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NARRATIVE REVIEW

Opioid dependence in patients with pain in chronic pancreatitis an emerging problem

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Abstract

Chronic pancreatitis is a progressive inflammatory disorder characterized by recurrent or persistent abdominal pain. Traditionally, pain in chronic pancreatitis has been linked to anatomical factors such as ductal hypertension, parenchymal pressure and disease-related complications, including pseudocysts and biliary obstruction. However, emerging evidence supports a neurobiological model of pancreatic pain, emphasizing neuropathic mechanisms and central sensitization as key contributors. Pain management in chronic pancreatitis requires a personalized, step-wise approach that combines pharmacologic titration, endoscopic decompression and, when necessary, surgical intervention. While the World Health Organization pain ladder, originally developed for cancer-related pain, offers a conceptual framework, its applicability to chronic pancreatitis remains insufficiently validated across diverse patient populations. In difficult cases, opioids are often prescribed despite increasing global concerns about opioid use disorder. The opioid epidemic highlights the importance of adopting responsible prescribing practices, employing validated screening tools and promoting interdisciplinary collaboration to balance effective pain relief with risk reduction. Recent advances such as neuromodulators (e.g. tricyclic antidepressants, pregabalin), celiac plexus blocks, pancreatic enzyme replacement therapy and antioxidant therapy, have improved outcomes in specific patients. Nonetheless, there is a significant need for innovative strategies that tailor pain management, lessen dependence on opioids and address the psycho-social aspects of chronic pain. This review emphasizes the burden of pain in chronic pancreatitis, assesses current treatment approaches and examines the relationship between opioid stewardship and quality of life. A paradigm shift—grounded in mechanistic understanding, multidisciplinary care and adaptable therapies—is vital to enhance long-term outcomes while minimizing opioid-related risks and harm.

Keywords Chronic pancreatitis · Pancreatic pain · Opioid dependence · Opioid-related bowel dysfunction · Opioid use disorder

Introduction

Chronic pancreatitis (CP) is a chronic inflammatory disorder of the pancreas. Population-based surveys in the United States indicate the prevalence of CP in the general population to be 45.52 per 100,000 persons [1]. In the United Kingdom (UK), it is estimated to be 163 per 100,000 persons [2]. In China, the estimated prevalence is 45.52/100,000 persons [3] and in southern India, the reported prevalence ranges from 114 to 200/100,000 persons [4]. The classical presenting feature of CP is chronic and severe abdominal pain. This particular symptom adversely affects an individual's quality of life and has deleterious psychological and economic effects [5]. Pain in abdomen is the presenting symptom in 75% of patients with CP and 85% to 97% of patients will develop pain at some point in the natural history of the disease, with many presenting with recurring episodes followed by pain-free intervals that may persist for several years or have persistent pain or recurrent pain clusters [6–9]. These pain patterns may alternate within the same individual, often despite surgical/endoscopic interventions [10].

The other two disease-defining symptoms of CP are exocrine and endocrine insufficiency. It was thought that pain

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subsides with prolonged disease duration [9]. Although this concept of "pancreatic burnout" has been challenged by several elegant studies on the subject. Thus, pain would probably be a prominent disease-defining symptom throughout the natural history of CP. The present management strategy for pancreatic pain involves the gradual introduction and dose titration of analgesics, besides endoscopic and surgical approaches. Psycho-social factors such as anxiety, depression and maladaptive coping styles significantly modulate pain perception in chronic pancreatitis, often amplifying its severity and persistence. Studies suggest that central sensitization and emotional distress can exacerbate pain independent of pancreatic pathology, highlighting the need for integrated psychological assessment and support in clinical management [11–13]. In this particular review, we discuss briefly the pathophysiology of pain in CP and the emerging issue of opioid use disorder (OUD) in this really "difficult to manage" subset of patients.

Understanding the pathophysiology of pain in CP

Due to the existing lacunae in the understanding of the complex patho-physiological processes initiating and propagating pain in CP, the management of pain is hampered. Traditionally, anatomical changes in the pancreas, namely increased ductal pressures in the pancreatic duct (PD), heightened pancreatic parenchymal pressures and complications arising due to the disease process including pseudocyst, biliary obstruction, peptic ulcers, all activate nociceptive pathways leading to pain. Contrary evidence to this traditional belief has prompted rigorous criticism and alternate theories have emerged emphasizing the neurobiological model of pancreatic pain [14–17].

Two afferent nerve fibers innervate the pancreas: the vagus nerve and those traversing the celiac plexus. These fibers innervate the lower thoracic spinal cord segments via the splanchnic nerves. Nociceptors located at the end of primary afferent nerve endings differ from other visceral organs in the fact that they convey solely the pain stimuli. The prolonged inflammatory process in CP activates these nociceptors via mechano-sensitive and chemo-sensitive mechanisms [18]. Noxious stimuli release inflammatory mediators, notably bradykinin, serotonin and growth factors, which sensitize the primary sensory neurons to further stimulation by both noxious (hyperalgesia) and non-noxious (allodynia) stimuli, a process often described as "peripheral sensitization." The action potentials generated by inflammatory mediators synapse with secondary order neurons in the dorsal horn of the spinal cord. Three receptors located in the secondary order neurons, namely N–methyl–D–aspartate (NMDA) receptors, neurokinin-1 (NK1) receptors, and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate, once excited by peripheral sensitization, decrease the firing threshold of dorsal horn neurons, a process termed "central sensitization" [19]. The action potentials travel via the spinothalamic tract to the tertiary-level neurons in the thalamus and further to the somatosensory cortex. The limbic system and hypothalamus are also involved in the autonomic integration of pain [20]. Two other processes are entwined in the perception of pain, specifically "neurogenic inflammation," i.e. the local action of inflammatory mediators in the pancreas (vasodilatation, infiltration of neutrophils) [21, 22] and the modulation of pain at the level of the dorsal horn of the spinal cord by the central nervous system (CNS), by either facilitating or inhibiting the spinal transmission of pain impulses [23]. Fregni and colleagues have hypothesized that in addition to anatomical and neuronal factors modulating pain, the immune system processes a "salutogenic" mechanism and perpetuates cycles of inflammation and continuous pain. The concept of a salutogenic mechanism in chronic pancreatitis reframes pain not merely as a symptom but as part of a brain-mediated healing response. The CNS may modulate the immune system through neuroplastic changes, initiating salutogenic responses aimed at tissue repair. However, in CP, this mechanism can become maladaptive: persistent nociceptive signalling from the inflamed pancreas leads to central sensitization, which in turn sustains immune activation and inflammation. This creates a self-perpetuating cycle where pain both reflects and reinforces ongoing pancreatic injury. The paradox lies in pain acting as a signal for healing while simultaneously exacerbating the disease process through neuroimmune feedback loops [24].

Figure 1 illustrates pain pathways and the neuroimmune feedback loop in chronic pancreatitis.

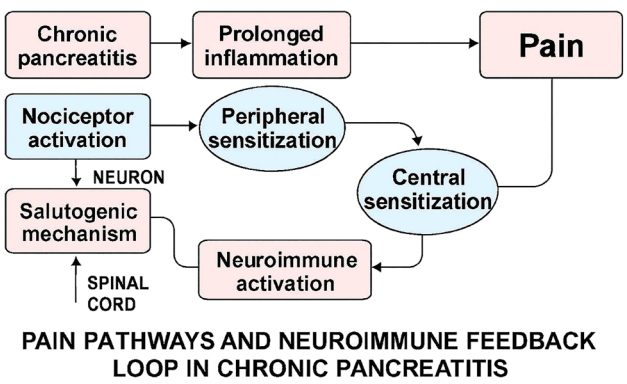

Fig. 1 Pain pathways and neuroimmune feedback loop in chronic pancreatitis

Impact of pain in CP

Among individuals with CP who experience pain, nearly half report persistent symptoms that adversely affect quality of life (QOL). The precise nature and severity of pain remain subjects of debate. Evidence—such as a small Polish study—suggests that pain intensity correlates more strongly with QOL metrics than its frequency [5, 25–29]. In a study, Machicado et al. provide compelling evidence that constant pain is the most significant determinant of reduced quality QOL in patients with CP. Using data from over 1000 patients in the North American Pancreatitis study II cohort, the authors found that persistent pain—especially when severe—was associated with a substantial decline in both physical and mental health scores. Additional factors such as pain-related disability or unemployment, current smoking and comorbid medical conditions further compounded the negative impact on QOL. Interestingly, pancreatic morphology, disease duration and prior interventions such as surgery or endotherapy did not independently affect QOL outcomes [30].

Another aspect of the impaired QOL due to the pain in CP is due to patients' beliefs about the pain. In a recent study by Keller et al., the researchers found a correlation between pain beliefs and QOL impairment, wherein patients with a tendency to self-blame and depressive beliefs had worse QOL [31]. Therefore, the emotional facet of pain does play a progressively significant role in the course of pain over time [32].

The component of central processes in altering pain perception suggests that cognitive factors are also associated with pain and data is consistent with the available research on this aspect [33–38]. Various studies have shown alterations in central pain processing (namely sensitization, cortical reorganization and alterations in endogenous pain modulation), similar to other chronic pain disorders and a few have demonstrated therapeutic effects of pregabalin on this central component of pain [39, 40]. This suggests that even infrequent but severe pain episodes can significantly impair physical functioning, vitality and general health perception. These findings underscore the importance of individualized pain assessment—not just how often pain occurs, but how deeply it affects daily life.

Assessment of pain in CP

Assessing pain associated with CP (PACP) remains a major clinical challenge due to its multidimensional nature and the limitations of current tools. Most commonly used instruments—such as the "Visual Analog Scale" and "Numeric Rating Scale"—are unidimensional, focusing only on pain intensity. Although simple and widely used, they do not capture important aspects such as pain character, frequency, triggers, emotional impact and how pain interferes with function.

Multidimensional tools such as the "Brief Pain Inventory" and "McGill Pain Questionnaire" offer broader insights but are not tailored to CP-specific pain, which often includes post-prandial exacerbations, visceral localization and autonomic symptoms. The Izbicki pain score, although designed for CP, lacks formal psychometric validation and includes static components such as workability, which may not reflect short-term treatment effects.

Emerging tools such as the "Comprehensive Pain Assessment Tool" (COMPAT) and its short form (COMPAT-SF) aim to address these gaps by integrating CP-specific domains and psychological comorbidities. However, their clinical utility is limited by time constraints and the need for further validation. Multiple guidelines have recognized the lack of adequately validated tools for pain assessment in CP [41–43]. Guidelines such as *Pancreas Fest* and Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) emphasize the importance of incorporating psychological scales, e.g. "Pain Anxiety Symptom Scale" (PASS), the "Pain Catastrophizing Scale" (PCS), the "Drug Abuse Screening Test" (DAST) and "Quantitative Sensory Testing" (QST) to assess central sensitization and hyperalgesia, yet these are rarely implemented in routine practice. QST, including pressure pain thresholds and thermal testing, is the most validated method for detecting hyperalgesia and central sensitization in CP. In summary, while several tools exist, no single validated instrument comprehensively captures the complexity of CP-associated pain, underscoring the need for a standardized, disease-specific and multidimensional assessment framework [44–48].

Therefore, to suggest some standardization in the assessment of PACP, Drewes et al. came out with an international consensus guideline with a few moderate to strong recommendations for a high-quality assessment and agreement among others. These recommendations are namely pain questionnaires to address multiple dimensions of pain and associated symptoms, to standardize outcome assessment in clinical trials in patients with PACP; use of additional questions about satisfaction with social roles, productivity and perception of treatment goal; utilization of primary, secondary and explorative endpoints for pain in general for studies of patients with PACP along with similar standards for optimizing the outcome of clinical trials; account for the placebo-related factors in randomized studies testing new treatments; application of optimized and validated QST in children; use of pain assessment instruments taking into account the different pain mechanisms in acute and chronic

pancreatitis and use of instruments to evaluate QOL and mental health and the utilization of QST in specialist settings to phenotype individual patients [49].

However, in a busy outpatient clinic, it would be worthwhile to adopt a hybrid approach, whereby one uses a brief multidimensional tool such as COMPAT-SF, which has been validated for CP and can be completed in under 10 minutes. It captures key domains—pain severity, pattern, provoking factors and qualitative descriptors—without overwhelming the clinician or patient. This can be supplemented with a unidimensional scale such as the NRS or VAS for quick tracking of pain intensity over time. For screening psychological comorbidities—ultra-brief tools such as DAST-10, especially in patients with persistent or disproportionate pain, may be utilized. This layered strategy balances clinical feasibility with diagnostic depth, allowing for meaningful pain assessment.

Managing pancreatic pain

The present understanding of managing pancreatic pain is based on the gradual introduction and dose titration of analgesics, besides endoscopic and surgical approaches. Endoscopic management with sphincterotomy and stent placement may be used in patients with distal pancreatic duct obstruction. Surgical techniques aim to achieve ductal decompression/parenchymal resection or both in patients refractory to other therapeutic measures [50, 51]. Surgical neuroablation, pancreatic head resection, selective splanchnicectomy and celiac ganglionectomy have been tried with variable results [52]. Denervation using celiac plexus block, utilization of neurostimulation involving spinal cord stimulation and trans-cranial magnetic stimulation are sparingly used in clinical practice because of the paucity of literature on these approaches [53, 54]. Celiac plexus block utilizes a combination of local anesthetic agents (e.g. Bupivacaine) and a steroid (e.g. triamcinolone) that is injected in/around celiac ganglia. The same can be under endoscopic ultrasound (EUS) guidance or via intervention radiology or surgical approaches [55, 56].

Detailed discussion on endoscopic and surgical approaches is beyond the scope of this review. Hence, we will highlight the various aspects of medical management of pancreatic pain with special emphasis on the role of opioids and their abuse potential.

Medical management of pancreatic pain and World Health Organization (WHO) pain ladder

Pain relief in CP, by and large, follows the WHO pain ladder principle, originally prescribed for pain relief in cancer patients [57]. Sequential and escalating dosages of analgesics are introduced to achieve optimal pain relief. Acetaminophen, a well-tolerated and relatively safe analgesic, forms the first step. Alternatively, non-steroidal anti-inflammatory drugs (NSAIDs) may also be used, but gastrointestinal side effects remain a concern. Tramadol, an opioid agonist and serotonin–norepinephrine reuptake inhibitor (SNRI), forms the second step of the ladder. Potent opioids such as morphine form the third step. Surgery and interventional procedures have been added to the WHO ladder, specifically catering to the management of CP. Adjuvant drugs, notably antidepressants (e.g. Tricyclic antidepressants), anticonvulsants (gabapentin) and anxiolytics, may be added at each step [11].

However, there are limitations of this approach in the context of CP. Pain in CP may be neuropathic and centrally sensitized, making the ladder's nociceptive focus insufficient. The ladder does not account for psychological comorbidities, hyperalgesia or functional pain syndromes common in CP. Moreover, long-term opioid use in CP raises concerns about tolerance, dependence and opioid-induced hyperalgesia.

Recent literature suggests modifying the ladder to include: Integrative therapies (e.g. antidepressants, anticonvulsants for neuropathic pain), interventional options (e.g. celiac plexus block, splanchnicectomy) and psychosocial screening and use of validated scales such as PASS and PCS. Table 1 summarizes the drugs used in the WHO pain ladder. Table 2 summarizes the drugs used in the modified WHO pain ladder. Table 3 summarizes the commonly used opioid drugs and their side effects.

Table 1 Commonly used analgesics as per the WHO pain ladder. *NMDA* N -methyl -d -aspartate, *NSAID* non-steroidal anti-inflammatory drug

WHO pain ladder	Class of drugs	Examples
Level 1	Analgesics	Paracetamol, aspirin, NSAID
Level 2	Weak opioids	Tramadol, codeine, buprenorphine
Level 3	Strong opioids	Morphine, pethidine, oxycodone, fentanyl, methadone
Adjuvant drugs	Antidepressants	Amitriptyline, nortriptyline, fluoxetine, paroxetine
	NMDA receptor antagonists	Ketamine
	Gabapentinoids	Gabapentin, pregabalin

Table 2 Commonly used analgesics as per the modified WHO pain ladder

Step	Class of drugs	Examples	CP-specific points
1	Non-opioids	Acetaminophen, NSAID	Best for mild nociceptive pain; requires monitoring GI side effects
2	Weak opioids ± non-opioids	Tramadol, codeine	Limited efficacy in neuropathic pain; risk of dependence
3	Strong opioids ± adjuvants	Morphine, fentanyl, pregabalin, amitriptyline	Risk of tolerance, opioid-induced hyperalgesia, functional decline
4	Interventional and multimodal	Celiac plexus block, neuromodulators, cognitive behavioral therapy	Tailored for refractory pain and central sensitization

CP chronic pancreatitis, *GI* gastrointestinal, *NSAID* non-steroidal anti-inflammatory drug

Challenges in pain management in CP

Some aspects of pain management are significant for patients with alcohol-related CP. These patients often have a history of alcohol abuse with frequent hospitalizations. Societal/marital discord is not too infrequent either. Loss of working hours, anxiety, poor sleep patterns and depression each contribute to difficulties in managing such patients. Patients have often tried multiple drugs for pain relief. Thus, polypharmacy, drug interactions and dependency on opioids for pain relief are peculiarly seen in such patients. The disease has a multifactorial impact on patients as well as the caregivers. Loss of employment and financial burden on patients and caregivers add to the hardships and often aggravate drug dependency/addictions [67]. Psycho-social factors, in particular alcohol use, are important determinants of pain severity in CP. Management must encompass not only treating the pancreas's morphological changes, but also the patient's QOL. Moreover, the feasibility and reliability of the WHO step-wise ladder have not been extensively studied across the spectrum of patients with CP. When a multitude of pain management techniques described above fail, medical practitioners often resort to opioids for pain management. The American College of Gastroenterology (ACG) guidelines recommend the use of opioids only once other palliative modalities have been exhausted [56]. Even though multiple formulations are commercially available, only one randomized controlled trial (RCT) has explored the efficacy and tolerability of transdermal fentanyl vs. sustained-release oral morphine in 18 patients with painful CP using an open-label, randomized crossover design. Both treatments provided comparable pain relief and patient preference when dosed appropriately. However, transdermal fentanyl required a 50% dose escalation beyond manufacturer recommendations to achieve adequate analgesia and 44% of patients experienced skin-related side effects. Additionally, patients on fentanyl used significantly more rescue morphine (30.7 mg/day vs. 14.7 mg/day on morphine SR), suggesting inferior baseline pain control. Notable limitations of this study were its small sample size ($n = 18$) and short treatment duration (four weeks per arm), which may not reflect long-term efficacy or safety [68]. There is thus an ardent need to select patients who would benefit from opioid therapy and minimize the risk of OUD. Distinguishing therapeutic opioid use from inappropriate or excessive consumption is critical to patient safety and clinical decision-making. Opioids may be appropriately prescribed for intractable abdominal pain when other modalities fail, provided they are carefully dosed and monitored. However, excessive use—especially in doses disproportionate to clinical need or without clear indication—raises concerns about misuse and potential progression to OUD. A structured approach to prescribing, along with regular reassessment and screening for OUD, helps safeguard against misuse while ensuring adequate analgesia.

The problem of OUD in CP

OUD can very well be considered a "health emergency" [43]. Diagnostics and Statistical Manual of Mental Disorders, 5th edition (DSM-5) defines OUD as a pattern of opioid use that leads to significant clinical impairment and distress. This results in frequent hospital visits, escalating healthcare costs and healthcare resource utilization [69]. To meet the criteria, at least two of the following 11criteria must occur in 12 months:

- Taking opioids in larger amounts or longer duration than intended
- Persistent desire or unsuccessful efforts to cut down or control use
- Spending excessive time obtaining, using or recovering from opioids
- Craving or strong urge to use opioids
- Failure to fulfill major obligations at work, school or home
- Continuous use despite social or interpersonal problems
- Giving up or reducing important activities
- Use in physically hazardous situations
- Continuous use despite physical or psychological harm

Table 3 Commonly used opioid drugs in pain relief

Drug	Mechanism of action	Half-life (hours)	Side effects	Available formulations	Reference
Tramadol	μ-opioid receptor agonist + SNRI, a serotonin and norepinephrine reuptake inhibitor	6.3	Nausea, constipation, vomiting, dyspepsia, dry mouth, diarrhea, abdominal pain, flatulence, sore throat, gastroenteritis, anxiety, euphoria, nervousness, sleep disorder, insomnia, depression, agitation, apathy and depersonalization, emotional liability, viral, toothache, appendicitis and pancreatitis, respiratory depression, seizures	IV/IM injection, tablet, capsule, syrup, ointment, gel	[58]
Codeine	Selective agonist of μ-opioid receptor	3–4	Constipation, nausea, vomiting, clouded mentation and sedation, decreased libido, fatigue, pruritus, urinary retention, tremors, abdominal cramps, pancreatitis, bronchospasm	Tablet, syrup	[59]
Methadone	μ-opioid receptor agonist + + NMDA receptor antagonist	27 ± 12	Sedation, constipation, hyperalgesia, nausea, vomiting, sweating, respiratory depression, cardiac rhythm disturbances, QT interval prolongation	IV/IM injection Sub-cutaneous, epidural, intrathecal injection, tablets, syrup	[60]
Buprenorphine	Partial μ-opioid receptor agonist + κ-opioid receptor antagonist	2.33 ± 0.24	Weakness, anxiety, dizziness, drowsiness, orthostatic hypotension and constipation may precipitate serotonin syndrome	IV/IM injection, transdermal patch, buccal film formulation, sub-cutaneous extended release, sub-dermal implant, sub-lingual tablets	[61]
Oxycodone	μ-opioid receptor agonist	3–5	Constipation, dry mouth, headache, nausea, vomiting, pruritus, sweating, drowsiness, bradycardia, hypotension, photosensitivity, confusion, hallucinations, seizures, respiratory depression	Tablet, capsule, oral syrup	[62, 63]
Fentanyl	μ-opioid receptor agonist + weak and κ opioid receptor agonist	3–7	Euphoria, confusion, respiratory depression, drowsiness, nausea, hallucinations, delirium, constipation, narcotic ileus, muscle rigidity	IV/IM injection, Transdermal reparation, Nasal spray, Intrathecal preparation	[64]
Morphine	μ-opioid receptor agonist	3–7	Nausea, vomiting, hypotension, drowsiness, sedation, constipation, addictive and abuse potential, hypogonadism, osteoporosis	IV/IM, sub-cutaneous preparation, Oral, transdermal, rectal suppository	[65, 66]

SNRI serotonin–norepinephrine reuptake inhibitor, *NMDA* N–methyl–d–aspartate

- Tolerance (needing more for the same effect or diminished effect with the same dose)
- Withdrawal symptoms or using opioids to avoid withdrawal

While opioid dependence refers to a physiological adaptation characterized by tolerance and withdrawal upon cessation, OUD encompasses a broader spectrum of behavioral, psychological and social impairments. Dependence can occur even with medically supervised opioid use, whereas OUD involves compulsive use despite harm, loss of control and significant functional disruption. The DSM-5 criteria for OUD emphasize maladaptive patterns of use, distinguishing it from mere physical dependence, which alone does not constitute a disorder [70].

"United Nations Office on Drugs and Crime (UNODC)" published the "World Drug Report" in 2021. It states that 275 million people used controlled substances worldwide and 36 million people met the criteria of substance abuse disorder [71]. Among the controlled drugs, opioids happen to be the primary cause for drug-related fatalities, contributing to 69% of all deaths secondary to drug abuse. As per the 2019 national survey, India's opioid use prevalence is three times the global average [72].

Recent research has also highlighted the polygenetic inheritance of OUD; whereby multiple genes contribute to the disease susceptibility. Key genetic variants identified involve the opioid receptor mu-01 gene (OPRM1) and the brain-derived neurotrophic factor (BDNF) gene. Genome-wide association studies have highlighted the role of other genes that affect the calcium signaling, circadian rhythm and opioid receptor sensitivity [73].

Clinical tools that can be used to establish the diagnosis of OUD include the "Rapid Opioid Dependence Screen" (RODS), "Opioid Risk Tool" (ORT) and "Clinical Opiate Withdrawal Scale" (COWS). RODS is a quick, eight-item screening tool based on DSM-IV criteria. Its two-minute administration time makes it ideal for primary care, correctional and human immunodeficiency virus (HIV) settings with a sensitivity of 97% and specificity of 76% [74].

ORT is a self-reported questionnaire that predicts the risk of opioid misuse before initiation of opioid therapy for chronic pain [75]. COWS, on the other hand, is a clinician-administered tool to assess the severity of opioid withdrawal symptoms [76].

Although the diagnosis of OUD relies primarily on clinical criteria, laboratory markers in serum and urine can support assessment, monitor treatment adherence and detect relapse. Urine drug testing (UDT) remains the cornerstone of biochemical evaluation, offering qualitative and quantitative detection of opioids and their metabolites. Common analytes include morphine, codeine, heroin (6-monoacetylmorphine), fentanyl, methadone and buprenorphine, often measured via liquid chromatography-tandem mass spectrometry (LC–MS/MS) for high specificity and sensitivity. UDT can also detect unexpected substances such as cocaine or methamphetamine, which may co-occur in polysubstance use.

Serum markers are less commonly used for direct opioid detection due to rapid metabolism and short half-lives, but emerging research highlights inflammatory biomarkers such as elevated cytokines (e.g. IL-6, TNF-α) and altered immune cell profiles in individuals with chronic opioid exposure. These may reflect systemic effects of opioid misuse and offer potential for future diagnostic refinement. Additionally, serum creatinine and liver enzymes are monitored to assess organ function, especially in patients on long-term opioid agonist therapy.

While no single biomarker definitively diagnoses OUD, combining clinical evaluation with targeted urine and serum testing enhances diagnostic accuracy and supports personalized treatment strategies [77–80].

OUD is associated with a wide spectrum of medical, psychological and social complications that significantly impact morbidity and mortality. One of the most critical complications is respiratory depression, particularly with potent synthetic opioids, including fentanyl, which can lead to fatal overdose due to suppressed brainstem respiratory centers. Injectable use predisposes to increased risk of transmission of viral infections such as hepatitis C, hepatitis B and HIV. Besides, psychiatric comorbidities—including depression, anxiety and increased suicide risk—are also prevalent. Repeated opioid exposure often leads to tolerance, necessitating escalating doses to achieve the same effect, while cessation or reduction can trigger withdrawal symptoms such as restlessness, muscle aches, gastrointestinal distress and dysphoria [81].

As per the available statistics, almost 66% of patients with CP use opioids. Over the last two decades, there has been an astounding 57.6% increase in the use of opioids in CP [44]. There is paucity of literature on clinical studies analyzing the magnitude of the problem in patients with CP. Nusrat et al. have retrospectively analyzed 112 in-hospital patients, with 51% having received opioids for pain relief with a mean daily morphine equivalent of < 200 mg and around 40% having received transdermal fentanyl. This study highlighted the interrelation between alcohol-related pancreatitis, the presence of pain and the use of opioid drugs and affective spectrum disorders, which in turn points to a higher abuse potential [82]. Shah et al. identified 48.9% of patients of CP visiting the outpatient department with a history of chronic opioid use. History of recurrent pancreatitis, ongoing alcohol and tobacco use, besides features of anxiety and depression led to chronic opioid use. These patients were more likely to undergo other therapeutic interventions such as surgery for celiac

plexus block, besides concurrent use of benzodiazepines and gabapentinoid [83].

In a large retrospective cohort study, Bila et al. screened 176,857 patients of CP and documented OUD in 3.8% of these patients. Disease severity, obesity and depression were independent predictors for the development of OUD [84]. Barth et al. have also emphasized that higher pain intensity, poor quality of life parameters and alcohol use as predictors of opioid use in CP [85]. Adejemo et al. screened 87,068 CP patients over two years and 4.9% of these had concomitant OUD. Females, younger patients, those visiting urban health centers, patients with mental health disorders and a history of non-opioid substance use were more likely to suffer from OUD [86].

A 2024 study from Kovai Medical Centre, Tamil Nadu, implemented an Opioid Stewardship Programme across departments, including gastroenterology and general medicine, relevant to CP care. Among 471 patients, tramadol was the most prescribed opioid, followed by fentanyl and buprenorphine patches. Morphine was reserved for chronic pain cases. Combination therapy (opioid + non-opioid) was common, especially when monotherapy failed to meet pain goals. Side effects such as constipation (21.6%), nausea (12.1%) and sleeping disturbances were frequently reported, especially with benzodiazepine co-prescription. The study emphasized multimodal pain management and documented opioid tapering plans, suggesting a shift toward safer prescribing practices in chronic pain settings [87]. A multicenter cohort study by Wu et al. [88] involving 4307 patients hospitalized for acute pancreatitis found that 40.7% of patients with alcohol use disorder (AUD) had received opioids at baseline, compared to 44.0% without AUD. However, patients with alcohol-related pancreatitis had a higher median morphine equivalent dose on admission (17.5 mg) than those with gallstone pancreatitis (12.5 mg) [88].

In a separate study by Perera et al., patients with alcohol-related AP received almost double the cumulative opioid dose over the first three days compared to gallstone AP (42.8 mg vs. 22.1 mg). These findings suggest that opioid exposure is significantly higher in alcohol-related pancreatitis, both in terms of frequency and dosage, which may reflect more severe pain or altered pain processing. While direct rates of OUD stratified by etiology are limited, the co-occurrence of AUD and higher opioid use points to a potentially elevated risk of misuse in this sub-group [89].

The "Epidemiology of chronic and acute pancreatitis study in India (EPICAP-India)" is a multi-center epidemiological study encompassing 110,000 patients across 10 Indian states. The study focuses on patients with AP and CP, including risk factors such as opioid abuse. This study aims to identify genetic and environmental factors of CP and associated substance abuse [90].

Risk of malignancy?

The use of prescription opioids for the management of chronic pain has increased unusually in the US and not unexpectedly, the opioid addiction rates among these patients have increased, with almost one-third of such patients misusing opioids and almost 12% developing an OUD. In the background of such numbers, an unusual association that has arisen is the risk of malignancy [91]. The genesis of possible carcinogenicity in cancers other than PC from opioid use stems from the mechanism of action of opioids and there is data about this effect [92]. Numerous studies have revealed that opioids may have the potential to promote cancer evolution and metastases in different types of cancers, including breast, prostate, lung, esophagus and liver. The various mechanisms include mTOR pathway activation, promotion of angiogenesis, epithelial-to-mesenchymal transition and alteration of the gut microbiome, which in turn has been associated with pancreatic carcinogenesis. Specifically concerning PC, a large retrospective study in patients with unresectable tumors found a negative correlation between opioid usage and survival time [93–95].

In a prospective cohort study involving 50,045 adults from northeastern Iran followed over a median of 7.4 years, Moossavi et al. found that high cumulative opium use (> 81 nokhod-years, where 1 nokhod ≈ 0.2 g) was associated with a markedly increased risk of pancreatic cancer (PC). Even after adjusting for age, sex, BMI, diabetes, smoking and cumulative cigarette use, the hazard ratios (HR) remained significant—HR: 3.01 (95% CI: 1.25–7.26) and HR: 3.56 (95% CI: 1.49–8.50), respectively. Sensitivity analyses that excluded early users continued to show elevated risk (HR: 2.75, 95% CI: 1.14–6.64), underscoring opium use as a potential modifiable risk factor for PC [96]. In another case-control study conducted across four endoscopic ultrasound centers in Tehran, Shakeri et al. investigated the associations of opium use, cigarette smoking and alcohol consumption with pancreatic cancer. The study included 357 incident cases of PC (316 histopathologically confirmed adenocarcinomas and 41 clinically diagnosed) and 328 controls with normal pancreatic findings. After adjusting for potential confounders, opium use (OR: 1.91; 95% CI: 1.06–3.43) and alcohol consumption (OR: 4.16; 95% CI: 1.86–9.31) were significantly associated with increased risk of PC. Notably, cigarette smoking was not associated with elevated risk (OR: 0.93; 95% CI: 0.62–1.39), diverging from findings in western populations. These results underscore opium and alcohol as potential modifiable risk factors in this region, while highlighting the need for further research into population-specific cancer determinants [97].

Additionally, a recent post-hoc analysis of two randomized controlled trials of patients with advanced malignancy

(including PC) revealed that the use of an opioid antagonist significantly improved overall survival compared to placebo [98].

Furthermore, in a recent study by Barlass et al., wherein they used regression models to test the association between levels of PC rate and opioid death/use rates during 17 years (1999–2016), an increase in PC over time was noted along with increased opioid death rates. In addition to the conventional risk factors for PC, a significant interaction between opioid death rate and obesity prevalence ($p = 0.0002$) was seen, thereby indicating higher rates of PC in regions with elevated levels of both obesity and opioid usage four years prior. They concluded that in addition to obesity prevalence showing an upward trend, the opioid death rate at four years prior significantly predicted the initial incidence of PC ($p < 0.0001$) and had a significant effect on the estimated annual change in the rate of PC ($p < 0.0001$). Thus, opioid use may yet be an unidentified risk factor contributing to the increasing incidence of PC in the US, although more global data is required in this regard. Furthermore, opioid use remained a significant predictor of the PC rates, although the overall effect becomes weaker over time, signifying a possible ceiling effect [99].

However, it is prudent to mention that while opioid use has been associated with increased PC risk in general populations, there is currently no direct evidence evaluating whether CP patients with opioid use disorder are at a higher risk compared to opioid-naïve CP individuals.

Opioid-related bowel dysfunction (OBD)

Opioids affect gut motility. The umbrella term OBD encompasses various manifestations such as constipation, bloating, nausea, ileus and, at times, pain aggravation. The most sinister among these are "narcotic bowel syndrome" (NBS) and "opioid-induced hyperalgesia" (OIH).

NBS is a peculiar sub-type of opioid-related bowel dysfunction characterized by recurrent episodes of abdominal pain that worsen with continuing narcotic use or with escalating doses of narcotics. To begin with, the pain is intermittent colicky, but worsens when the effect of the narcotic wears off. Over time, pain-free periods become shorter, requiring repeated doses and often escalation of narcotics. These further precipitate adverse effects on pain sensation and delayed motility. Thus, a full-blown syndrome of NBS manifests. During the acute phase, the radiological picture mimicking adynamic ileus and pseudo-obstruction erroneously leads to a diagnosis of partial bowel obstruction. Early recognition is imperative to avoid narcotic dose escalation [100].

OIH is a distinct, characteristic entity that explains the loss of drug efficacy in a subset of patients. Basic pathophysiology is the "nociceptive sensitization" secondary to opioid use. The postulated hypothesis implicates the role played by neuroplastic changes in the peripheral and central nervous systems that further cause sensitization of pronociceptive pathways. Unexplained pain, diffuse allodynia not associated with original pain and increasing pain with increasing doses of opioids should alert the physician to the possible diagnosis. NMDA receptor agonists such as ketamine, methadone, propofol and alpha receptor agonists have all been used in post-op settings. However, it has not been evaluated in managing OIH in patients with CP [101].

Managing opioid use disorder

Managing OUD can be difficult. The following methods may help when treating patients with CP: adopting a "Medication-Assisted Treatment (MAT)" approach, which mainly combines medications with behavioral therapies. FDA-approved options include extended-release naltrexone, methadone and buprenorphine. These medications effectively reduce cravings, ease withdrawal symptoms and improve retention in treatment programs. Naltrexone, a pure opioid antagonist, binds competitively to mu-opioid receptors, blocking the euphoric and analgesic effects of opioids. Methadone is a full opioid agonist, while buprenorphine is a partial opioid receptor agonist. Naloxone is a rapid-acting opioid antagonist used primarily to reverse overdoses, restoring breathing and consciousness in emergencies. When combined with naloxone, buprenorphine has a ceiling effect that lowers overdose risk. It is preferred for its safety profile and flexibility in outpatient settings, although studies suggest it may have lower retention rates than methadone. Methadone, also a full opioid agonist, remains the most established opioid agonist therapy, showing better retention and effectiveness, especially in high-risk patients such as those with injection opioid use or unstable social situations. A recent population-based cohort study in British Columbia compared buprenorphine/naloxone and methadone, finding methadone associated with lower treatment discontinuation rates, while both treatments had similar mortality outcomes. These findings emphasize the importance of customizing treatment choices based on individual patient characteristics, risk factors and clinical environments.

The "Integrated care model" regards OUD as akin to other chronic disorders such as diabetes and hypertension. It envisages a multidisciplinary approach involving physicians, psychologists, social support and peer groups. This model proposes integrating treatment of OUD into primary care and community health settings (Table 4).

There is an ardent need to streamline and regularize the opioid prescription system for CP. Healthcare professionals should carefully select patients who would benefit from opioid therapy and assess their baseline risk of misuse potential.

Table 4 Severity of OUD as per DSM-5 criteria. *OUD* opioid use disorder, *DSM*-5 Diagnostics and Statistical Manual of Mental Disorders, 5th edition

Severity level	No. of symptoms	Description
Mild	02–03	Early signs of problematic use Social and occupational functioning may still be maintained
Moderate	04–05	Clear impairment in functioning Increased risk of health and social consequences
Severe	> 06	High level of dependence Significant disruption in daily life and health

Current opioid misuse measure (COMM), though validated in non-alcohol-related CP, is one such tool that may be utilized across other patients with CP. COMM comprises a 17-item self-reported tool. The questionnaire enquires about patients' current medication administration details. Each question consists of the relative frequency of a thought or behavior over the last 30 days, varying from 0 (never) to 4 (very often). The questionnaire has been suitably modified for patients who may not be completely truthful in their replies. A score of 9 or more in this validated and cross-validated questionnaire suggests a 30-day misuse potential of the prescription drug. Barth et al. have analyzed the use of COMM in addition to other "Brief Pain Inventory", "short form-12", "Quality of Life Measure", "Center for Epidemiological Studies 10-item depression scale" and "single item current alcohol use." Their research emphasizes that current alcohol use, depression, poor quality of life and pain intensity may be used as variables to identify patients with a high risk of opioid misuse in patients with pancreatitis [85]. A one to four-week course of low-dose opioids (< 40 morphine mEq) before considering long-term opioid therapy is generally recommended by most experts in managing non-cancer-related pain [103–106]. At present, there is no evidence to suggest better efficacy of one opioid over the other. Most experts prefer tramadol over extended-release preparation owing to their higher risk of overdosage. Patients who are unable to tolerate oral formulations should be prescribed transdermal preparations. Patient education and follow-up using validated questionnaires about opioid misuse should be religiously followed in clinical practice. Table 5 highlights the morphine milligram equivalents (MME) of commonly used opioids [102, 107].

For managing NBS, an effective treatment strategy is the biopsychosocial approach. A strong physician-patient relationship and timed narcotic withdrawal are imperative. Temporary use of long-acting benzodiazepines such as lorazepam, tricyclic antidepressants for antidepressant action, clonidine, an alpha 2 receptor agonist for sympathetic control, treatment of constipation using polyethylene glycol as osmotic laxatives and psychological counseling are the other pillars of disease management [108].

In patients with CP who develop OUD, managing withdrawal requires a tailored, multidisciplinary approach. Shah et al. highlighted that CP patients with chronic opioid use often exhibit polypharmacy, psychiatric comorbidities and higher healthcare utilization, underscoring the need for structured withdrawal protocols. Strategies include gradual tapering under supervision, use of non-opioid analgesics (e.g. acetaminophen, gabapentinoid) and incorporation of neuromodulators such as pregabalin to mitigate both pain and withdrawal symptoms. Collaboration with pain specialists and use of prescription monitoring programs can help

Table 5 Morphine milligram equivalents (MME) of commonly used opioids

Opioid	Conversion factor	Notes
Morphine	1.0	Reference standard
Hydrocodone	1.0	Commonly used in combination products
Oxycodone	1.5	Higher potency, associated with more GI side effects
Hydromorphone	4.0	Potent; useful in severe pain
Oxymorphone	3.0	Available as an extended-release formulation
Codeine	0.15	Weak opioid: used in mild pain
Tramadol	0.1	Dual mechanism of action, lower abuse potential
Tapentadol	0.4	Dual mechanism (μ-opioid receptor agonism + noradrenaline reuptake inhibition), less constipation
Methadone	Variable (4–12)	Non-linear conversion requires physician oversight
Fentanyl patch	2.4 (mcg/h)	Transdermal; conversion based on patch strength

Each opioid has a conversion factor based on its strength compared to morphine. MME is calculated as follows: Multiply the dose of the opioid by the number of times it is taken per day. And then multiply that total by the drug's conversion factor

Table 6 Proposed multilevel strategy to minimize misuse of opioids in CP. *CP* chronic pancreatitis, *COMM* current opioid misuse measure, *ORT* Opioid Risk Tool

Level	Key considerations	Reference
Patient-level	- Use validated screening tools (e.g. COMM, ORT) - Assess psychiatric comorbidities, substance use, polypharmacy - Engage in shared decision-making	[84]
Clinician-level	- Start with immediate-release opioids at lowest effective dose - Reassess within 1 to 4 weeks - Avoid escalation > 90 morphine milligram equivalent (MME)/day - Co-prescribe naloxone	[110]
Regulatory/Government-level	Implement prescription drug monitoring programs (PDMPs) and prescriber education - Support multidisciplinary pain clinics - Promote non-opioid research and access	[86]

reduce misuse while ensuring continuity of care [83, 109]. Table 6 highlights a multilevel strategy to minimize misuse of opioids in CP.

Lifestyle modification

The bio-physiological model of pain encompasses the complex interplay between physical, social and psychological factors that affect the perception of pain. These domains provide valuable intervention targets that may be employed in managing pain in CP. Almost 40% of patients with CP have higher levels of anxiety and depression as compared to the general population [110]. Substance abuse, especially alcohol and tobacco, is well-recognized cause for recurring pain in CP [111, 112]. Psychosocial factors, namely emotional function, sleep quality and pain-related interference with day-to-day activities. Patients' belief systems and expectations, catastrophizing, all play a pivotal role in the perception of pain. Thus, cognitive behavioral therapies that aim to challenge negative thoughts, change behavior patterns that worsen pain and enhance a patient's ability to cope with pain may be employed in the management of painful CP. A multidisciplinary approach utilizing psychosocial interventions in managing painful CP has been incorporated into recent guidelines [87].

To conclude, opioids are an important component of therapeutic algorithms while managing patients with CP. However, the ongoing opioid epidemic and the real risk of OUD warrant careful monitoring and incorporating newer and probably innovative therapeutic approaches while managing pain in CP.

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CRediT (Contributor Role Taxonomy) author role in manuscript.

Manish Manrai: conceptualization, validation, investigation, resources, formal analysis, data curation, writing original draft, review and editing. Saurabh Dawra: investigation, resources, formal analysis, data curation, writing original draft, conceptualization, resources, validation. Rakesh Kochhar: resources, formal analysis, review and editing

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Declarations

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References

1. Yadav D, Timmons L, Benson JT, Dierkhising RA, Chari ST. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. Am J Gastroenterol. 2011;106:2192–9. https://doi.org/10.1038/ajg.2011.328.
2. Spagnolo DM, Greer PJ, Ohlsen CS, et al. Acute and chronic pancreatitis disease prevalence, classification, and comorbidities: a cohort study of the UK BioBank. Clin Transl Gastroenterol. 2022;13:e00455. https://doi.org/10.14309/ctg.0000000000000455.
3. Cai QY, Tan K, Zhang XL, et al. Incidence, prevalence, and comorbidities of chronic pancreatitis: a 7-year population-based

study. World J Gastroenterol. 2023;29:4671–84. https://doi.org/10.3748/wjg.v29.i30.4671.
4. Garg PK. Chronic pancreatitis in India and Asia. Curr Gastroenterol Rep. 2012;14:118–24. https://doi.org/10.1007/s11894-012-0241-0.
5. Dunbar EK, Saloman JL, Phillips AE, Whitcomb DC. Severe pain in chronic pancreatitis patients: considering mental health and associated genetic factors. J Pain Res. 2021;14:773–84.. https://doi.org/10.2147/JPR.S274276.
6. Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology. 1994;107:1481–7. https://doi.org/10.1016/0016-5085(94)90553-3.
7. Ammann RW, Akovbiantz A, Largiader F, Schueler G. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. Gastroenterology. 1984;86:820–8.
8. Cavallini G, Frulloni L, Pederzoli P, et al. Long-term follow-up of patients with chronic pancreatitis in Italy. Scand J Gastroenterol. 1998;33:880–9. https://doi.org/10.1080/00365529850171567.
9. Lankisch PG, Löhr-Happe A, Otto J, Creutzfeldt W. Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. Digestion. 1993;54:148–55. https://doi.org/10.1159/000201029.
10. Kempeneers MA, Issa Y, Verdonk RC, et al. Pain patterns in chronic pancreatitis: a nationwide longitudinal cohort study. Gut. 2021;70:1724–33. https://doi.org/10.1136/gutjnl-2020-322117.
11. Löhr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J. 2017;5:153–99. https://doi.org/10.1177/2050640616684695.
12. Hirth M, Weiss C, Hardt P, et al. Analysis of the course of chronic pancreatitis: pancreatic burnout rates are only increased in a subgroup of patients with alcoholic chronic pancreatitis. Pancreas. 2019;48:726–33. https://doi.org/10.1097/MPA.0000000000001302.
13. Hirth M, Härtel N, Weiss C, et al. Clinical course of chronic pancreatitis in elderly patients. Digestion. 2019;100:152–9. https://doi.org/10.1159/000494349.
14. Olesen SS, Krauss T, Demir IE, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: mechanisms and implications for treatment. Pain Rep. 2017;2: e625. https://doi.org/10.1097/PR9.0000000000000625.
15. Yadav D, Palermo TM, Phillips AE, Bellin MD, Conwell DL. Painful chronic pancreatitis - new approaches for evaluation and management. Curr Opin Gastroenterol. 2021;37:504–11. https://doi.org/10.1097/MOG.0000000000000769.
16. Nadella S, Lieb JG 2nd. Minimal change patients versus obvious chronic pancreatitis: a comparison of classical secretin stimulation testing results. Pancreas. 2022;51:75–9. https://doi.org/10.1097/MPA.0000000000001965.
17. Bahuva R, Walsh RM, Kapural L, Stevens T. Morphologic abnormalities are poorly predictive of visceral pain in chronic pancreatitis. Pancreas. 2013;42:6–10. https://doi.org/10.1097/MPA.0b013e318258cd9c.
18. Drewes AM, Olesen AE, Farmer AD, Szigethy E, Rebours V, Olesen SS. Gastrointestinal pain. Nat Rev Dis Primers. 2020;6:1. https://doi.org/10.1038/s41572-019-0135-7.
19. Olesen SS, Krarup AL, Brock C, Drewes AM. Gastrointestinal sensations and pain: a review on basic, experimental and clinical findings. Minerva Gastroenterol Dietol. 2009;55:301–13.
20. Lieb JG 2nd, Forsmark CE. Review article: pain and chronic pancreatitis. Aliment Pharmacol Ther. 2009;29:706–19. https://doi.org/10.1111/j.1365-2036.2009.03931.x.
21. Liddle RA, Nathan JD. Neurogenic inflammation and pancreatitis. Pancreatology. 2004;4:551–9; discussion 559–60. https://doi.org/10.1159/000082180.
22. Anaparthy R, Pasricha PJ. Pain and chronic pancreatitis: is it the plumbing or the wiring? Curr Gastroenterol Rep. 2008;10:101–6. https://doi.org/10.1007/s11894-008-0029-4.
23. Atsawarungruangkit A, Pongprasobchai S. Current understanding of the neuropathophysiology of pain in chronic pancreatitis. World J Gastrointest Pathophysiol. 2015;6:193–202. https://doi.org/10.4291/wjgp.v6.i4.193.
24. Fregni F, Pascual-Leone A, Freedman SD. Pain in chronic pancreatitis: a salutogenic mechanism or a maladaptive brain response? Pancreatology. 2007;7:411–22. https://doi.org/10.1159/000108958.
25. Mokrowiecka A, Pińkowski D, Małecka-Panas E. Assessment of quality of life in patients with chronic pancreatitis. Med Sci Monit. 2011 ;17:CR583–8. https://doi.org/10.12659/msm.881985.
26. Chen JY, Wang YC, Xi HJ, et al. Translation and validation of a Chinese version of the pancreatitis quality of life instrument (PANQOLI) in patients with chronic pancreatitis. Qual Life Res. 2023;32:3417–26. https://doi.org/10.1007/s11136-023-03479-x.
27. Fitzsimmons D, Kahl S, Butturini G, et al. Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26. Am J Gastroenterol. 2005;100:918–26. https://doi.org/10.1111/j.1572-0241.2005.40859.x.
28. Pezzilli R, Morselli-Labate AM, Fantini L, Campana D, Corinaldesi R. Assessment of the quality of life in chronic pancreatitis using SF-12 and EORTC Qlq-C30 questionnaires. Dig Liver Dis. 2007;39:1077–86. https://doi.org/10.1016/j.dld.2007.06.014.
29. Vege SS, Chari ST. Chronic pancreatitis. N Engl J Med. 2022;386:869–78. https://doi.org/10.1056/NEJMcp1809396.
30. 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;112:633–42. https://doi.org/10.1038/ajg.2017.42.
31. Keller CE, Wilcox CM, Gudleski GD, Branham S, Lackner JM. Beyond abdominal pain: pain beliefs, pain affect, and distress as determinants of quality of life in patients with chronic pancreatitis. J Clin Gastroenterol. 2018;52:563–8. https://doi.org/10.1097/MCG.0000000000000922.
32. Chapman CR, Gavrin J. Suffering: the contributions of persistent pain. Lancet. 1999;353:2233–7. https://doi.org/10.1016/S0140-6736(99)01308-2.
33. Olesen SS, Bouwense SA, Wilder-Smith OH, van Goor H, Drewes AM. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Gastroenterology. 2011;141:536–43. https://doi.org/10.1053/j.gastro.2011.04.003.
34. Demir IE, Tieftrunk E, Maak M, Friess H, Ceyhan GO. Pain mechanisms in chronic pancreatitis: of a master and his fire. Langenbecks Arch Surg. 2011;396:151–60. https://doi.org/10.1007/s00423-010-0731-1.
35. Drewes AM, Krarup AL, Detlefsen S, Malmstrøm ML, Dimcevski G, Funch-Jensen P. Pain in chronic pancreatitis: the role of neuropathic pain mechanisms. Gut. 2008;57:1616–27. https://doi.org/10.1136/gut.2007.146621.
36. Lelic D, Olesen SS, Hansen TM, Valeriani M, Drewes AM. Functional reorganization of brain networks in patients with painful chronic pancreatitis. Eur J Pain. 2014;18:968–77. https://doi.org/10.1002/j.1532-2149.2013.00442.x.

37. Bouwense SA, Ahmed Ali U, ten Broek RP, et al. Altered central pain processing after pancreatic surgery for chronic pancreatitis. Br J Surg. 2013;100:1797–804. https://doi.org/10.1002/bjs.9322.
38. Knoph CS, Nedergaard RB, Olesen SS, Kuhlmann L, Drewes AM. Spinal excitability in patients with painful chronic pancreatitis. J Pain Res. 2023;16:2287-98. . https://doi.org/10.2147/JPR.S408523.
39. Gurusamy KS, Lusuku C, Davidson BR. Pregabalin for decreasing pancreatic pain in chronic pancreatitis. Cochrane Database Syst Rev. 2016;2: CD011522. https://doi.org/10.1002/14651858.CD011522.pub2.
40. Olesen SS, Graversen C, Olesen AE, et al. Randomised clinical trial: pregabalin attenuates experimental visceral pain through sub-cortical mechanisms in patients with painful chronic pancreatitis. Aliment Pharmacol Ther. 2011;34:878–87. https://doi.org/10.1111/j.1365-2036.2011.04802.x.
41. Delhaye M, Van Steenbergen W, Cesmeli E, et al. Belgian consensus on chronic pancreatitis in adults and children: statements on diagnosis and nutritional, medical, and surgical treatment. Acta Gastroenterol Belg. 2014;77:47–65.
42. Frulloni L, Falconi M, Gabbrielli A, et al. Italian consensus guidelines for chronic pancreatitis. Dig Liver Dis. 2010;42 Suppl 6:S381-406. https://doi.org/10.1016/S1590-8658(10)60682-2.
43. Anderson MA, Akshintala V, Albers KM, et al. Mechanism, assessment and management of pain in chronic pancreatitis: recommendations of a multidisciplinary study group. Pancreatology. 2016;16:83–94. https://doi.org/10.1016/j.pan.2015.10.015.
44. Maydeo A, Kamat N, Dalal A, Patil G. Advances in the management of pain in chronic pancreatitis. Curr Gastroenterol Rep. 2023;25:260–6. https://doi.org/10.1007/s11894-023-00898-1.
45. Mayerle J, Hoffmeister A, Werner J, Witt H, Lerch MM, Mössner J. Chronic pancreatitis–definition, etiology, investigation and treatment. Dtsch Arztebl Int. 2013;110:387–93. https://doi.org/10.3238/arztebl.2013.0387.
46. DiMagno EP, DiMagno MJ. Chronic pancreatitis: landmark papers, management decisions, and future. Pancreas. 2016;45:641–50. https://doi.org/10.1097/MPA.0000000000000599.
47. Wassef W, Bova C, Barton B, Hartigan C. Pancreatitis quality of life instrument: development of a new instrument. SAGE Open Med. 2014;2:2050312114520856. https://doi.org/10.1177/2050312114520856.
48. Wassef W, DeWitt J, McGreevy K, et al. Pancreatitis quality of life instrument: a psychometric evaluation. Am J Gastroenterol. 2016;111:1177–86. https://doi.org/10.1038/ajg.2016.225.
49. Drewes AM, van Veldhuisen CL, Bellin MD, et al. Assessment of pain associated with chronic pancreatitis: an international consensus guideline. Pancreatology. 2021;21:1256–84. https://doi.org/10.1016/j.pan.2021.07.004.
50. Bellin MD, Abu-El-Haija M, Morgan K, et al. A multicenter study of total pancreatectomy with islet autotransplantation (TPIAT): POST (prospective observational study of TPIAT). Pancreatology. 2018;18:286–90. https://doi.org/10.1016/j.pan.2018.02.001.
51. Kesseli SJ, Smith KA, Gardner TB. Total pancreatectomy with islet autologous transplantation: the cure for chronic pancreatitis? Clin Transl Gastroenterol. 2015;6:e73. https://doi.org/10.1038/ctg.2015.2.
52. Ni Q, Yun L, Roy M, Shang D. Advances in surgical treatment of chronic pancreatitis. World J Surg Oncol. 2015;13:34. https://doi.org/10.1186/s12957-014-0430-4.
53. Sachdev AH, Gress FG. Celiac plexus block and neurolysis: a review. Gastrointest Endosc Clin N Am. 2018;28:579–86. https://doi.org/10.1016/j.giec.2018.06.004.
54. Ratnayake CB, Bunn A, Pandanaboyana S, Windsor JA. Spinal cord stimulation for management of pain in chronic pancreatitis: a systematic review of efficacy and complications. Neuromodulation. 2020;23:19–25. https://doi.org/10.1111/ner.13051.
55. Wyse JM, Battat R, Sun S, et al. Practice guidelines for endoscopic ultrasound-guided celiac plexus neurolysis. Endosc Ultrasound. 2017;6:369–75. https://doi.org/10.4103/eus.eus_97_17.
56. Gardner TB, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. ACG clinical guideline: chronic pancreatitis. Am J Gastroenterol. 2020;115:322–39. https://doi.org/10.14309/ajg.0000000000000535.
57. Ventafridda V, Saita L, Ripamonti C, De Conno F. WHO guidelines for the use of analgesics in cancer pain. Int J Tissue React. 1985;7:93–6.
58. Yang J, Bauer BA, Wahner-Roedler DL, Chon TY, Xiao L. The modified WHO analgesic ladder: is it appropriate for chronic non-cancer pain? J Pain Res. 2020;13:411–7. https://doi.org/10.2147/JPR.S244173.
59. Subedi M, Bajaj S, Kumar MS, Yc M. An overview of tramadol and its usage in pain management and future perspective. Biomed Pharmacother. 2019;111:443–51. https://doi.org/10.1016/j.biopha.2018.12.085.
60. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 5284371, Codeine; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Codeine
61. Sunilkumar MM, Lockman K. Practical pharmacology of methadone: a long-acting opioid. Indian J Palliat Care. 2018;24 Suppl 1:S10–4. https://doi.org/10.4103/IJPC.IJPC_180_17.
62. Poliwoda S, Noor N, Jenkins JS, et al. Buprenorphine and its formulations: a comprehensive review. Health Psychol Res. 2022;10: 37517. https://doi.org/10.52965/001c.37517.
63. Torabi R, Bourn L, Mundinger GS, et al. American Society of Plastic Surgeons member post-operative opioid prescribing patterns. Plast Reconstr Surg. 2019;7: e2125. https://doi.org/10.1097/GOX.0000000000002125.
64. Huddart R, Clarke M, Altman RB, Klein TE. PharmGKB summary: oxycodone pathway, pharmacokinetics. Pharmacogenet Genomics. 2018;28:230–7. https://doi.org/10.1097/FPC.0000000000000351.
65. Comer SD, Cahill CM. Fentanyl: receptor pharmacology, abuse potential, and implications for treatment. Neurosci Biobehav Rev. 2019;106:49–57. https://doi.org/10.1016/j.neubiorev.2018.12.005.
66. James A, Williams J. Basic opioid pharmacology - an update. Br J Pain. 2020;14:115–21. https://doi.org/10.1177/2049463720911986.
67. Goulden MR. The pain of chronic pancreatitis: a persistent clinical challenge. Br J Pain. 2013;7:8–22. https://doi.org/10.1177/2049463713479230.
68. Niemann T, Madsen LG, Larsen S, Thorsgaard N. Opioid treatment of painful chronic pancreatitis. Int J Pancreatol. 2000;27:235–40. https://doi.org/10.1385/ijgc:27:3:235.
69. Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatry. 2013;170:834–51. https://doi.org/10.1176/appi.ajp.2013.12060782.
70. Volkow ND, Blanco C. Medications for opioid use disorders: clinical and pharmacological considerations. J Clin Invest. 2020;130:10–3. https://doi.org/10.1172/JCI134708.
71. United Nations Office on Drugs and Crime. World Drug Report 2021.Vienna. UNODC;2021. Available at: https://www.unodc.org/unodc/en/data-and-analysis/wdr2021.html
72. Singh B, Rao R. Perspectives is there an opioid epidemic in India? J Public Health (Oxf). 2021;43:ii43–50. https://doi.org/10.1093/pubmed/fdab391.

73. Panday SK, Shankar V, Lyman RA, Alexov E. Genetic variants linked to opioid addiction: a genome-wide association study. Int J Mol Sci. 2024;25:12516. https://doi.org/10.3390/ijms252312516.
74. Wickersham JA, Azar MM, Cannon CM, Altice FL, Springer SA. Validation of a brief measure of opioid dependence: the rapid opioid dependence screen (RODS). J Correct Health Care. 2015;21:12–26. https://doi.org/10.1177/1078345814557513.
75. Tanaka M, Fernández-del Castillo C, Adsay V, et al; International Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183–97. https://doi.org/10.1016/j.pan.2012.04.004.
76. Wesson DR, Ling W. The clinical opiate withdrawal scale (COWS). J Psychoactive Drugs. 2003;35:253–9. https://doi.org/10.1080/02791072.2003.10400007.
77. Huhn AS, Whitley P, Bolin BL, Dunn KE. Fentanyl, heroin, methamphetamine, and cocaine analyte concentrations in urine drug testing specimens. JAMA Netw Open. 2024;7:e2441063. https://doi.org/10.1001/jamanetworkopen.2024.41063.
78. Bertholf RL, Reisfield GM. Opioid use disorders, medication-assisted treatment, and the role of the laboratory. Lab Med. 2017;48:e57–61. https://doi.org/10.1093/labmed/lmx054.
79. Sobel HG, Warrington JS, Francis-Fath S, Crocker AM, Berger CA. A descriptive analysis of urine drug screen results in patients with opioid use disorder managed in a primary care setting. Addict Sci Clin Pract. 2021;16: 59. https://doi.org/10.1186/s13722-021-00264-4.
80. Bryant BM, Eaton E, Li L. A systematic review of opioid use disorder and related biomarkers. Front Psychiatry. 2021;12: 708283. https://doi.org/10.3389/fpsyt.2021.708283.
81. Bogler O, Incze MA. Endocrine adverse effects of long-term opioid use. JAMA Intern Med. 2024;184:831–2. https://doi.org/10.1001/jamainternmed.2024.0863.
82. Nusrat S, Yadav D, Bielefeldt K. Pain and opioid use in chronic pancreatitis. Pancreas. 2012;41:264–70. https://doi.org/10.1097/MPA.0b013e318224056f.
83. Shah I, Sheth SG, Kothari DJ. Pain management in chronic pancreatitis incorporating safe opioid practices: challenge accepted. World J Gastroenterol. 2021;27:3142–7. https://doi.org/10.3748/wjg.v27.i23.3142.
84. Bilal M, Chatila A, Siddiqui MT, et al. Rising prevalence of opioid use disorder and predictors for opioid use disorder among hospitalized patients with chronic pancreatitis. Pancreas. 2019;48:1386–92. https://doi.org/10.1097/MPA.0000000000001430.
85. Barth KS, Balliet W, Pelic CM, et al. Screening for current opioid misuse and associated risk factors among patients with chronic nonalcoholic pancreatitis pain. Pain Med. 2014;15:1359–64. https://doi.org/10.1111/pme.12403.
86. Adejumo AC, Akanbi O, Alayo Q, et al. Predictors, rates, and trends of opioid use disorder among patients hospitalized with chronic pancreatitis. Ann Gastroenterol. 2021;34:262–72. https://doi.org/10.20524/aog.2021.0579.
87. Dhandapani C, Rajkumar KS, Lokesh P, et al. A dashboard for monitoring opioids: initiating and assessing the impact of opioid stewardship programme in pain management at a multispeciality hospital in India. Indian Journal of Pharmacy Practice. 2024;17:317–24.
88. Wu BU, Butler RK, Chen W. Factors associated with opioid use in patients hospitalized for acute pancreatitis. JAMA Netw Open. 2019;2:e191827. https://doi.org/10.1001/jamanetworkopen.2019.1827.
89. Perera MRS, Tattersall MZ, Wysocki AP. Analgesia in patients with acute pancreatitis: a cry for help. Int J Gastroenterol Res Pract. 2014;2014: 343907. https://doi.org/10.5171/2014.343907.
90. Krishnan A, Pillai D, Amarchand R, et al. Epidemiology of chronic and acute pancreatitis in India (EPICAP-India): protocol for a multicentre study. BMJ Open Gastroenterol. 2024;11:e001562. https://doi.org/10.1136/bmjgast-2024-001562.
91. Deak JD, Johnson EC. Genetics of substance use disorders: a review. Psychol Med. 2021;51:2189–200. https://doi.org/10.1017/S0033291721000969.
92. Singleton PA, Moss J, Karp DD, Atkins JT, Janku F. The mu opioid receptor: a new target for cancer therapy? Cancer. 2015;121:2681–8. https://doi.org/10.1002/cncr.29460.
93. Wang F, Roy S. Gut homeostasis, microbial dysbiosis, and opioids. Toxicol Pathol. 2017;45:150–6. https://doi.org/10.1177/0192623316679898.
94. Vitiello GA, Cohen DJ, Miller G. Harnessing the microbiome for pancreatic cancer immunotherapy. Trends Cancer. 2019;5:670–6. https://doi.org/10.1016/j.trecan.2019.10.005.
95. Oh TK, Do SH, Yoon YS, Song IA. Association between opioid use and survival time in patients with unresectable pancreatic cancer: 10 years of clinical experience. Pancreas. 2018;47:837–42. https://doi.org/10.1097/MPA.0000000000001094.
96. Moossavi S, Mohamadnejad M, Pourshams A, et al. Opium use and risk of pancreatic cancer: a prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2018;27:268–73. https://doi.org/10.1158/1055-9965.EPI-17-0592.
97. Shakeri R, Kamangar F, Mohamadnejad M, et al. Opium use, cigarette smoking, and alcohol consumption in relation to pancreatic cancer. Medicine (Baltimore). 2016;95: e3922. https://doi.org/10.1097/MD.0000000000003922.
98. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer. Ann Oncol. 2016;27:2032–8. https://doi.org/10.1093/annonc/mdw317.
99. Barlass U, Deshmukh A, Beck T, Bishehsari F. Opioid use as a potential risk factor for pancreatic cancer in the United States: an analysis of state and national level databases. PLoS One. 2021;16:e0244285. https://doi.org/10.1371/journal.pone.0244285.
100. Farmer AD, Gallagher J, Bruckner-Holt C, Aziz Q. Narcotic bowel syndrome. Lancet Gastroenterol Hepatol. 2017;2:361–8. https://doi.org/10.1016/S2468-1253(16)30217-5.
101. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14:145–61.
102. Mégarbane B, Chevillard L, Vodovar D. Naloxone should remain the appropriate antidote to treat opioid overdose. Crit Care. 2020;24: 173. https://doi.org/10.1186/s13054-020-2835-5.
103. Nosyk B, Min JE, Homayra F, et al. Buprenorphine/naloxone vs methadone for the treatment of opioid use disorder. JAMA. 2024;332:1822–31. https://doi.org/10.1001/jama.2024.16954.
104. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. MMWR Recomm Rep. 2022;71:1–95. https://doi.org/10.15585/mmwr.rr7103a1.
105. Black E, Khor KE, Demirkol A. Responsible prescribing of opioids for chronic non-cancer pain: a scoping review. Pharmacy (Basel). 2020;8:150. https://doi.org/10.3390/pharmacy8030150.
106. Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician. 2017Feb;20:S3–92.
107. Adams MCB, Sward KA, Perkins ML, Hurley RW. Standardizing research methods for opioid dose comparison: the NIH HEAL morphine milligram equivalent calculator. Pain. 2025;166:1729–37. https://doi.org/10.1097/j.pain.0000000000003529.

108. Kurlander JE, Drossman DA. Diagnosis and treatment of narcotic bowel syndrome. Nat Rev Gastroenterol Hepatol. 2014;11:410–8. https://doi.org/10.1038/nrgastro.2014.53.
109. Shah I, Bocchino R, Yakah W, et al. Evaluating outcomes and misuse in opioid-dependent chronic pancreatitis using a state-mandated monitoring system. Dig Dis Sci. 2022;67:5493–9. https://doi.org/10.1007/s10620-022-07459-y.
110. Phillips AE, Faghih M, Drewes AM, Singh VK, Yadav D, Olesen SS, Pancreatic Quantitative Sensory Testing (P-QST) Consortium. Psychiatric comorbidity in patients with chronic pancreatitis associates with pain and reduced quality of life. Am J Gastroenterol. 2020;115:2077–85. https://doi.org/10.14309/ajg.0000000000000782.
111. Yadav D, Hawes RH, Brand RE. North American Pancreatic Study Group Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009;169:1035–45. https://doi.org/10.1001/archinternmed.2009.125.
112. Drewes AM, Bouwense SAW, Campbell CM, Ceyhan GO, Delhaye M, Demir IE, Working group for the International (IAP – APA – JPS – EPC) Consensus Guidelines for Chronic Pancreatitis, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology. 2017;17:720–31. https://doi.org/10.1016/j.pan.2017.07.006.