

# Severe Pain in Chronic Pancreatitis Patients: Considering Mental Health and Associated Genetic Factors

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**Abstract:** Pain is the most distressing and disruptive feature of recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) resulting in low quality of life (QOL) and disabilities. There is no single, characteristic pain pattern in patients with RAP and CP. Abdominal imaging features of CP accurately reflect morphologic features but they do not correlate with pain. Pain is the major driver of poor quality of life (QOL) and it is the constant pain, rather than intermittent pain that drives poor QOL. Furthermore, the most severe constant pain experience in CP is also a complex condition. The ability to target the etiopathogenesis of severe pain requires new methods to detect the exact pain mechanisms in an individual at cellular, tissue, system and psychiatric levels. In patients with complex and severe disease, it is likely that multiple overlapping mechanisms are simultaneously driving pain, anxiety and depression. Quantitative sensory testing (QST) shows promise in detecting alterations in central processing of pain signals and to classify patients for mechanistic and therapeutic studies. New genetic research suggests that genetic loci for severe pain in CP overlap with genetic loci for depression and other psychiatric disorders, providing additional insights and therapeutic targets for individual patients with severe CP pain. Well-designed clinical trials that integrate clinical features, QST, genetics and psychological assessments with targeted treatment and assessment of responses are required for a quantum leap forward. A better understanding of the context and mechanisms contributing to severe pain experiences in individual patients is predicted to lead to better therapies and quality of life.

**Keywords:** pancreatitis, pain management, mental health, depression, genetic research

## Introduction

Chronic pancreatitis (CP) is a pathologic fibro-inflammatory syndrome of the pancreas that results in persistent pathologic responses to parenchymal injury or stress, manifesting as debilitating abdominal pain in up to 90% of patients.<sup>1,2</sup> CP is the end-stage of a pathogenic process that typically includes episode(s) of acute pancreatitis (AP) or recurrent AP (RAP). The clinical features of the established and end stages of CP differ among patients as the failure or dysfunction of the different cell types involved in pancreatic physiology reveals different amounts of resilience or susceptibility to recurrent or sustained injury or stress. Thus, the appearance of the pancreas on cross-sectional abdominal imaging measures fibrosis, atrophy, cysts, calcifications, etc. but cannot predict whether or not the patient has exocrine pancreatic insufficiency (EPI),<sup>3</sup> diabetes mellitus (DM)<sup>4</sup> or pain.<sup>5</sup>

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Pain in RAP and CP significantly and negatively impacts the quality of life (QOL) and results in progressively higher rates of disability.<sup>6,7</sup> Pain in CP is multifactorial and is notoriously challenging to treat.<sup>8–11</sup> Currently, pain management in RAP and CP is based on questionnaire-based measurements of pain severity<sup>12</sup> and analgesic therapy is based on general recommendations from the World Health Organization on the treatment of chronic pain.<sup>13</sup> Treatment options in CP focus on symptom relief with most CP patients being prescribed opioids for the treatment of their pain.<sup>13</sup> In some patients, duct-obstructing pancreatic duct stones or strictures can be treated with invasive treatments (endotherapy, extracorporeal shockwave lithotripsy [ESWL] or surgery) to relieve suspected intraductal hypertension, although these interventions are effective in only a subset of patients.<sup>9,14–17</sup> Total pancreatectomy with islet cell auto-transplantation (TPIAT) has been offered as radical treatment and the last resort to patients with severe, unmanageable pain.<sup>18</sup> Unfortunately, these current pain management strategies for CP are suboptimal. National and international scientific and clinical teams are working to develop methods for assessing and treating pain—an important unmet need in CP.<sup>19–21</sup>

Pain is a complex experience that includes both sensory input to the brain and the interpretation of the pain based on many adaptive and psychological factors. The experience of pain and impact on QOL can be markedly exacerbated by the coexistence of psychiatric diagnoses such as depression.<sup>22–24</sup> Our knowledge of predisposing genetic risks and how to treat mental health issues in patients with CP are in their early stages, but understanding the interaction between mental health and pancreatic pain may be very important for optimal patient management in the future. We conducted a literature search in PubMed for relevant English-language articles published before December 1, 2020. Search terms included chronic pancreatitis and pain, and each of the followings: genetics, genetic mutations, genetic polymorphisms, risk factors, mental health, anxiety, depression, mood disorder, neural networks and pain, neural networks and mood disorders, anxiety and depression, psychiatric condition, mood disorder, cannabinoids, opioids, and gabapentinoids. Publications on chronic pancreatitis and pain were reviewed in depth, and additional references from those publications were reviewed for relevant content and included. Case reports and case series were excluded. All other relevant articles were reviewed by the author group

and those with the greatest relevance were considered for inclusion.

## Clinical Characteristics of Pancreatic Pain

Pain is a subjective and emotional response to actual or potential tissue damage; therefore, objective methods of pain assessment based on end-organ pathology alone are impossible.<sup>25</sup> Furthermore, assessment of pancreatic pain is challenging due to the multiple pathologies contributing to the overall experience, including pancreatic parenchymal oxidative/metabolic stress, inflammation, neuritis/neuropathy, pancreatic ductal obstruction, ischemia, and alterations in peripheral and central neural pain processing.<sup>8</sup> In addition, there are emotional aspects of pain that are likewise complex. Multiple general pain assessment tools have been used to assess some aspects of pain in CP. CP-specific tools now include the Comprehensive Pain Assessment Tool for CP (COMPAT) and Pancreatic Quality of Life Instrument (PANQOLI) and they show promise for future evaluation and classification of characteristics specific to CP.<sup>26,27</sup> However, these tools cannot decipher or specify the mechanisms of pain and how risk factors interact with these mechanisms or how they affect the QOL.

Historically, pain in CP was divided into two specific patterns (Types A and B) by Ammann et al in their 1999 study of alcoholic CP, which was widely adopted for the clinical classification of CP pain.<sup>28</sup> Type A pain was characterized by short-lived pain episodes lasting fewer than 10 days, and separated by long pain-free intervals. Type B pain was characterized by prolonged periods of daily pain, punctuated by clusters of recurrent, severe pain exacerbations. Some patients experience both types of pain: of the 207 patients in their series, all patients experienced at least one attack of Type A pain, but only 116 (56%) reported experiencing Type B pain. B-type pain was associated with pancreatic pseudocysts (or walled-off necroses), cholestasis, and presumptive pancreatic ductal hypertension.<sup>28</sup>

A 2011 publication by Mullady and the investigators of the North American Pancreatitis Study (NAPS2) group evaluated over 400 CP patients of all etiologies from 20 tertiary medical centers across the United States, and asked patients to self-identify their pattern of pain from 5 choices based on temporal nature (intermittent versus constant) and severity (mild, moderate, severe) (Table 1).<sup>29</sup> Patients with constant pain (as compared to intermittent) had higher rates of disability, hospitalization, pain medication use, and lower quality of life as

**Table 1** Possible Choices for the Self-Designation of Pain Pattern and Severity Level Experienced by Patients with Chronic Pancreatitis from the North American Pancreatitis Study (NAPS2). Patients Were Asked to Choose One of the Five Patterns (A Through E) That Best Described Their Experience. Letters in the “Pattern” Column Identify the Label Assigned to Each Type of Pain. Table Modified to Include Category O This Expands the Classifications to Include “Painless” Chronic Pancreatitis, a Well-Described Phenomena

Pattern	Definition
O	No pain
A	Episodes of mild/moderate pain—but no constant pain
B	Constant mild/moderate pain—but no episodes of pain
C	Episodes of severe pain—but no constant pain
D	Constant mild/moderate pain PLUS episodes of more severe pain
E	Constant severe pain

**Note:** Reproduced from Gut, 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, 60(1):77–84. Copyright 2011, with permission from BMJ Publishing Group Ltd.<sup>29</sup>

measured by the Short Form 12 (SF-12) instrument. A similar pattern, but at an intermediate level is seen with patients with RAP.<sup>7</sup> In addition to the features described above, patients with constant pain were more likely to have an alcoholic etiology of CP than their counterparts with intermittent pain.<sup>6,29</sup> Interestingly, approximately 10% of patients with CP have no pain for reasons that are not yet understood.<sup>30</sup> The variability indicates unidentified intrinsic factors, such as genetic variants, psychiatric or other risk factors that affect the nature and severity of pain signaling since the imaging features of pancreatitis do not correlate with CP pain pattern or severity.<sup>5</sup>

## Biology of Pancreatic Pain

The variability in pain experiences and responses to treatment indicates that multiple mechanisms are involved in the detection, transmission, interpretation and responses to pain generation between individuals. While there is complex circuitry of the integrated sensory system in humans, pancreatic pain begins with pancreas-derived noxious stimuli.<sup>31</sup> However, central processing including psychological and emotional states also shapes the pain experience.

A brief summary of local mechanisms of pain is addressed here (Table 2). A more in-depth discussion of

**Table 2** Categories of Contributing Factors and Underlying Etiologies That Influence the Experience of Pain in Patients with Chronic Pancreatitis

Contributors to the Experience of Pain in Chronic Pancreatitis
Tissue Injury
Cellular Metabolic Stress (Oxidative, etc)
Inflammation
Pancreatic Duct Obstruction
Neuropathy
Central Nervous System Changes
Psychiatric Comorbidities

the central and psychological aspects of pain is discussed in detail below.

## Injury and Pain in Acute Pancreatitis

Acute pancreatitis typically triggers pain through initial injury signals from acinar cells that are followed by an inflammatory response that subsequently activates pancreatic afferents. The pain of acute pancreatitis is typically severe, characterized as sharp or stabbing in nature. As inflammation evolves the patient also develops nausea and even vomiting. The pain of acute pancreatitis may also be connected to visceral ischemia in more severe acute pancreatitis with capillary leak, hypovolemia and multi-organ dysfunction.<sup>32</sup> Marked improvement in AP pain may occur with adequate fluid resuscitation (personal observation).

## Inflammatory Pain

Pain of ongoing inflammation is generally not sharp and stabbing as in acute injury, but rather gnawing, burning, nauseating or tender. If pain is being driven by oxidative or metabolic stress, then antioxidants are often useful in treating pain.<sup>33–37</sup> In some animal and human studies, the pain of pancreatic, as well as other types of visceral inflammation, is also effectively treated with cannabinoids.<sup>38–40</sup> Further research is needed to evaluate these types of therapy specifically for pancreatic pain.

Chronic pancreatitis is a complex syndrome in which patients have variable types and degrees of pathology, such as fibrosis, duct dilatation, calcifications, atrophy or inflammatory masses. The importance of inflammation in pain can be argued by the fact that pancreatic atrophy is often painless, while even moderate inflammation can be painful.

Inflammatory masses in the head of the pancreas are typically highly painful and debilitating, more common in alcohol etiologies, and are resistant to most non-surgical management approaches.<sup>41–43</sup>

## Obstruction/Pressure

Obstruction of the pancreatic duct can also cause pain. This type of pain may be more colicky or steady and is often linked to signs of obstruction on abdominal imaging studies, including endoscopic retrograde cholangiopancreatography (ERCP). This type of pain may be alleviated by endoscopic procedures, such as ESWL to break up intraductal stones, ERCP to clear the pancreatic duct and cross strictures with pancreatic duct stenting, or by surgical drainage procedures.<sup>9,44,45</sup>

## Neuritis and Neuropathies

Another source of severe pain arising from the pancreas in painful CP is neuritis—the infiltration of the nerves by leukocytes. This process may also be accompanied by nerve hypertrophy and is typically seen in inflammatory masses and is resistant to standard treatments.<sup>46–51</sup> Surgical resection may be required, and it should be done before there are permanent changes in the central nervous system.<sup>8,52</sup>

The major differential diagnosis in patients with pancreatitis-like pain is distinguishing between RAP, CP and functional abdominal pain (ie irritable bowel syndrome). Recent reports suggest that specific criteria on CT imaging of the pancreas can be useful.<sup>53</sup> The differential diagnosis of less common types of abdominal pain that mimic pancreatic pain is given elsewhere.<sup>54–56</sup> A rapid change in pain pattern, especially with new weight loss or development of diabetes, may be a sign of pancreatic cancer,<sup>57,58</sup> especially since patients with CP are at high risk of developing pancreatic cancer.<sup>52,59,60</sup>

## Central Sensitization/Central Pain

Patients with severe, painful CP that is not controlled within 2–3 years often develop a syndrome called central sensitization or central pain.<sup>8–10</sup> In its early stages before spreading to the central nervous system, neurologic changes may be confined to the spinal cord and peripancreatic nerves of the pancreatic viscerotome, resulting in a condition termed segmental sensitization.<sup>61</sup>

There are multiple localized and integrated brain networks involved in the perception of physical and psychological pain. Activation of nociceptors is an alarm signal to

the brain. Under chronic pain conditions, a constant alarm drives functional reorganization of the brain. As a result, patients with chronic pain can exhibit a range of cognitive and neurological deficits. Indeed, different chronic pain conditions are associated with distinct patterns of brain activity and morphological alterations (reviewed elsewhere).<sup>62–64</sup>

## Overlap of Pain and Emotion Areas of the Brain

Chronic pain also drives changes in psychological processes including perception, attention, mood, motivation, learning and memory.<sup>65</sup> Changes in corticolimbic networks, which are involved in these psychological processes are direct predictors of chronic pain.<sup>66,67</sup> With the transition from acute to chronic pain, the brain representation shifts toward emotional circuits.<sup>68</sup> There is also a decrease in functional connectivity between the medial prefrontal cortex and hippocampus.<sup>69</sup> Patients with chronic low back pain or pain from irritable bowel syndrome also exhibit reduced gray matter volume in the striatum, particularly the nucleus accumbens.<sup>66,70</sup> Chronic pain patients with reduced striatal function exhibit a dampening of incentive-related behaviors, a common feature of those with major depression.<sup>71</sup> Patients with painful craniomandibular disorder show increased activation of the insula and concomitant increases in anxiety, both of which are reversed with successful therapy.<sup>72</sup> Similar changes may accompany pain from CP.

## Effects of Emotions on Pain Perception

While chronic pain can drive changes in brain activity that influence mood, so too can cognitive or emotional state also directly modulate pain. For instance, subjects expecting analgesia failure report no relief from a clinically efficacious dose of opioids.<sup>73</sup> Following induction of a sad state, subjects report significantly higher pain ratings as compared to a neutral mood state.<sup>74</sup> In patients with major depression, thermal pain thresholds are significantly increased and they exhibit altered brain activity patterns.<sup>75,76</sup> Like chronic pain patients, people with major depressive or anxiety disorder exhibit altered functional connectivity (see reviews).<sup>77–79</sup> For example, in anticipation of a painful stimulus, patients exhibit increased activity in the amygdala and decreased activity in the anterior cingulate and prefrontal cortices.<sup>80</sup> This suggests that patients with major depressive disorder

have increased emotional reactivity during anticipation of pain that may impair their ability to modulate pain experience. Pain, anxiety, or depression can lead to alterations in signaling in overlapping brain regions, including hippocampus, amygdala, striatum, anterior cingulate cortex, and medial prefrontal cortex. Since the same circuits are utilized for pain and psychological processing it is not surprising that there is significant comorbidity in these patient populations.

## Variation in Physical Pain Perception and Processing Among Patients with CP

Clinicians recognize that pain patterns do not always follow the pathologic appearance of the pancreas on imaging studies.<sup>5</sup> Some patients appear to be hypersensitive to various types of pain, while others either feel less pain with the same injury or are less likely to externalize their pain. The variable clinical features of pain (Table 1) and the multiple mechanisms of pain (Table 2) must be connected to decipher the pain drivers and potentiators in individual patients. New clinical tools are needed to sort out the components of the pain syndrome in individual patients so that the best treatment can be given to each person. An algorithm for the treatment of painful chronic pancreatitis was previously developed through a consensus agreement of the major pancreatic research societies.<sup>9</sup> Figure 1 is a modification of this guidance on CP treatment using currently available therapies.

## Quantitative Sensory Testing

While pain is a subjective experience, nociception is defined by the International Association for the Study of Pain as the neural process of encoding noxious stimuli.<sup>83</sup> Thus, unlike pain, nociception is amenable to evaluation by systematic testing. Quantitative sensory testing (QST) is a method used to measure nociception by administering a series of external stimuli of controlled intensity. A collaboration of researchers has developed and tested a pancreas-specific quantitative sensory testing protocol (P-QST) that can separate patients into three phenotypes suggestive of normal nociception, altered nociception at the level of the pancreatic viscerotome, and widespread hyperalgesia suggestive of systemic central sensitization.<sup>13</sup> Although this method does not test pain per se, it can assess alterations in neural signaling. Widespread hyperalgesia in CP patients has been

associated with higher pain intensity, constant pain, lower QOL, and lower physical functioning.<sup>61</sup> Of note, these associations were seen as independent of any psychiatric comorbidities.

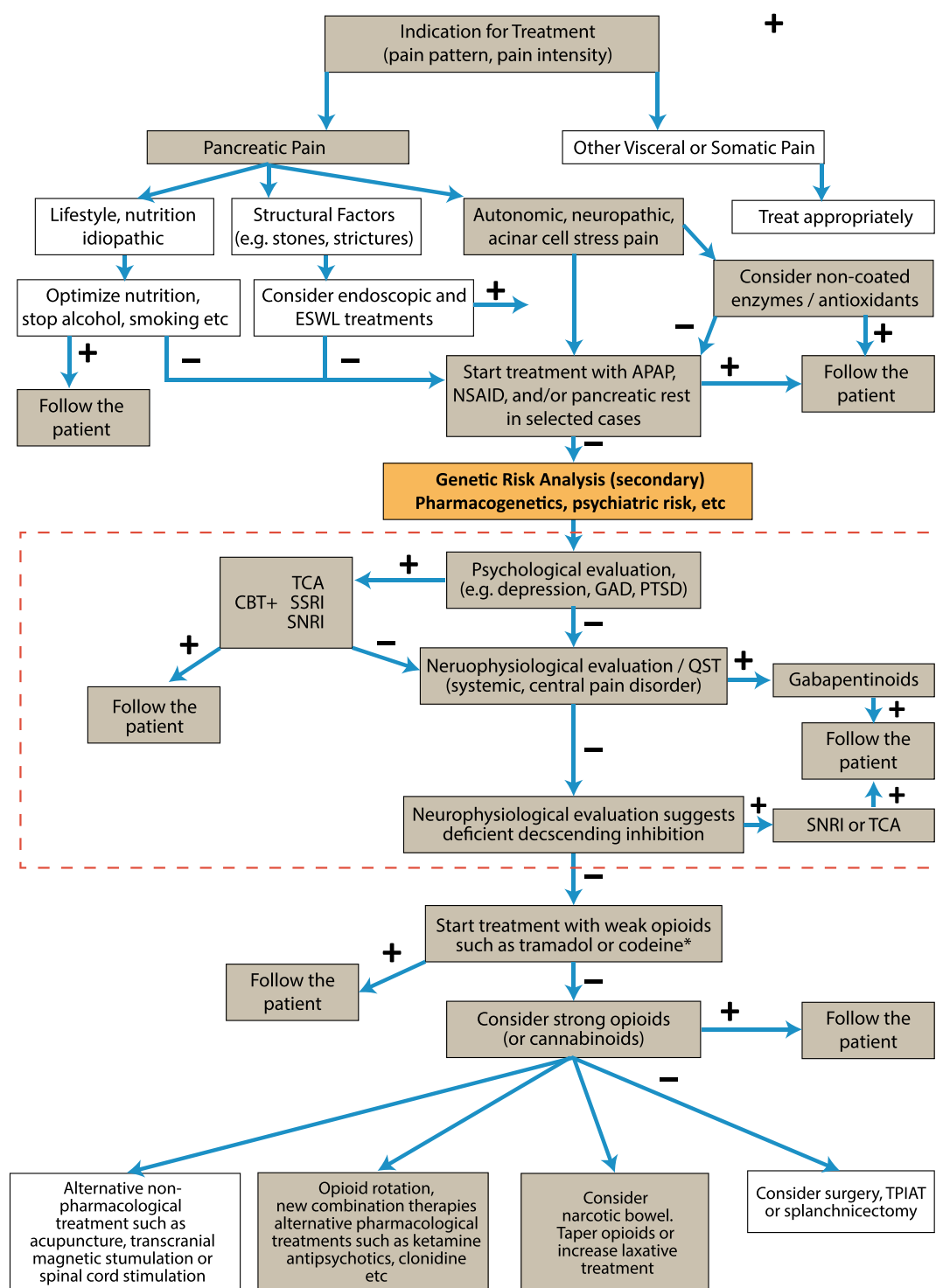
## CP as a Complex Gene-Environment-Metabolic Disease

Understanding CP requires the transition from a traditional monolithic view of disease (eg WHO pain step-up model of pain management) to a more holistic view<sup>81</sup> where each case is an independent combination of multiple risk factors<sup>82</sup> that act in a pathogenic way to cause disease.<sup>83–85</sup> While the science of the new approach is beyond the scope of this review, the importance of genetics cannot be underestimated. Indeed, the role of genetic variants in drug-metabolizing genes (pharmacogenetics) is well established and is highly relevant for variable responses and even toxic outcomes in the treatment of pain and depression.<sup>86–91</sup>

Genetic variant evaluation is a powerful tool since it can direct the analyst to specific mechanisms in the body that are likely to be dysfunctional under injury or stress, and other systems that are likely to be normal.<sup>92</sup> These tools are therefore most useful early in the course of disease before the damage of poorly managed pathogenic pathways becomes irreversible.<sup>93</sup> The primary utility of genetic testing is to identify risk factors contributing to pancreatitis etiology and the mechanism of disease. A secondary analysis is indicated as pharmacologic therapies are being considered for pain management including genetic loci and variants associated with psychiatric disorders as well as pharmacogenetics to select medications that are most likely to be effective at standard or modified doses (Figure 1, orange box)

Future expert physicians and health care workers must adopt a more sophisticated analysis of patients where multiple risk factors (ie factors that are neither necessary nor sufficient to cause disease alone but are more common in patients with disease than controls) combine in ways that can be modeled to determine their combined effect on cell disorders and disease development.<sup>83</sup> Thus, classic genetic testing reports are inadequate. Integration of all known factors must be considered within appropriate contexts so that strong clinical decision support reports are available to provide guidance.<sup>92</sup> The information below may provide critical insights into these complex





**Figure 1** Clinical pain management algorithm for pharmacological treatment (tan boxes) of pain in chronic pancreatitis highlighting the steps related to management of psychiatric disease overlay (red dash-line box). Combination therapies may be necessary. When initial treatment fails, pharmacogenetic (eg *CYP2D6*) and genetic analysis of high-risk psychiatric loci should be reviewed at this point (orange box). Treatment with antidepressants is currently guided by psychological evaluation including assessment of catastrophizing, depression, etc., but genetic testing for genetic predisposition to severe pain linked to psychiatric disorders may guide specific therapy especially when linked to cognitive behavioral therapy (CBT). Treatment shall be individualized due to major differences in receptor properties and analgesic mechanisms between patients. Opioids shall be avoided if possible due to the major side effects on the gastrointestinal tract, etc., but in severe pain they may be prescribed for limited periods and the physician shall always be aware of opioid-induced bowel dysfunction and hyperalgesia (narcotic bowel). \*The FDA-approved drug label for codeine has a black box warning that respiratory depression and death have occurred in children who had evidence of being *CYP2D6* ultra-rapid metabolizers. Reprinted from *Pancreatology*, 17(5), Drewes AM, Bouwense SAW, Campbell CM, et al. Guidelines for the understanding and management of pain in chronic pancreatitis, 720–731. Copyright (2017), with permission from Elsevier.<sup>9</sup>

**Abbreviations:** APAP, acetaminophen; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

mechanisms so that useful reports including clinical decision support recommendations will be available in the future.

## Pancreatic Pain and Mental Health

Depression, anxiety and physical pain often occur concomitantly, and their co-occurrence can have an exponentially detrimental effect.<sup>22,94–97</sup> Approximately 85% of patients suffering from chronic pain also suffer from depression, and between 30% and 60% of chronic pain sufferers also experience anxiety.<sup>22,96,98</sup> The combination of pain with depression and/or anxiety is very difficult to treat, and increases suicide risk as compared to individuals without pain.<sup>22</sup>

Pain in CP significantly and negatively impacts the quality of life and results in higher rates of disability.<sup>6</sup> In a recent cohort study of 171 patients with CP by Phillips et al, anxiety and depression (as defined by Hospital Anxiety and Depression Scale scores of >7) were present in 46.8% and 38.6% of patients, respectively.<sup>99</sup> Overlap of anxiety and depression was seen in 29% of patients. Patients who had anxiety or depression reported higher prevalence rates of pain, pain severity, and interference of pain with their daily activities compared to their non-anxious, non-depressed counterparts. Patients with depression were more likely to be taking opioids. The presence of anxiety or depression was also associated with lower QOL as measured by the European Organization for the Treatment of Cancer Quality of Life Questionnaire global health score and subscores. The presence of pain (intermittent or constant) was independently associated with decreased global health, and an association between global health status and depression was confirmed independently of pain.<sup>99</sup>

In the previously mentioned North American Pancreatitis Study (NAPS2) of 414 patients with CP, patients with constant pain exhibited lower physical and mental health scores than their counterparts with intermittent pain (Table 1, BDE, constant vs AC, intermittent).<sup>29</sup> Additionally, non-alcoholic chronic pancreatitis patients with depression often report experiencing higher levels of pain and lower quality of life.<sup>100</sup>

The presence of a psychiatric comorbidity or substance use disorder in any patient may increase the risk of the patient developing the other.<sup>101–103</sup> Although a unidirectional causal association has not been established there exists a strong association between addiction to alcohol, anxiety, post-traumatic stress, and depression.<sup>101–106</sup> This connection, as

well as that between smoking, anxiety and depression, are of unique importance in painful CP. Alcohol and tobacco negatively impact RAP and CP as well as promote progression of the former to the latter.<sup>107</sup> Active smoking status in CP patients has been seen to associate with lower physical and mental quality of life and more frequent use of antidepressants.<sup>6,108,109</sup>

## Mental Health in CP Patients and Links to the Genetics of Pain

The mental aversion of pain is encoded in brain regions that also process reward and motivation. Evidence from preclinical animal studies suggests that the neuroplasticity in corticolimbic circuits underlies the anxiety and depression symptoms that are often associated with chronic pain.<sup>110</sup> In pain patients, striatal hypofunction correlates with mood alterations.<sup>71</sup> With the overlap in both prefrontal cortex and limbic pathways, it is not surprising that functional alterations driven by either pain or mood disorders affect the manifestation of the other. However, the fact that there are marked effects in some people and not others is not defined by brain activity alone. New evidence is emerging that genetic risk for depression and anxiety plays a major role in the psychiatric phenotypes, and that co-existence of genetic risk for depression and anxiety in patients with RAP and CP results in a more severe pain experience.

To date, and to the best of our knowledge, only one study has been published examining the overlap of psychiatric risk genes and pancreatitis pain.<sup>96</sup> This study identified 15 loci significantly associated with constant severe pain in pancreatitis that were also previously associated with depression.<sup>96</sup> Loci represent regions of DNA that have multiple SNPs and genes that tend to be transmitted over multiple generations together. So, it is usually not possible to pinpoint the actual risk factor(s) within a locus without extensive genomic tests – but the true risk factor and the SNP under evaluation are statistically and physically linked. Several of these CP pain loci are also associated with response to antidepressants as well.<sup>96</sup> Identifying associations with pain in pancreatitis within psychiatric risk genes shows that the pain in pancreatitis is not only phenotypically associated with psychiatric disorders but also genotypically associated.<sup>96</sup> These are exciting findings, but require replication and clinical studies to verify that the candidate risk loci do not represent a statistical aberration (false discovery), and so that the

information can be moved into clinical practice as a target for precision therapies.

## Examples of Depression Risk Genes in Patients with CP and a Constant Severe Pain Phenotype

We recently identified five candidate genes with variants in the coding or regulatory regions of the patient's DNA loci that were associated with the constant severe pain phenotype.<sup>96</sup> The location and function of these genes are briefly described.

The *ROBO2* (roundabout guidance receptor 2) gene located at 3p12.3 codes for the roundabout homolog 2 protein. *ROBO2* is an immunoglobulin transmembrane receptor for slit homolog 2 and is most well known for mediating cell migration and axon guidance during development. However, *ROBO2* plays an important part in maintaining inhibitory synapses in the adult ventral tegmental area, which is a source of dopamine production.<sup>111</sup> Dysregulation of dopamine can have a profound effect on both pain and comorbid mood disorders.<sup>112</sup>

The *CTNND2* (catenin delta 2, 5p15.2) gene encodes a protein in the armadillo/beta-catenin superfamily that is an adhesive junction-associated protein. The catenin delta 2 protein interferes with E-cadherin-based junctions and promotes cell spreading. During development, *CTNND2* is highly expressed in the fetal brain in humans and is associated with neuronal adhesion, migration, and functioning.<sup>113</sup> However, the Rat Genome Consortium was the first group to demonstrate that *CTNND2* is associated with hippocampal volume and dysfunctional synapses in adult mice. Nivard et al replicated this finding in humans, showing an association between *CTNND2* and anxiety and depression.<sup>113</sup>

The protein zeta-sarcoglycan coded by the *SGCZ* (8p22) is part of the sarcoglycan complex. *SGCZ* is primarily expressed in the ovaries and brain.<sup>114</sup> Bipolar disorder, schizophrenia, and major depressive disorder have all been associated with genes on chromosome 8 including *SGCZ*.<sup>115</sup> Additionally, *SGCZ* is associated with antidepressant response and paliperidone efficacy in schizophrenia.<sup>116,117</sup>

Contactin 5 (*CNTN5*, 11q22.1) belongs to the immunoglobulin superfamily and contactin family that is involved with nervous system development. Contactin 5 is expressed mainly in the placenta, thyroid, and brain.<sup>114</sup> *CNTN5*, an immunoglobulin cell adhesion protein, plays a role in axon connection in cortical neurons and neurite outgrowth.<sup>118</sup>

There is evidence that autism spectrum disorder phenotypes may result from increased activity of glutamatergic neurons that only have a single copy of *CNTN5*.<sup>119</sup> The role in altered pain perception is not yet clear, but glutamate is a key neurotransmitter in sensory, spinal and cortical neurons.

The *BAIAP2* (BAR/IMD domain-containing adaptor protein 2, 17q25.3) gene codes the brain-specific angiogenesis inhibitor 1-associated protein 2, which is involved with G-protein coupling. The protein is involved in the regulation of neuronal membrane actin dynamics at excitatory synapses. In mice, deleting the gene homologous to *BAIAP2* increases the activity of NMDA receptors and results in abnormal behaviors.<sup>120</sup> These behaviors are reversed in mice treated with memantine, an uncompetitive antagonist of NMDA receptors. *BAIAP2* is also implicated in psychiatric disorders, such as ADHD, autism spectrum disorders, and schizophrenia in humans.

## Conclusions

Severe pain in patients with CP can be identified and quantified, but tools to understand the underlying and variable mechanisms contributing to the severe pain experience in these patients are lacking. Thus, the most effective approach remains surgically removing some or all of the pancreas. In patients with complex and severe disease, it is likely that multiple overlapping mechanisms are simultaneously driving pain, anxiety and depression. New tools are needed to identify key pathogenic mechanisms, such as better questionnaires, QST and genetic testing – beginning with pharmacogenetics. New investigations of the overlap of pain, depression and anxiety demonstrate that multiple genetic risk loci for depression and anxiety are associated with constant severe pain experience and that the effects are manifest in the brain. Well-designed clinical trials that integrate clinical features, QST, genetics and psychological assessments with targeted treatment and assessment of responses are required for a quantum leap forward.

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## Disclosure

Prof. Dr. David C Whitcomb reports consulting for Abbvie, BioNTech, Nestle, Regeneron, and Samsung. He is also the co-founder, unpaid consultant for and may have equity with Ariel Precision Medicine. The authors report no other conflicts of interest in this work.

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