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Adjunctive Therapy in Chronic Pancreatitis

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Introduction

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease of the pancreas for which there is no cure. Therapies in CP are directed at managing symptoms of the disease, mainly the dominant symptom of abdominal pain. Patients with evidence of pancreatic ductal obstruction are often managed with endoscopic or surgical therapy to relieve obstruction in addition to analgesia, whereas patients without clear signs of ductal obstruction are managed medically. The foundation of medical management consists of analgesic therapy, including both opioids and non-opioid analgesics. Adjunctive therapies are used to address pain by targeting mechanisms of pain that differ from traditional analgesia, as well as treating concomitant affective disorders, digestive disorders, and malnutrition. Pain treatment studies in CP are difficult to compare as endpoints vary widely between studies; however, the clinical need for pain treatment in this population persists and requires creativity and open-mindedness on the part of healthcare providers [1]. This chapter will review adjunctive therapies in CP, which are meant to serve as complementary therapies addressing pain or CP sequelae that are inadequately treated by traditional analgesia or interventions.

Therapies for Affective Disorders

Pain-related factors in CP including anxiety and depression can overlap and have a cumulatively detrimental effect on patients with CP [2]. Affective psychiatric disorders including anxiety and depression are highly prevalent in patients with CP, and frequently coexist [3]. In a cross-sectional analysis of an international cohort of CP patients, the prevalence of anxiety or depression symptoms was seen to be 46.8% and 38.6%, respectively, and their presence was associated with increased severity of pain and interference of pain with daily living [3]. The presence of depression in this study was independently associated with decreased quality of life, further highlighting the impact that psychiatric comorbidity can have in this patient population [3]. Assessment for and treatment of affective disorders concomitant with CP should be a high priority in clinical practice and symptoms can be detected effectively with questionnaire screening instruments.

Antidepressant Medications

Medical therapy for affective disorders including tricyclic antidepressants (TCA), selective serotonin uptake inhibitors (SSRI), and serotonin noradrenergic reuptake inhibitors (SNRI) have been recommended by clinical guidelines for treatment of painful CP as part of a multifaceted approach to therapy due to their analgesic effects (SNRI and TCA) and effect on concomitant depression (all three) [1]. Although they may be used in clinical practice, there is little data on the prevalence of their use or their effects in this population. The North American Pancreatitis Study 2 (NAPS2) group assessed the association between constant severe pain and genetic loci for depression and noted that 56% of that population self-reported taking an SSRI when asked for current medications [4]. There is much evidence for neuropathy in CP [5]. Multiple studies have been conducted to assess the efficacy of duloxetine, an SNRI, at treating neuropathic pain in diabetic neuropathy, fibromyalgia, and pain associated with depression, prompting a Cochrane review in 2009 and subsequent update in 2014 [6,7]. Together, the studies showed that duloxetine is effective

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in reducing pain in diabetic neuropathy, as well as for pain symptoms of depression. The direct analgesic effect of duloxetine is considered to be independent of the drug's effect on depression symptoms [8], making it particularly relevant in patients with painful CP and concomitant depression. Studies in other chronic pain conditions have shown antidepressant medications broadly to have varying degrees of direct analgesia, with SSRI medications being the least analgesic but having a more acceptable tolerance profile than others [9]. While these results may be extrapolated to subgroups within the CP population, it is noted that no clinical trials have evaluated the effect of SSRI or other antidepressant medications in CP patients specifically.

Psychosocial Therapies

When regarded through the lens of the biopsychosocial model of illness, painful CP is understood as a complex phenomenon where pain, quality of life, stigma, self-blame, and addictive behaviors (for a subset of patients) impact and often exacerbate one another [10]. Psychologic therapies including mindfulness therapy and cognitive behavioral therapy are important tools to impact these forces individually. Combining any such therapies with interventions intended to address addictive behaviors including alcohol-, tobacco-, or opioid-use disorders is a priority in this population as the first two are independent risk factors for progression of CP and all can exacerbate or amplify the pain experience.

Mindfulness therapy, a talk therapy often linked to Buddhism, encourages patients to focus nonjudgmentally on the present lived experience and teaches coping mechanisms for dealing with challenges including stress and pain. In a pilot study of 10 CP patients with pain compared with 5 healthy controls, a 28-day telephone-based mindfulness therapy intervention was completed, showing improvement in social aspects of quality of life as measured by the SF-36 [11]. While there was no significant improvement in physical quality of life, and the study was limited by small sample size and a broad definition of CP, the effort did establish feasibility of such an intervention and illustrates the potential impact this could have for CP patients suffering from poor quality of life.

Cognitive behavioral therapy (CBT), a psychosocial intervention aiming to challenge cognitive distortions and improve emotional regulation and coping, has also previously been tested in an internet-based randomized, controlled pilot trial of 30 subjects with painful CP [12]. Not only was the intervention deemed feasible and acceptable, but the proportion of those who responded with reduced pain intensity and pain interference at 3 months was significantly greater in the internet-based CBT group than the control group. Psychological therapies show significant promise in CP patients with pain who are suffering from concomitant psychiatric illness and should be strongly considered in this patient subpopulation.

Although published literature on these types of interventions remains rare, patients who are suffering from painful CP and additional psychiatric illness may strongly benefit from referral to expert providers of psychosocial therapies, and there is at least some evidence that they are effective.

Treatments for Neuropathy

Neuropathy is an additional contributor to the experience of many patients with CP, and pain related to this can be particularly challenging to treat [5]. Alterations in pain processing due to changes in the nerves themselves or in patterns of transmission of pain signals can result in pain that is resistant to traditional analgesia.

Medications

Pregabalin, a lipophilic analog to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), has been approved by the US Food and Drug Administration for treatment of neuropathic pain and may have a role in treatment of painful CP. Pregabalin has previously been shown to reduce the pain intensity of patients with CP in a randomized, double-blind, placebo-controlled trial of 64 patients after 3 weeks compared to placebo [13]. In a separate placebo-controlled randomized trial of 90 patients, those who received a combination of antioxidant therapy and pregabalin were shown to have significant reduction in pain intensity, non-opioid analgesic requirement, and hospital admissions for pain during the 12-week study period compared to those who received placebo [14]. A randomized, double-blind, placebo-controlled study of 88 patients with recurrent pain following pancreatic ductal clearance additionally showed significant reduction of pain intensity after 8 weeks of therapy in those who received antioxidants and pregabalin compared with placebo [15]. It is noted that in the study from Sureshkumar et al. [13], patients with concomitant major depression, and those with intractable pain who had previously failed medical management were excluded, and in the study from Talukdar et al. [14], patients who had received high-potency narcotics were excluded. Given the prevalence of major depression and narcotic use among CP patients, these results are potentially difficult to extrapolate to the broader CP population. Additional neuromodulators including olanzapine, quetiapine, ketamine, and others may have effect in CP

pain though they have not been specifically studied in this population. The role of neuropathic agents is additionally discussed in the chapter on pain management, and the role of antioxidant therapy is further discussed in a dedicated chapter in this text.

Nerve Blocks

Blockade of specific nerves or nerve groups has been attempted for painful CP with varying degrees of success. Celiac plexus blockade is a technique performed via radiographic, CT-guided, or endoscopic-guided approaches in which steroids and local anesthetic are injected at the celiac plexus [16]. Response rates following therapy vary across studies but in general are lower than 60% [17,18]. The duration of response is only approximately 3–6 months, making this more of a temporizing measure than a treatment from which durable pain response is expected. Importantly, the risk of nerve damage associated with the procedure may actually worsen neuropathy, leading some to consider this treatment obsolete in painful pancreatic disease that is nonmalignant [19].

A small study of subcostal transversus abdominis plane blockade has shown reduction in pain from myofascial pain syndrome associated with CP [20]. This study was limited by the fact that the technique is ineffective for visceral pain as well as for pain from ongoing pancreatic inflammation: there was additionally no control arm making the results less robust. A single-blinded randomized crossover trial of acupuncture did show pain relief from treatment as compared to sham, but the effect was short-lived and disappeared after one week [21]. Several other small studies have shown some degree of benefit in research settings from experimental interventions including cervical transcutaneous neuromodulation, and transcranial magnetic stimulation [22,23]. The potential for clinical use of these techniques are limited by the fact that they are often administered only in research settings, require specific expertise, have short-lived effects, and are not widely available.

Central Sensitization

Central sensitization, a phenomenon of altered processing of nociception, has been described in patients with painful CP and is thought to be a critical aspect of the pain experience in this disease [24]. The presence of central sensitization has the potential to render traditional therapies such as decompression of an obstructed pancreatic duct or surgical drainage procedures ineffective in providing pain relief [25]. Techniques to reliably identify patterns of central sensitization including manifestations of widespread hyperalgesia or altered central pain modulation have previously been only available in research settings; however, a bedside technique intended for clinical adaptation has been recently developed [26]. Pancreatic quantitative sensory testing (P-QST) differentiates CP patients into distinct phenotypes by characterizing their nociceptive patterns and identifies patients with characteristics of central sensitization [27]. There is no treatment for central sensitization; however, both pregabalin and S-ketamine have shown promise in initial trials in modulating measures of hyperalgesia [28–30]. A randomized trial of S-ketamine treatment has been proposed but not yet completed [31].

Therapy for Nutritional Disorders

Malnutrition is a frequent complication of CP due to exocrine pancreatic insufficiency (EPI) and maldigestion [32]. This can be further exacerbated by concomitant disorders of delayed gastric transit, small intestinal bacterial overgrowth (SIBO), and sarcopenia [33–36]. While nutritional evaluation of CP is covered elsewhere in this text in detail, diagnosis of concomitant gastrointestinal disorders, vitamin and mineral deficiencies, and their treatment or supplementation may be effective adjuncts in the treatment of CP. Delayed intestinal transit, bloating from fat malabsorption, and neuropathy due to underlying vitamin deficiency are all possible sources of pain in CP complicated by malnutrition [37]. Diagnostic testing to include anthropometric, biochemical, and clinical markers of malnutrition for those patients at high risk on an annual basis have been recommended as a means of identifying those patients with possible vitamin and mineral deficiencies complicating their underlying CP [37].

Pancreatic Enzyme Replacement Therapy

Pancreatic enzyme replacement therapy (PERT) is designed to assist with the absorption of fat, protein, and micronutrients in EPI. Pain reduction from PERT is mostly secondary to decreased symptoms of maldigestion including hypermotility of the colon in the setting of steatorrhea, though some contribution from suppression of pancreatic enzyme release may be possible [38,39]. In a large systematic review and meta-analysis of clinical trials PERT has been shown to improve fat absorption in patients with CP both compared to patient baseline levels and compared to therapy with placebo [40]. In the same study, PERT was also shown to improve abdominal pain without significant adverse events. The perceived efficacy of PERT (by patients) for treatment of pain in CP in the absence of EPI was found to be low (36.3%); perceived efficacy of PERT rose only to 50% in patients with

both EPI and pain [41]. High-quality large rigorous studies on the efficacy of PERT for malnutrition in CP are needed, as is more consistent education for practitioners regarding indications for PERT therapy and potential benefit. Evaluation of an insured US population showed that both testing for EPI and adequate dosing of prescribed PERT were infrequent and inconsistent, suggesting that this therapy is underutilized and used in a suboptimal fashion in CP patients overall [42].

Vitamins, Antioxidants, and Octreotide

Fat-soluble vitamin levels are a frequent concern in patients with CP, especially in patients with symptoms of fat malabsorption. Vitamin D deficiency is the most common fat-soluble vitamin deficiency in CP patients (>50%), though it also common in patients without CP [32]. Vitamin A and E deficiencies have been seen in approximately 15% and 25% of CP patients, respectively [32]. Supplementation of fat-soluble vitamins is recommended to avoid the potentially serious complications of prolonged or severe deficiency including night blindness (vitamin A), neuropathy (vitamin E), and mineral bone disease such as osteopenia or osteoporosis (vitamin D). In particular, the prevalence of osteopathy in CP patients has been found to be significantly higher than that of the general population, and assessment and treatment has been recommended as part of routine care [43–45]. Diagnosis and supplementation of water-soluble vitamin and micronutrient deficiencies in patients with poor diet or other markers of malnutrition are also recommended.

Indications for, efficacy of, and evidence regarding antioxidant use is reviewed in a separate chapter, but they are mentioned here as part of the adjunctive armamentarium for painful CP, through reduction of acinar cell injury by protecting against oxidative stress [41]. It is noted that their use is infrequent and dosing is quite varied across practitioners, and reported data has been highly variable on their efficacy [41,46,47]. Similarly, octroeotide—a synthetic somatostatin analog that has an inhibitory effect on pancreatic secretion—has been utilized to decrease pancreatic stimulation and release of enzymes. Its use in CP has been infrequent, and the reported efficacy for symptoms of CP has been highly variable [41].

Cannabinoids

Reported cannabinoid use has increased in recent years as an analgesic agent for patients with painful CP concomitant with the spread of medically directed marijuana therapies, though high-quality randomized study data is scarce and cannabinoids represent a heterogenous group of chemical substances [48]. Delta-9 tetrahydrocannabinol (THC), the most abundant cannabinoid in the plant, was tested in a phase-2 placebo-controlled clinical trial of patients with chronic abdominal pain, but unfortunately did not show any significant improvement compared to placebo [49]. This study was notably limited by heterogeneity of the etiology of abdominal pain in the studied patients, with CP and post-surgical patients combined into a single group. A separate small study was not designed to evaluate pain response to cannabis, but detected a reduction in opioid use, hospitalizations, and emergency room visits for CP patients after their enrollment in a state-directed therapeutic cannabis program compared to before their enrollment in the program [50]. A recent observational study shows that medical marijuana is used more frequently in patients maintained on chronic opioid therapy than those who are not on chronic opioids, suggesting that its utility is mainly seen as an adjunctive agent in this patient population [51].

Conclusions

Adjunctive therapies in CP are initiated because existing analgesic and interventional therapies result in suboptimal relief of symptoms for this disease. A thorough evaluation for concomitant and complicating disorders should be conducted, and directed adjunctive agents can be initiated based on the individual patient situation after traditional therapies for CP have been optimized. The evidence for the efficacy of adjunctive therapies in CP remains quite limited even though there are hints that they can form part of an overall treatment regime for painful CP.

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