomes of chronic pain in childhood pancreatitis based on developmental age at which it occurs.
- Define how neuroplasticity in young children may exacerbate the impact of pain, but may also allow more neural recovery.
- Determine if treating cognitive difficulties in children and adults should be an adjunct to treatment of chronic pain.
- Develop methods to measure chronic co-existent opioid use and associated complications (e.g. hyperalgesia, hyperkatifeia and addiction).
- Conduct studies of cannabis and its specific purified components for management of pancreatic pain.
- Conduct randomized clinical trials of spinal cord stimulation, cognitive behavioral therapy and other modalities for management of pancreatic pain.

- Conduct randomized clinical trials targeting specific molecular factors involved in peripheral sensitization shown to be efficacious in pre-clinical and clinical studies.

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References

1. Thompson BS, Philcox S, Devereaux B, et al. Prodromal Signs and Symptoms of Chronic Pancreatitis: A Systematic Review. J Clin Gastroenterol. May 29 2021. [Epub ahead of print].
2. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. Am Fam Physician. 2006;73:485–492. [PubMed: 16477897]
3. D'Haese JG, Hartel M, Demir IE, et al. Pain sensation in pancreatic diseases is not uniform: the different facets of pancreatic pain. World J Gastroenterol. 2014;20:9154–9161. [PubMed: 25083089]
4. Wilcox CM, Yadav D, Ye T, et al. Chronic pancreatitis pain pattern and severity are independent of abdominal imaging findings. Clin Gastroenterol Hepatol. 2015;13:552–560; quiz e28–9. [PubMed: 25424572]
5. Schwarzenberg SJ, Uc A, Zimmerman B, et al. Chronic Pancreatitis: Pediatric and Adult Cohorts Show Similarities in Disease Progress Despite Different Risk Factors. J Pediatr Gastroenterol Nutr. 2019;68:566–573. [PubMed: 30897605]
6. Mullady DK, Yadav D, Amann ST, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut. 2011;60:77–84. [PubMed: 21148579]
7. Machicado JD, Amann ST, Anderson MA, et al. Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co-Morbidities. Am J Gastroenterol. 2017;112:633–642. [PubMed: 28244497]
8. Perito ER, Palermo TM, Pohl JF, et al. Factors Associated With Frequent Opioid Use in Children With Acute Recurrent and Chronic Pancreatitis. J Pediatr Gastroenterol Nutr. 2020;70:106–114. [PubMed: 31567889]

9. Ceyhan GO, Bergmann F, Kadihasanoglu M, et al. Pancreatic neuropathy and neuropathic pain--a comprehensive pathomorphological study of 546 cases. Gastroenterology. 2009;136:177–186 e1. [PubMed: 18992743]
10. Muller MW, Friess H, Koninger J, et al. Factors influencing survival after bypass procedures in patients with advanced pancreatic adenocarcinomas. Am J Surg. 2008;195:221–228. [PubMed: 18154768]
11. Oh TK, Do SH, Yoon YS, et al. Association Between Opioid Use and Survival Time in Patients With Unresectable Pancreatic Cancer: 10 Years of Clinical Experience. Pancreas. 2018;47:837–842. [PubMed: 29939907]
12. Steele GL, Dudek AZ, Gilmore GE, et al. Impact of Pain, Opioids, and the Mu-opioid Receptor on Progression and Survival in Patients With Newly Diagnosed Stage IV Pancreatic Cancer. Am J Clin Oncol. 2020;43:591–597. [PubMed: 32482952]
13. Drewes AM, Olesen AE, Farmer AD, et al. Gastrointestinal pain. Nat Rev Dis Primers. 2020;6:1. [PubMed: 31907359]
14. Larino-Noia J, de la Iglesia D, Iglesias-Garcia J, et al. Morphological and functional changes of chronic pancreatitis in patients with dyspepsia: A prospective, observational, cross-sectional study. Pancreatology. 2018;18:280–285. [PubMed: 29496438]
15. Hashimoto S, Futagami S, Yamawaki H, et al. Epigastric pain syndrome accompanying pancreatic enzyme abnormalities was overlapped with early chronic pancreatitis using endosonography. J Clin Biochem Nutr. 2017;61:140–145. [PubMed: 28955132]
16. Palsson OS, Whitehead W, Tornblom H, et al. Prevalence of Rome IV Functional Bowel Disorders Among Adults in the United States, Canada, and the United Kingdom. Gastroenterology. 2020;158:1262–1273 e3. [PubMed: 31917991]
17. Singh VK, Yadav D, Garg PK. Diagnosis and Management of Chronic Pancreatitis: A Review. JAMA. 2019;322:2422–2434. [PubMed: 31860051]
18. Ashok A, Faghih M, Azadi JR, et al. Morphologic Severity of Acute Pancreatitis on Imaging Is Independently Associated with Opioid Dose Requirements in Hospitalized Patients. Dig Dis Sci. Apr 9 2021. [Epub ahead of print].
19. Buxbaum J, Quezada M, Chong B, et al. The Pancreatitis Activity Scoring System predicts clinical outcomes in acute pancreatitis: findings from a prospective cohort study. Am J Gastroenterol. 2018;113:755–764. [PubMed: 29545634]
20. Mackay TM, Latenstein AEJ, Sprangers MAG, et al. Relationship Between Quality of Life and Survival in Patients With Pancreatic and Periampullary Cancer: A Multicenter Cohort Analysis. J Natl Compr Canc Netw. 2020;18:1354–1363. [PubMed: 33022643]
21. Kuhlmann L, Teo K, Olesen SS, et al. Development of the Comprehensive Pain Assessment Tool Short Form for Chronic Pancreatitis: Validity and Reliability Testing. Clin Gastroenterol Hepatol. Jun 2 2021. [Epub ahead of print].
22. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med. 2007;356:676–684. [PubMed: 17301298]
23. Cahen DL, Gouma DJ, Laramee P, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology. 2011;141:1690–1695. [PubMed: 21843494]
24. Issa Y, Kempeneers MA, Bruno MJ, et al. Effect of Early Surgery vs Endoscopy-First Approach on Pain in Patients With Chronic Pancreatitis: The ESCAPE Randomized Clinical Trial. JAMA. 2020;323:237–247. [PubMed: 31961419]
25. Siddappa PK, Hawa F, Prokop LJ, et al. Endoscopic pancreatic duct stenting for pain palliation in selected pancreatic cancer patients: a systematic review and meta-analysis. Gastroenterol Rep (Oxf). 2021;9:105–114. [PubMed: 34026217]
26. Koulouris AI, Alexandre L, Hart AR, et al. Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) technique and analgesic efficacy in patients with pancreatic cancer: A systematic review and meta-analysis. Pancreatology. 2021;21:434–442. [PubMed: 33461931]
27. Asif AA, Walayat SK, Bechtold ML, et al. EUS-guided celiac plexus neurolysis for pain in pancreatic cancer patients - a meta-analysis and systematic review. J Community Hosp Intern Med Perspect. 2021;11:536–542. [PubMed: 34211665]

28. Kanno Y, Koshita S, Masu K, et al. Efficacy of EUS-guided celiac plexus neurolysis compared with medication alone for unresectable pancreatic cancer in the oxycodone/fentanyl era: a prospective randomized control study. Gastrointest Endosc. 2020;92:120–130. [PubMed: 31953188]
29. Fujii-Lau LL, Bamlet WR, Eldrige JS, et al. Impact of celiac neurolysis on survival in patients with pancreatic cancer. Gastrointest Endosc. 2015;82:46–56 e2. [PubMed: 25800661]
30. Yang AL, Jin DX, Srivoleti P, et al. Are Opioid-Naive Patients With Acute Pancreatitis Given Opioid Prescriptions at Discharge? Pancreas. 2019;48:1397–1399. [PubMed: 31688608]
31. Ahmed A, Yakah W, Freedman SD, et al. Evaluation of Opioid Use in Acute Pancreatitis in Absence of Chronic Pancreatitis: Absence of Opioid Dependence an Important Feature. Am J Med. 2020;133:1209–1218. [PubMed: 32272099]
32. LeBrett WG, Chen FW, Yang L, et al. Increasing Rates of Opioid Prescriptions for Gastrointestinal Diseases in the United States. Am J Gastroenterol. 2021;116:796–807. [PubMed: 33982950]
33. Novy DM, Nelson DV, Koyyalagunta D, et al. Pain, opioid therapy, and survival: a needed discussion. Pain. 2020;161:496–501. [PubMed: 31693537]
34. Woolf CJ, Costigan M. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. Proc Natl Acad Sci U S A. 1999;96:7723–7730. [PubMed: 10393888]
35. Dimcevski G, Sami SA, Funch-Jensen P, et al. Pain in chronic pancreatitis: the role of reorganization in the central nervous system. Gastroenterology. 2007;132:1546–1556. [PubMed: 17408654]
36. Gebhart GF. It's chickens and eggs all over again: is central reorganization the result or cause of persistent visceral pain? Gastroenterology. 2007;132:1618–1620. [PubMed: 17418168]
37. Baron R, Hans G, Dickenson AH. Peripheral input and its importance for central sensitization. Ann Neurol. 2013;74:630–636. [PubMed: 24018757]
38. Ceyhan GO, Michalski CW, Demir IE, et al. Pancreatic pain. Best Pract Res Clin Gastroenterol. 2008;22:31–44. [PubMed: 18206811]
39. Pasricha PJ. Unraveling the mystery of pain in chronic pancreatitis. Nat Rev Gastroenterol Hepatol. 2012;9:140–151. [PubMed: 22269952]
40. Hoogerwerf WA, Gondesen K, Xiao SY, et al. The role of mast cells in the pathogenesis of pain in chronic pancreatitis. BMC Gastroenterol. 2005;5:8. [PubMed: 15745445]
41. Liu L, Zhu Y, Noe M, et al. Neuronal Transforming Growth Factor beta Signaling via SMAD3 Contributes to Pain in Animal Models of Chronic Pancreatitis. Gastroenterology. 2018;154:2252–2265 e2. [PubMed: 29505748]
42. Winston JH, He ZJ, Shenoy M, et al. Molecular and behavioral changes in nociception in a novel rat model of chronic pancreatitis for the study of pain. Pain. 2005;117:214–222. [PubMed: 16098667]
43. Xu GY, Winston JH, Shenoy M, et al. Transient receptor potential vanilloid 1 mediates hyperalgesia and is up-regulated in rats with chronic pancreatitis. Gastroenterology. 2007;133:1282–1292. [PubMed: 17698068]
44. Zhu Y, Colak T, Shenoy M, et al. Nerve growth factor modulates TRPV1 expression and function and mediates pain in chronic pancreatitis. Gastroenterology. 2011;141:370-377.
45. Olesen SS, Bouwense SA, Wilder-Smith OH, et al. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Gastroenterology. 2011;141:536–543. [PubMed: 21683078]
46. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol. 2009;87:81–97. [PubMed: 18952143]
47. Baliki MN, Apkarian AV. Nociception, Pain, Negative Moods, and Behavior Selection. Neuron. 2015;87:474–491. [PubMed: 26247858]
48. Farmer MA, Baliki MN, Apkarian AV. A dynamic network perspective of chronic pain. Neurosci Lett. 2012;520:197–203. [PubMed: 22579823]
49. Baliki MN, Schnitzer TJ, Bauer WR, et al. Brain morphological signatures for chronic pain. PLoS One 2011;6:e26010.

50. Hashmi JA, Baliki MN, Huang L, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain. 2013;136:2751–2768. [PubMed: 23983029]
51. Baliki MN, Petre B, Torbey S, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci. 2012;15:1117–1119. [PubMed: 22751038]
52. Mansour A, Baria AT, Tetreault P, et al. Global disruption of degree rank order: a hallmark of chronic pain. Sci Rep. 2016;6:34853. [PubMed: 27725689]
53. Ren W, Centeno MV, Berger S, et al. The indirect pathway of the nucleus accumbens shell amplifies neuropathic pain. Nat Neurosci. 2016;19:220–222. [PubMed: 26691834]
54. Ren W, Centeno MV, Wei X, et al. Adaptive alterations in the mesoaccumbal network following peripheral nerve injury. Pain. 2020;162:895–906.
55. Reckziegel DT P; Apkarian AV Gender dependent pharmacotherapy for blocking transition to chronic back pain: a proof of concept randomized trial. medrxiv. 2019.
56. Mullady DK, Yadav D, Amann ST, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut. 2011;60:77–84. [PubMed: 21148579]
57. Abu-El-Haija M, Lowe M, Barth B, et al. Pediatric chronic pancreatitis without prior acute or acute recurrent pancreatitis: A report from the INSPPIRE consortium. Pancreatology. 2020;20:781–784. [PubMed: 32332002]
58. Murray M, Stone A, Pearson V, et al. Clinical solutions to chronic pain and the opiate epidemic. Prev Med. 2019;118:171–175. [PubMed: 30315848]
59. Treisman GJ, Clark MR. A behaviorist perspective. Adv Psychosom Med 2011;30:8–21. [PubMed: 21508624]
60. Clark MR, Treisman GJ. Perspectives on pain and depression. Adv Psychosom Med. 2004;25:1–27. [PubMed: 15248364]
61. Clark MR, Treisman GJ. Neurobiology of pain. Adv Psychosom Med. 2004;25:78–88. [PubMed: 15248368]
62. Cella D, Choi SW, Condon DM, et al. PROMIS(®) Adult Health Profiles: Efficient Short-Form Measures of Seven Health Domains. Value Health. 2019;22:537–544. [PubMed: 31104731]
63. Dunbar E, Greer PJ, Melhem N, et al. Constant-severe pain in chronic pancreatitis is associated with genetic loci for major depression in the NAPS2 cohort. J Gastroenterol. 2020;55:1000–1009. [PubMed: 32681239]
64. Dunbar EK, Greer PJ, Amann ST, et al. Pain Experience in Pancreatitis: Strong Association of Genetic Risk Loci for Anxiety and PTSD in Patients With Severe, Constant, and Constant-Severe Pain. Am J Gastroenterol. Jul 8 2021. [Epub ahead of print].
65. Dunbar EK, Saloman JL, Phillips AE, et al. Severe Pain in Chronic Pancreatitis Patients: Considering Mental Health and Associated Genetic Factors. J Pain Res. 2021;14:773–784. [PubMed: 33762844]
66. Colloca L, Barsky AJ. Placebo and Nocebo Effects. N Engl J Med 2020;382:554–561. [PubMed: 32023375]
67. Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? Nat Rev Neurosci. 2005;6:545–552. [PubMed: 15995725]
68. Colloca L.Nocebo effects can make you feel pain. Science. 2017;358:344. [PubMed: 29051375]
69. Colloca L.The Placebo Effect in Pain Therapies. Annu Rev Pharmacol Toxicol. 2019;59:191–211. [PubMed: 30216744]
70. Colloca L, Lopiano L, Lanotte M, et al. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. Lancet Neurol. 2004;3:679–684. [PubMed: 15488461]
71. Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. J Pediatr. 2015;166:890–896.e1. [PubMed: 25556020]
72. Logan DE, Simons LE, Stein MJ, et al. School impairment in adolescents with chronic pain. J Pain. 2008;9:407–416. [PubMed: 18255341]

73. Murray CB, Groenewald CB, de la Vega R, et al. Long-term impact of adolescent chronic pain on young adult educational, vocational, and social outcomes. Pain. 2020;161:439-445.
74. Pohl JF, Limbers CA, Kay M, et al. Health-related quality of life in pediatric patients with long-standing pancreatitis. J Pediatr Gastroenterol Nutr. 2012;54:657–663. [PubMed: 22094900]
75. Yang S, Chang MC. Chronic Pain: Structural and Functional Changes in Brain Structures and Associated Negative Affective States. Int J Mol Sci. 2019;20;3130. [PubMed: 31248061]
76. Walker SM. Long-term effects of neonatal pain. Semin Fetal Neonatal Med 2019;24:101005.
77. Baker KS, Georgiou-Karistianis N, Gibson SJ, et al. Optimizing Cognitive Function in Persons With Chronic Pain. Clin J Pain. 2017;33:462–472. [PubMed: 28379916]
78. Forsmark CE, Andersen DK, Farrar JT, et al. Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis: Summary of the Working Group on Drug Development and Trials in Chronic Pancreatitis at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop. Pancreas. 2018;47:1200–1207. [PubMed: 30325858]
79. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106:337–345. [PubMed: 14659516]
80. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9:105–121. [PubMed: 18055266]
81. Teo K, Johnson MH, Truter S, et al. Pain assessment in chronic pancreatitis: A comparative review of methods. Pancreatology. 2016;16:931–939. [PubMed: 27693097]
82. Teo K, Johnson MH, Drewes AM, et al. A comprehensive pain assessment tool (COMPAT) for chronic pancreatitis: Development, face validation and pilot evaluation. Pancreatology. 2017;17:706–719. [PubMed: 28733149]
83. Drewes AM, Bellin MD, Besselink MG, et al. Assessment of pain associated with chronic pancreatitis: An international consensus guideline. Pancreatology. (In Press).
84. Kuhlmann L, Olesen SS, Gronlund D, et al. Patient and Disease Characteristics Associate With Sensory Testing Results in Chronic Pancreatitis. Clin J Pain. 2019;35:786–793. [PubMed: 31268890]
85. Grosen K, Fischer IW, Olesen AE, et al. Can quantitative sensory testing predict responses to analgesic treatment? Eur J Pain. 2013;17:1267–1280. [PubMed: 23658120]
86. Olesen SS, Graversen C, Bouwense SA, et al. Quantitative sensory testing predicts pregabalin efficacy in painful chronic pancreatitis. PLoS One. 2013;8:e57963.
87. Phillips AE, Faghih M, Kuhlmann L, et al. A clinically feasible method for the assessment and characterization of pain in patients with chronic pancreatitis. Pancreatology. 2020;20:25–34. [PubMed: 31787527]
88. Drewes AM, Bouwense SAW, Campbell CM, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology. 2017;17:720–731. [PubMed: 28734722]
89. Ballantyne JC, Koob GF. Allostasis theory in opioid tolerance. Pain. Mar 22 2020. [Epub ahead of print].
90. Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997;278:52–58. [PubMed: 9311926]
91. Koob GF. Neurobiology of Opioid Addiction: Opponent Process, Hyperkatifeia, and Negative Reinforcement. Biol Psychiatry. 2020;87:44–53. [PubMed: 31400808]
92. Koob GF, Powell P, White A. Addiction as a Coping Response: Hyperkatifeia, Deaths of Despair, and COVID-19. Am J Psychiatry. 2020;177:1031–1037. [PubMed: 33135468]
93. Koob GF. Drug Addiction: Hyperkatifeia/Negative Reinforcement as a Framework for Medications Development. Pharmacol Rev. 2021;73:163–201. [PubMed: 33318153]
94. Kapural L, Lee N, Badhey H, et al. Splanchnic block at T11 provides a longer relief than celiac plexus block from nonmalignant, chronic abdominal pain. Pain Manag. 2019;9:115–121. [PubMed: 30681022]
95. Kapural L, Nagem H, Tlucek H, et al. Spinal cord stimulation for chronic visceral abdominal pain. Pain Med. 2010;11:347–355. [PubMed: 20088856]

96. Kapural L, Cywinski JB, Sparks DA. Spinal cord stimulation for visceral pain from chronic pancreatitis. Neuromodulation. 2011;14:423–426; discussion 426–427. [PubMed: 21854493]

97. Phillips NL, Moore T, Teng A, et al. Behavioral interventions for sleep disturbances in children with neurological and neurodevelopmental disorders: a systematic review and meta-analysis of randomized controlled trials. Sleep. 2020;43:zsaa040.

98. Palermo TM, Law EF, Topazian MD, et al. Internet Cognitive-Behavioral Therapy for Painful Chronic Pancreatitis: A Pilot Feasibility Randomized Controlled Trial. Clin Transl Gastroenterol. 2021;12:e00373.

99. Palermo TM, Murray C, Aalfs H, et al. Web-based cognitive-behavioral intervention for pain in pediatric acute recurrent and chronic pancreatitis: Protocol of a multicenter randomized controlled trial from the study of chronic pancreatitis, diabetes and pancreatic cancer (CPDPC). Contemp Clin Trials. 2020;88:105898.

100. Piomelli D, Sasso O. Peripheral gating of pain signals by endogenous lipid mediators. Nat Neurosci. 2014;17:164–174. [PubMed: 24473264]

101. Piomelli D, Scalvini L, Fotio Y, et al. -Acylethanolamine Acid Amidase (NAAA): Structure, Function, and Inhibition. J Med Chem. 2020;63:7475–7490. [PubMed: 32191459]

102. Artukoglu BB, Beyer C, Zuloff-Shani A, et al. Efficacy of Palmitoylethanolamide for Pain: A Meta-Analysis. Pain Physician. 2017;20:353–362. [PubMed: 28727699]

103. Tran K, McCormack S. Ketamine for Chronic Non-Cancer Pain: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 May 28.

104. The Helping to End Addiction Long-term Initiative. Supporting science-based solutions to the opioid crisis. Available at: https://heal.nih.gov. Accessed August 18, 2021.

105. Early Phase Pain Investigation Clinical Network (EPPIC-Net). Page last updated August 18, 2021. Available at: www.heal.nih.gov/research/clinical-research/eppic-net. Accessed August 18, 2021.

106. Back Pain Consortium Research Program. Page last updated August 5, 2021. Available at: www.heal.nih.gov/research/clinical-research/back-pain. Accessed August 18, 2021.

107. Pain Management Effectiveness Research network. Page last updated September 29, 2020. Available at: https://heal.nih.gov/research/clinical-research/pain-management-research. Accessed August 18, 2021.

108. Pragmatic and Implementation Studies for the Management of Oain to Reduce Opioid Prescribing (PRISM). Page last updated January 28, 2021. Available at: www.heal.nih.gov/research/clinical-research/prism. Accessed August 18, 2021.

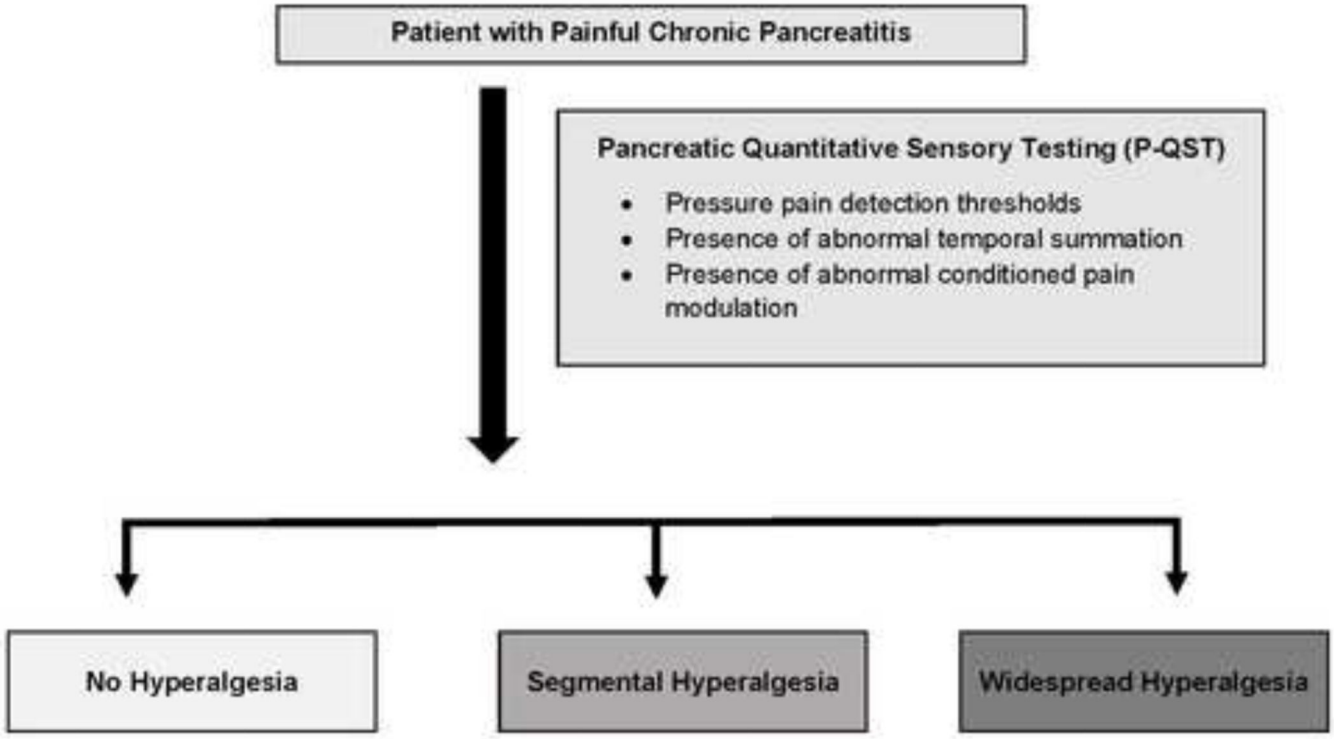

Figure 1.

Patients with chronic pancreatitis can undergo pancreatic quantitative sensory testing (P-QST), a series of external tests designed to evaluate neurosensory patterns and identify their nociceptive phenotype (Reference 87).

Table 1.

The Dimensions of the Comprehensive Pain Assessment Tool – Short Form (COMPAT-SF) for Pain Associated With Chronic Pancreatitis.

Pain dimensions	Description
Pattern score	Intermittent versus constant (± exacerbations)
Provocation score	Diet, lifestyle, other factors
Spreading score	Involvement of other body areas with pain
Descriptive score	Different qualities of pain and related symptoms
Severity score	• Average, worst, least • Pain medication use (type, dose, frequency)

Scoring for individual dimensions are calculated in response to 7 questions (see details in scoring manual in Supplement to reference 21). Total weighted score = (2 x pain severity score + 2 x pain pattern score + 2 x pain provocation score + spreading pain score + qualitative pain-describing score)/8.