Prevalence and Patterns of Opioid Use in Chronic Pancreatitis

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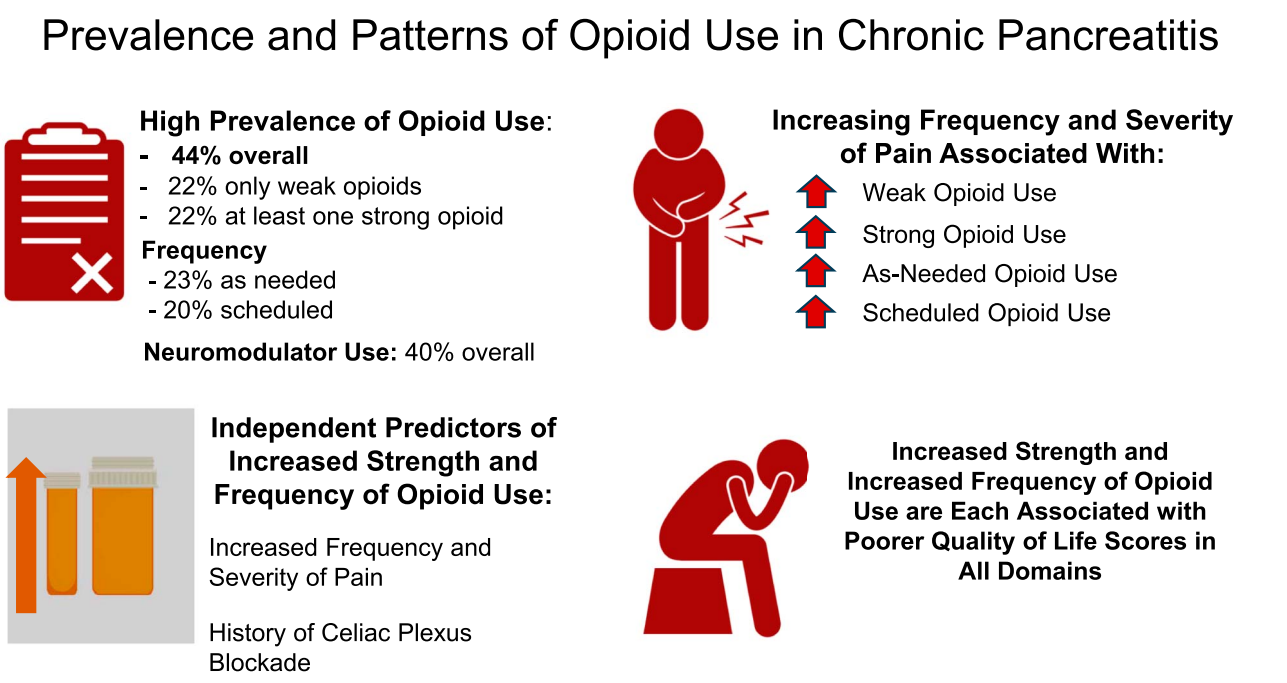
INTRODUCTION: **Opioids are used to treat pain in chronic pancreatitis (CP), but little is known about current use patterns. The aim of this study was to characterize the utilization of opioids and associations with clinical characteristics in adult patients with CP.**



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METHODS: **This cross-sectional analysis used baseline data from participants with definite CP enrolled in a cohort study in the United States (PROspective Evaluation of CP for EpidEmiologic and Translational StuDies). Data on demographics, pain medication use, healthcare utilization, disability, and pain patterns were systematically collected in case report forms while quality of life was assessed with patient-reported outcome instruments. Opioid use was classified according to strength (weak or strong) and frequency (scheduled or as-needed).**

RESULTS: **A total of 681 participants (n = 364, 53% male) were included: 299 (44%) were current opioid users (22% only weak opioids and 22% at least 1 strong opioid). Increasing frequency and severity of pain was associated with increase of weak, strong, as-needed, or scheduled opioids. Neuromodulators were used by ~40% of participants; increasing use was associated with increasing frequency and severity of pain. On multivariate analysis, independent predictors associated with strength and frequency of current opioid use were pain patterns (odds ratios [ORs] 1.84–8.32 and ORs 1.92–8.52, respectively, $P < 0.001$) and prior celiac plexus block (OR 3.54, 95% confidence intervals 1.82–6.87 and OR 3.42, 95% confidence intervals 1.76–6.64, respectively). Participants using opioids had higher prevalence of disability, healthcare utilization, and poorer quality of life.**

DISCUSSION: **Opioid use in CP is common and associated with increased pain severity and constancy. These data provide foundational estimates for future trials that can elucidate the complex interactions between patient factors, pain, and interventions.**

KEYWORDS: chronic pancreatitis; chronic pain; opioid; neuromodulator

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B284

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INTRODUCTION

Abdominal pain affects approximately 90% of patients with chronic pancreatitis (CP) during the course of their disease (1). Abdominal pain in CP is difficult to treat, resulting in escalation of medical therapies through the ladder of analgesics and often involves invasive treatments such as endoscopic therapy or surgery. Opioid medications—at the upper steps of the analgesic ladder—can generate many side effects including constipation, sedation, and nausea, as well as carry risks of drug tolerance, dependence, and/or overuse. The high prevalence of psychiatric comorbidities in patients with CP and history of substance abuse in those with a toxic etiology raises the risk of opioid use disorder (2), which has previously been shown to be rising in this population (3). Opioid use has been associated with opioid-induced visceral hyperalgesia, which may further complicate the pain experience of patients with painful CP (4,5).

While factors associated with frequent opioid use in the pediatric recurrent acute pancreatitis and CP population include constant pain, more healthcare use, and higher levels of pain interference with functioning (6), opioid use in the adult CP population has mainly been studied in a retrospective fashion or been incorporated into studies as a proxy outcome for measuring baseline pain or pain response (5,7,8). In fact, rates of opioid use for pain control in patients with CP range widely (between 25% and 60%) (9–13). Although frequently used, little is known about current patterns of opioid use in patients with CP including demographic trends, associated quality of life (QOL), burden of disease, or clinical outcomes.

The opioid overdose epidemic has changed prescribing practices in the United States over the past 10 years. Moreover, as part of changing prescribing practices, adjuvant analgesics have been increasingly used in an attempt to mitigate opioid use in patients with CP (14). The rates and types of other analgesics including neuromodulators, antidepressant, antianxiety, and other neuroleptic medications used in patients with CP remain largely unknown, as does their relationship with dose and frequency of opioid use (15).

The aims of this cross-sectional analysis were to (i) characterize the prevalence and pattern of opioid use for pain control in patients with CP; (ii) identify sociodemographic, behavioral, and disease-related factors associated with opioid use; and (iii) describe the QOL, disability, and healthcare utilization in CP patients with opioid use. We hypothesized that opioid use for the treatment of pain in CP is widespread and associated with self-reported pain experience, behavioral and psychological factors, high disease burden and healthcare utilization, and poor QOL.

METHODS

Study population

Baseline data were analyzed for participants with definite CP who were enrolled in the PROspective Evaluation of CP for EpidEmiologic and Translational StuDies, an ongoing multicenter, prospective, longitudinal cohort study of CP in the United States between 2017 and 2021 (NCT03099850) (16). Diagnosis of definite CP was determined by the presence of definitive changes on CT scan and/or magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) (Cambridge 3–4 stage, parenchymal or ductal calcifications) or on pancreatic histology (16). Imaging findings were determined from review by a designated radiologist at each institution according to a standardized protocol (17). Approval for the study was obtained from all institutional review boards at the participating centers as well as the institutional review boards at the Coordinating and Data Management Center (16). Informed consent was completed for participants before any study procedures were performed.

Clinical data

Demographic, socioeconomic, and clinical data including education, marital status, annual income, employment status, risk factors, etiology, temporal nature and severity of pain, diabetes mellitus, exocrine pancreatic dysfunction (EPD), treatment, and healthcare utilization including emergency department (ER) visits and hospitalizations were systematically collected using structured case report forms and standardized patient-reported outcome tools (16). Self-reported pain within the past 1 year was characterized using differentiating levels of severity (no pain, mild-moderate pain, severe pain) and temporal nature (no pain, intermittent pain, constant pain); the categories of constant mild-to-moderate pain with episodes of severe pain and constant severe pain have been combined to provide a total of 5 predefined categories (11). Tobacco and alcohol use was defined as never, past, or current. Duration of CP and of any pancreatitis was defined by the difference between the age at CP diagnosis or the date at first diagnosis of acute pancreatitis (AP) or CP and the date of enrollment.

Medication data

Information on outpatient opioid use at enrollment was obtained from participants and corroborated with the electronic health records. Opioid medication strength was classified as weak or strong according to World Health Organization criteria relative to morphine (18). Opioid medication frequency was determined by assessing whether the participant was taking it on a scheduled or as-needed (prn) basis. Daily milligrams of morphine equivalent were not calculated because the frequency of prn medications was difficult to ascertain (and highly variable between and among) individual participants. Illicit opioid use could not be assessed. Additional analgesic use including acetaminophen, nonsteroidal anti-inflammatory drugs, and neuromodulators was assessed by name and dose of medication at the time of enrollment. Finally, treatment of diabetes, use of pancreatic enzyme replacement therapy (PERT), and use of vitamins and antioxidants were also recorded.

Disability, ER visits, and hospitalizations

At enrollment, the number of pancreatitis-related hospital admissions for each participant in the preceding 12 months and the number of lifetime hospital admissions were collected through participant interview and review of the electronic health record. In addition, the number of presentations to the ER in the preceding 12 months that did not result in a hospital admission were tabulated. Participants were asked to report disability due to upper abdominal pain, pancreatic pain, or pancreatitis.

Quality of life

All participants completed the Patient-Reported Outcomes Measurement Information System (PROMIS) 29 Profile Version 2.0 and the PROMIS Global Health (PROMIS-GH) Version 1.2 instruments at enrollment. The PROMIS 29 includes 29 items that assess subdomains of anxiety, depression, sleep disturbance, pain interference, fatigue, physical function, and social role participation. The PROMIS-GH questionnaire includes 10 items that contribute to an overall Mental Health score and overall Physical Health score, as well as an average pain rating in the preceding 7 days. Scores on each item from both questionnaires range from 1 to 5 (i.e., never/not at all to always/very much) with the exception of pain rating (range 0–10). The final scores for each PROMIS 29 domain and for mental and physical health scores for PROMIS-GH were calculated using conversion from raw sum scores to T-scores using the standard methods described in the PROMIS HealthMeasures protocol (19).

Statistical analysis

To investigate the pattern of opioid use, we performed univariate analyses to compare patient characteristics among 3 groups according to opioid strength (no opioid, weak opioid only, at least 1 strong opioid) and then according to frequency of use (no opioid, as-needed opioid, scheduled opioid). Categorical variables were summarized by frequencies and percentages and compared between groups with Fisher exact tests; continuous variables were summarized using medians and ranges and compared between groups by Kruskal-Wallis test. Bar graphs were used to display opioid use patterns by frequency of specific medications used, and stacked bar graphs were used to display opioid use patterns by strength and frequency across pain categories.

Missing data were identified as random and addressed through multiple imputations by fully conditional specification methods using a separate conditional distribution for each imputed variable. For each imputation, a preliminary fill-in phase was followed by an imputation phase. In the fill-in phase, missing values for all variables were filled in sequentially over the variables obtained one at a time. The filled-in values then provided starting values for missing values at the imputation phase. Missing values for each variable were imputed sequentially for a number of burn-in iterations before the imputation.

We used a multivariable proportional odds model to investigate patient and disease-related factors independently associated with the strength and frequency of opioid use. This model had a proportional odds assumption that used the intrinsic ordering of the opioid strength and frequency as an ordinal outcome variable and was verified during model diagnosis. Separate models were used to determine the associations for opioid use patterns based on strength (none vs weak or strong; weak vs strong) and frequency of use (none vs as needed or scheduled; as needed vs scheduled). The candidate variables included demographics, socioeconomic status, drinking status, tobacco use status, duration of pancreatitis, etiology, imaging findings, diabetes, EPD, prior endotherapy, pancreatic surgery, celiac plexus block, and pain pattern. Backward selection was performed across each imputed data set, removing variables based on preset significance levels ($P > 0.05$). Significant variables selected in all 5 imputed data sets were included in the final model, creating a more concise model overall. Odds ratios (ORs) and confidence intervals (CIs) were determined using Rubin formula. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), and a 2-sided P value of <0.05 was considered statistically significant.

RESULTS

A total of 681 participants with definite CP (male n = 364, 53%) were selected for this analysis. Of these, 299 (44%) were current opioid users, 148 (22%) of whom using only weak opioids and 151 (22%) were using at least 1 strong opioid. Demographic and clinical characteristics by the 3 opioid-use categories by strength and frequency of use are presented in Tables 1 and 2. The frequency of each specific type of opioid used and their strength relative to morphine are shown in Figure 1a. Participants could be taking more than 1 type of opioid, and frequency reflects reported

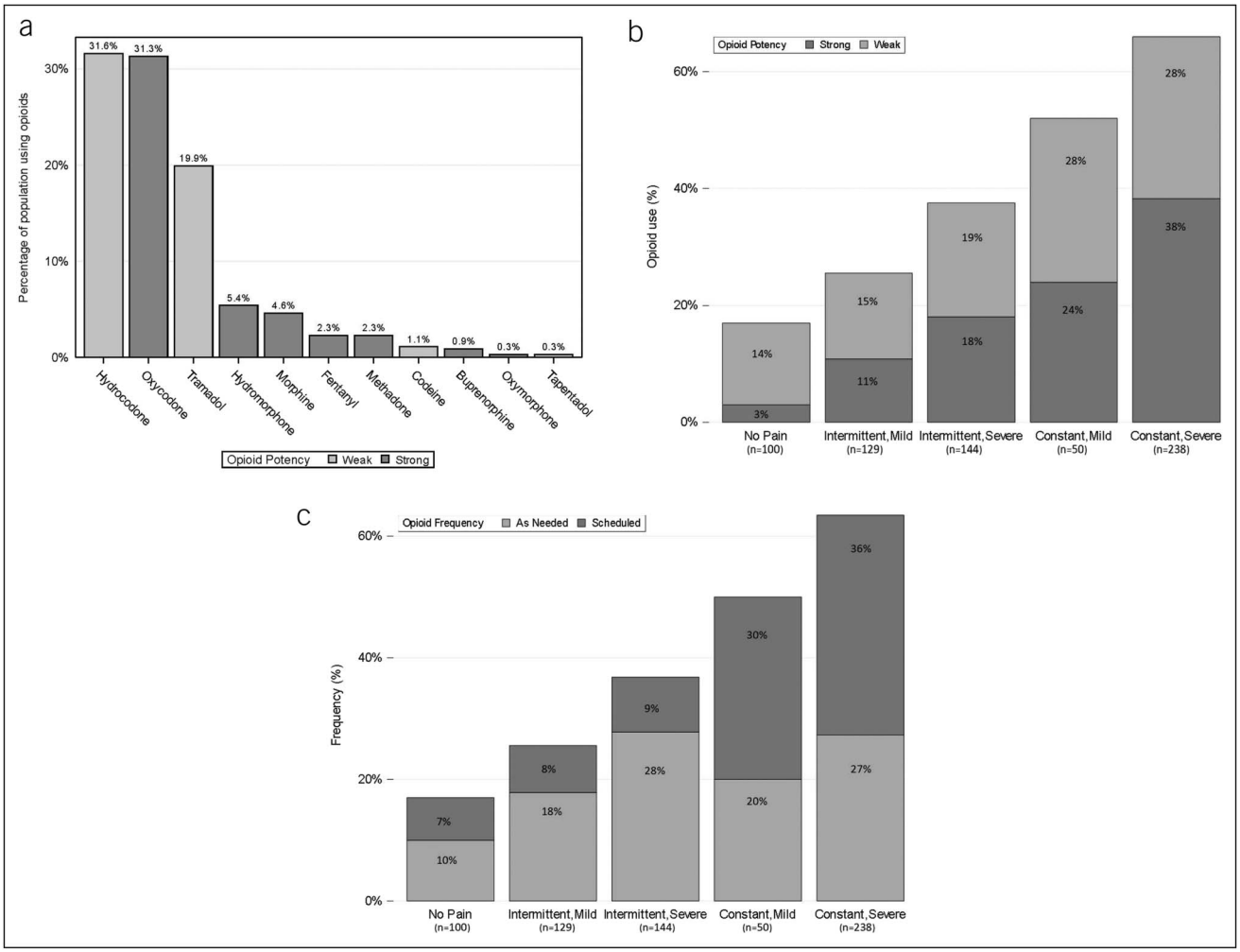

Figure 1. Patterns of opioid usage in 681 adults with chronic pancreatitis according to the specific opioid (**a**), opioid potency by pain severity (**b**), and opioid frequency by pain severity (**c**).

use of each agent. Importantly, an increase in use of both weak and strong opioids was noted with increasing frequency and severity of pain (Figure 1b). In a similar fashion, an increase in the use of both as-needed and scheduled opioids was seen with increasing frequency and severity of pain (Figure 1c).

Opioid strength

In univariate analysis, compared with those not using any opioids, participants using either weak or strong opioids were younger and were more likely to be female, to be unemployed, to have lower income, and to be current smokers (Table 1). Increasing strength of opioids was associated with the duration of CP, and these participants were more likely to have had a history of AP and were more likely to have alcohol etiology. Participants using strong opioids were more likely to have pancreatic duct stricture on imaging studies seen at the time of enrollment. A history of invasive therapies such as celiac plexus block, endotherapy, and pancreatic surgery was more frequent with increasing strength of opioid use. Finally, increasing strength of opioids was associated with the presence, severity, and temporal nature of pain.

On multivariate analysis by a proportional odds model, independent predictors associated with the strength of current opioid use were pain pattern (OR 1.84–8.32, $P < 0.001$) and prior celiac plexus block (OR 3.54, 95% CI 1.82–6.87) (Table 3.1). Being a 3-level comparison, the interpretation of OR in a proportional odds model yields similar estimates for 2 comparisons—for example, when compared with participants with no pain, the odds of using either weak or strong opioids were 1.84 times greater than the odds of using no opioids in participants with intermittent mild-moderate pain and the odds of using strong opioids were 1.84 times greater than the odds of using weak opioids in those with intermittent mild-moderate pain. ORs for other associations can be interpreted in the same fashion.

Opioid frequency

In univariate analysis, compared with those not using any opioids, participants using either as-needed or scheduled opioids were also more likely to be younger, be female, be unemployed, have lower income, and be current smokers (Table 2). Increasing frequency of opioid use was associated with lower age at AP (for those participants with prior AP) and duration of CP. Participants using scheduled opioids were more likely to have pancreatic calcifications on a prior imaging study and to have EPD. A history of invasive therapies including endotherapy and celiac

Table 1. Demographics, socioeconomics, pancreatitis history, and pain patterns in participants by opioid strength category

	No opioids (n, %)	Weak opioids (n, %)	At least 1 strong opioid (n, %)	*P* value
	N = 382 (56%)	N = 148 (22%)	N = 151 (22%)	
Male sex, n (%)	226 (60)	72 (51)	66 (45)	0.0024
Age at enrollment, median years (IQR)	56 (45, 65)	54 (43.5, 64)	52 (41, 59)	0.0018
Race, n (%)				
White	313 (84)	123 (87)	129 (88)	0.80
Black	29 (8)	11 (8)	7 (5)	
Other (includes multiple and no response)	40 (11)	14 (10)	15 (10)	
Ethnicity, n (%)				
Hispanic	14 (4)	5 (3)	2 (1)	0.37
Non-Hispanic	368 (98)	143 (97)	149 (99)	
Education, n (%)				
Bach. Deg. or Grad. School	211 (56)[8]	74 (52)[8]	66 (45)[8]	0.28
Some training after high school	35 (9)	16 (11)	15 (10)	
High school (GED or less)	128 (34)	50 (35)	62 (42)	
Employment status, n (%)				
Employed	176 (47)[10]	51 (36)[8]	43 (29)[4]	<0.001
Retired	94 (25)	41 (29)	24 (16)	
Unemployed	102 (27)	48 (34)	80 (55)	
Annual household income category, n (%)				
≥ $100,000	99 (26)[44]	35 (25)[22]	13 (9)[20]	<0.001
≥ $50,000 to < $100,000	86 (23)	43 (30)	36 (25)	
< $50,000	153 (41)	48 (34)	82 (56)	
Marital status, n (%)				
Divorced/separated/widowed	78 (21)[2]	29 (21)[5]	31 (21)[1]	0.084
Married	213 (57)	93 (66)	78 (53)	
Single	89 (24)	41 (28)	41 (28)	
Drinking status, n (%)				
Never	49 (13)[8]	17 (12)[3]	19 (13)[2]	<0.001
Past	217 (58)	98 (70)	112 (77)	
Current	108 (29)	30 (21)	18 (12)	
Tobacco use, n (%)				
Never	130 (35)[7]	33 (23)[3]	34 (23)[2]	<0.001
Past	114 (30)	51 (36)	37 (25)	
Current	131 (35)	61 (43)	78 (53)	
Age at CP diagnosis, median years (IQR)	54 (42, 62)[9]	48 (38, 59)[6]	47 (39, 55)[4]	<0.001
Duration of any pancreatitis, median years (IQR)	4 (1, 10)[1]	5 (2, 11)[1]	7 (3, 14)	<0.001
Duration of CP, median years (IQR)	1 (0, 3)[9]	2 (0, 5)[6]	3 (1, 7)[4]	<0.001
AP history, n (%)	296 (79)[13]	122 (87)[9]	133 (91)[4]	0.0067
Etiology, n (%)				
Alcohol	146 (39)	64 (45)	75 (51)	0.047
Idiopathic	153 (41)	61 (43)	44 (30)	
Other	83 (22)	23 (16)	32 (22)	
Pancreatic duct stricture, n (%)	174 (47)[4]	69 (49)	88 (60)	0.033
Pancreatic duct dilation, n (%)	293 (78)[4]	111 (79)	116 (79)	0.83

Table 1. (*continued*)

	No opioids (n, %)	Weak opioids (n, %)	At least 1 strong opioid (n, %)	*P* value
Pancreatic calcifications, n (%)	286 (76)	112 (79)	115 (79)	0.96
Diabetes, n (%)				
Yes	167 (45)	62 (44)	56 (38)	0.28
No	200 (53)	75 (53)	89 (61)	
Not tested	15 (4)	62 (44)	56 (38)	
Exocrine pancreatic dysfunction, n (%)				
Yes	139 (37)	62 (44)	62 (42)	0.091
No	102 (27)	28 (20)	25 (17)	
Not tested	141 (38)	58 (41)	58 (41)	
Endotherapy, n (%)	175 (47)[9]	86 (61)[2]	99 (68)[1]	<0.001
Pancreatic surgery, n (%)	26 (7)[2]	8 (6)[1]	24 (16)	0.0023
Celiac plexus block, n (%)	6 (2)[5]	12 (9)[2]	26 (18)[4]	<0.001
Pain pattern, n (%)				
No pain	83 (22)[8]	14 (10)[7]	3 (2)[5]	<0.001
Intermittent, mild-moderate	96 (26)	19 (13)	14 (10)	
Intermittent, severe	90 (24)	28 (20)	26 (18)	
Constant, mild-moderate	24 (6)	14 (10)	12 (8)	
Constant, severe	81 (22)	66 (47)	91 (62)	

AP, acute pancreatitis; CP, chronic pancreatitis; GED, General Educational Development test; IQR, interquartile range. Superscript numbers denote participants with missing data in this category.

plexus block was more frequent with increasing frequency of opioid use. Finally, in parallel to the data on opioid strength, a clear trend of increasing frequency of opioid use was seen with increasing frequency and severity of pain.

On multivariate analysis by a proportional odds model, independent predictors associated with the frequency of opioid use were pain pattern (OR 1.92–8.52, $P < 0.001$) and prior celiac plexus block (OR 3.42, 95% CI 1.76–6.64) (Table 3.2).

Adjuvant medication use

Neuromodulator use was reported in approximately 40% of participants overall—most commonly using a gabapentinoid (Supplemental Figure 1, http://links.lww.com/CTG/B284). Neuromodulator use increased with increasing strength and frequency of opioid use and was approximately twice as common in participants who used at least 1 strong opioid or scheduled opioids compared with those who did not use opioids (Table 4). Nonsteroidal anti-inflammatory drug use was similar among participants in all groups, as were vitamin and antioxidant use. The proportion of participants who used PERT also increased with increasing strength and frequency of opioid use.

ER visits, hospitalizations, and disability

Increasing strength and frequency of opioid use was also associated with higher rates of reported disability and healthcare use. The number of ER visits in the preceding 12 months and hospital admissions were highest in participants using at least 1 strong opioid and in those using scheduled opioids (Table 4). The proportion of participants with disability due to upper abdominal pain in the setting of pancreatitis or other pancreatitis-related reasons was higher among opioid users, with approximately one-half of the participants using either strong opioids or scheduled opioids reporting disability ($P < 0.01$).

Quality of life

QOL as measured by PROMIS-GH and PROMIS 29 was visibly worse among participants using increasing strength and frequency of opioids (,). Specifically, the physical QOL based on the PROMIS-GH instrument progressively decreased in participants based on strength and frequency of opioids, while the mental QOL was significantly lower among participants who used at least 1 strong opioid and scheduled opioid. *T*-scores for each of the 7 domains from the PROMIS 29 were progressively worse in participants based on strength and frequency of opioids.

DISCUSSION

To our knowledge, this is the most in-depth study to date of opioid use patterns in patients with CP. We found that opioid use is widespread (44%) with half of these patients using at least 1 strong opioid and in a scheduled fashion. The primary determinant of opioid use was the presence, severity, and constancy of pain. We noted that adjunctive treatments, such as neuromodulators, are used frequently in patients with CP, especially in those with concurrent opioid use. Patients with CP using opioids had a high prevalence of disability, healthcare utilization, and poor QOL. These findings together emphasize the need for continued work to develop and test alternative medical and interventional therapies for pain in this disease.

We noted 44% of patients with CP were using opioids at the time of enrollment. Opioid use for the treatment of painful CP in

Table 2. Demographics, socioeconomics, pancreatitis history, and pain patterns in participants by opioid frequency category

	No opioids (n, %)	As needed opioids (n, %)	Scheduled opioids (n, %)	*P* value
	N = 382 (57%)	N = 155 (23%)	N = 136 (20%)	
Male sex	226 (59)	75 (48)	61 (45)	0.055
Age at enrollment, median years (IQR)	56 (45, 65)	53 (41, 63)	53 (44, 60)	0.012
Race, n (%)				
White	313 (82)	130 (84)	114 (84)	0.86
Black	29 (8)	8 (5)	10 (7)	
Other	40 (10)	17 (11)	12 (9)	
Ethnicity, n (%)				
Hispanic	14 (4)	5 (3)	2 (1)	0.49
Non-Hispanic	368 (96)	150 (97)	134 (99)	
Education, n (%)				
Bach. Deg. or Grad. School	211 (56)[8]	82 (55)[7]	54 (43)[9]	0.098
Some training after high school	35 (9)	15 (10)	16 (13)	
High school (GED or less)	128 (34)	51 (34)	57 (45)	
Employment status, n (%)				
Employed	176 (47)[10]	52 (35)[5]	40 (31)[6]	<0.001
Retired	94 (25)	44 (29)	21 (16)	
Unemployed	102 (27)	54 (36)	69 (53)	
Annual household income category, n (%)				
≥$100,000	99 (29)[44]	35 (26)[20]	12 (10)[20]	<0.01
≥$50,000 to < $100,000	86 (25)	43 (32)	34 (29)	
<$50,000	153 (45)	57 (42)	70 (60)	
Marital status, n (%)				
Divorced/separated/widowed	78 (21)[2]	29 (19)[4]	29 (22)[2]	0.79
Married	213 (56)	93 (62)	75 (56)	
Single	89 (23)	29 (19)	30 (22)	
Drinking status, n (%)				
Never	49 (13)[8]	17 (12)[3]	19 (13)[2]	<0.001
Past	217 (58)	98 (70)	112 (77)	
Current	108 (29)	30 (21)	18 (12)	
Tobacco use (n, %)[a]				
Never	130 (35)[7]	40 (26)[3]	24 (18)[2]	<0.001
Past	114 (30)	49 (32)	38 (28)	
Current	131 (35)	63 (41)	72 (54)	
Age at CP diagnosis, median years (IQR)	54 (42, 62)[9]	48 (38, 59)[6]	47 (39, 55)[4]	<0.001
Duration of any pancreatitis, median years (IQR)	4 (1, 10)[1]	5 (2, 11)[1]	7 (3, 14)	<0.001
Duration CP to enrollment, median years (IQR)	1 (0, 3)[9]	2 (0, 5)[6]	3 (1, 7)[4]	<0.001
AP history, n (%)	296 (80)[13]	136 (91)[6]	113 (87)[6]	0.004
Etiology, n (%)				
Alcohol	146 (38)	70 (45)	66 (49)	0.26
Idiopathic	153 (40)	54 (35)	46 (34)	
All others	83 (22)	31 (20)	24 (18)	
Pancreatic duct stricture, n (%)	174 (46)[4]	83 (54)	71 (52)	0.21
Pancreatic duct dilation, n (%)	293 (78)[4]	116 (75)	104 (76)	0.77

Table 2. (*continued*)

	No opioids (n, %)	As needed opioids (n, %)	Scheduled opioids (n, %)	*P* value
Pancreatic calcifications, n (%)	286 (75)	108 (70)	112 (82)	0.041
Diabetes, n (%)				
Yes	167 (44)	58 (37)	58 (43)	0.068
No	200 (52)	83 (54)	75 (55)	
Not tested	15 (4)	14 (9)	3 (2)	
Exocrine pancreatic dysfunction, n (%)				
Yes	139 (36)	53 (34)	66 (49)	0.021
No	102 (27)	35 (23)	16 (12)	
Not tested	141 (37)	67 (43)	54 (40)	
Endotherapy, n (%)	175 (47)[9]	90 (59)[2]	90 (67)[1]	<0.001
Pancreatic surgery, n (%)	26 (7)[2]	14 (9)[1]	17 (13)	0.12
Celiac plexus block, n (%)	6 (2)[5]	13 (9)[3]	23 (17)[2]	<0.001
Pain pattern, n (%)[a]				
No pain	83 (22)[8]	10 (7)[7]	7 (5)[5]	<0.001
Intermittent, mild-moderate	96 (26)	23 (16)	10 (8)	
Intermittent, severe	90 (24)	40 (27)	13 (10)	
Constant, mild-moderate	24 (6)	10 (7)	15 (11)	
Constant, severe	81 (22)	65 (44)	86 (66)	

AP, acute pancreatitis; CP, chronic pancreatitis; GED, General Educational Development test; IQR, interquartile range. Superscript numbers denote participants with missing data in this category.
[a]Included for all those that reported.

the United States has remained high despite concerns from both patients and providers about dependence, addiction, opioid-induced hyperalgesia, and other side effects (20,21). In the past 20 years, the proportion of patients with CP prescribed opioids in the United States has ranged between 49 and 62% (5,12,22). The prevalence is also high in other countries; for example, approximately 54% of Dutch patients enrolled in an observational registry between 2011 and 2018 reported using strong opioids and

Table 3. **Multivariate analysis of independent predictors of opioid use using a proportional odds model, by opioid strength and frequency**

Table 3.1 Results by opioid strength (no opioids, weak opioids, at least 1 strong opioid)

Variable: Category (reference)	Odds ratio	95% Wald confidence limits		*P* value
Prior celiac plexus block: Yes (no)	3.54	1.82	6.87	0.0036
Abdominal pain pattern: Intermittent, mild-moderate (no pain)	1.84	0.97	3.49	<0.001
Abdominal pain pattern: Intermittent, severe (no pain)	3.18	1.73	5.84	
Abdominal pain pattern: Constant, mild-moderate (no pain)	5.38	2.63	11.02	
Abdominal pain pattern: Constant, severe (no pain)	8.32	4.71	14.71	

Table 3.2 Results by opioid frequency (no opioids, as needed opioids, scheduled opioids)

Variable: Category (reference)	Odds ratio	95% Wald confidence limits		*P* value
BL: EPD yes (no)	1.96	1.23	3.12	0.094
Prior celiac plexus block: Yes (no)	3.42	1.76	6.64	0.008
Abdominal pain pattern: Intermittent, mild-moderate (no pain)	1.92	0.98	3.75	<0.001
Abdominal pain pattern: Intermittent, severe (no pain)	2.93	1.56	5.50	
Abdominal pain pattern: Constant, mild-moderate (no pain)	6.54	2.93	14.61	
Abdominal pain pattern: Constant, severe (no pain)	8.52	4.68	15.53	

BL EPD, baseline exocrine pancreatic dysfunction.

Table 4. Medication, healthcare utilization, disability, and global health in patients with chronic pancreatitis by opioid strength and frequency

	No opioids, n (%)	Weak opioids only, n (%)	At least 1 strong opioid, n (%)	*P* value
	N = 382	N = 148	N = 151	
NSAID use	69 (18)[8]	25 (18)[2]	25 (17)[10]	0.8
Neuromodulator use	91 (24)[8]	52 (37)[2]	78 (53)[10]	<0.01
PERT use	159 (43)[8]	81 (57)[2]	99 (68)[10]	<0.01
Vitamin/antioxidant use	175 (47)[9]	71 (50)[6]	64 (44)[12]	0.6
ER visits in past 12 mo	0 (0, 1)[5]	0 (0, 2)[3]	1 (0, 3)[3]	<0.01
Hospital admissions in past 12 mo	1 (0, 2)[5]	1 (0, 3)[2]	1 (0, 3)[3]	<0.01
Hospital admissions in lifetime	2 (1, 6)[5]	5 (2, 10)[2]	6 (3, 18)[3]	<0.01
Disability due to upper abdominal pain or pain from pancreas or pancreatitis/pancreatitis (for reasons other than pain)	73 (20)[8]	46 (33)[2]	66 (45)[10]	<0.01
PROMIS global physical health	45 (40, 51)	40 (35, 48)	37 (32, 42)	<0.01
PROMIS global mental health	48 (44, 53)	46 (40, 53)	41 (36, 48)	<0.01
	No opioids, n (%)	**As needed opioids, n (%)**	**Scheduled opioids, n (%)**	***P* value**
	N = 382	N = 155	N = 136	
NSAID use	69 (19)[11]	31 (20)	19 (14)	0.4
Neuromodulator use	91 (25)[11]	62 (40)	65 (48)	<0.01
PERT use	159 (43)[11]	84 (54)	89 (65)	<0.01
Vitamin/antioxidant use	175 (47)[9]	69 (47)[9]	63 (50)[9]	0.7
ER visits in past 12 mo	0 (0, 1)[5]	0 (0, 3)[3]	1 (0, 3)[3]	<0.01
Hospital admissions in past 12 mo	1 (0, 2)[5]	1 (0, 3)[2]	1 (0, 3)[3]	<0.01
Hospital admissions in lifetime	2 (0, 6)[5]	5 (2, 10)[2]	7 (3, 16)[3]	<0.01
Disability due to upper abdominal pain or pain from pancreas or pancreatitis/pancreatitis (for reasons other than pain)	73 (20)[8]	42 (28)[5]	65 (50)[5]	<0.01
PROMIS global physical health	45 (40, 51)	40 (35, 48)	37 (32, 42)	<0.01
PROMIS global mental health	48 (44, 53)	44 (39, 53)	44 (39, 48)	<0.01

ER, emergency department; NSAID, nonsteroidal anti-inflammatory drug; PERT, pancreatic enzyme replacement therapy; PROMIS, Patient-Reported Outcomes Measurement Information System. Superscript numbers denote participants with missing data in this category.

42% using weak opioids for pain control (10), and 39% of Indian patients in a 2016–2017 prospective study were treated with opioids (23). In light of the fact that few alternatives to opioids have been used efficaciously for pain control, recent literature in the United States has pivoted to focus more on safe opioid prescribing practices in this population and on incremental means to reducing or mitigating opioid use (24).

Neuromodulators, such as gabapentin and pregabalin, have been introduced as adjunctive therapies to address the neuropathic component of pain in CP that is untreated by either opioid or nonsteroidal anti-inflammatory analgesics (1,25). Pregabalin use has been shown in a randomized controlled trial to effectively decrease pain in CP (14). We noted current neuromodulator use in approxiamtely one-third of patients using weak or as-needed opioid and approximately 50% of those using strong or scheduled opioid. Gabapentinoid medications were the most frequently used class of medications. While we evaluated neuromodulator use in this population, the cross-sectional nature of data collection does not allow us to determine their impact on reducing opioid use in this study. Although we did not specifically record what fraction of patients who were currently not on neuromodulators had previously tried and failed such therapy, our result highlights an opportunity for maximizing the use of such agents in the management of pain in CP.

Presence of pain, pain severity, and temporality, as expected, were strong independent predictors for opioid use in our study. Interestingly, approximately 1 in 5 patients who self-reported having no pain in the year preceding enrollment were taking opioids—the rationale for continued use of opioids in these patients is difficult to determine, but it is possible that their lack of pain reflects effective pain control with maintenance opioids. The association of celiac plexus block with opioid use is likely an indirect reflector of pain because celiac block is performed for the treatment of significant pain symptoms. It is important to highlight that the use of opioids was not limited to etiology, and patients who did not have alcohol etiology were equally likely to

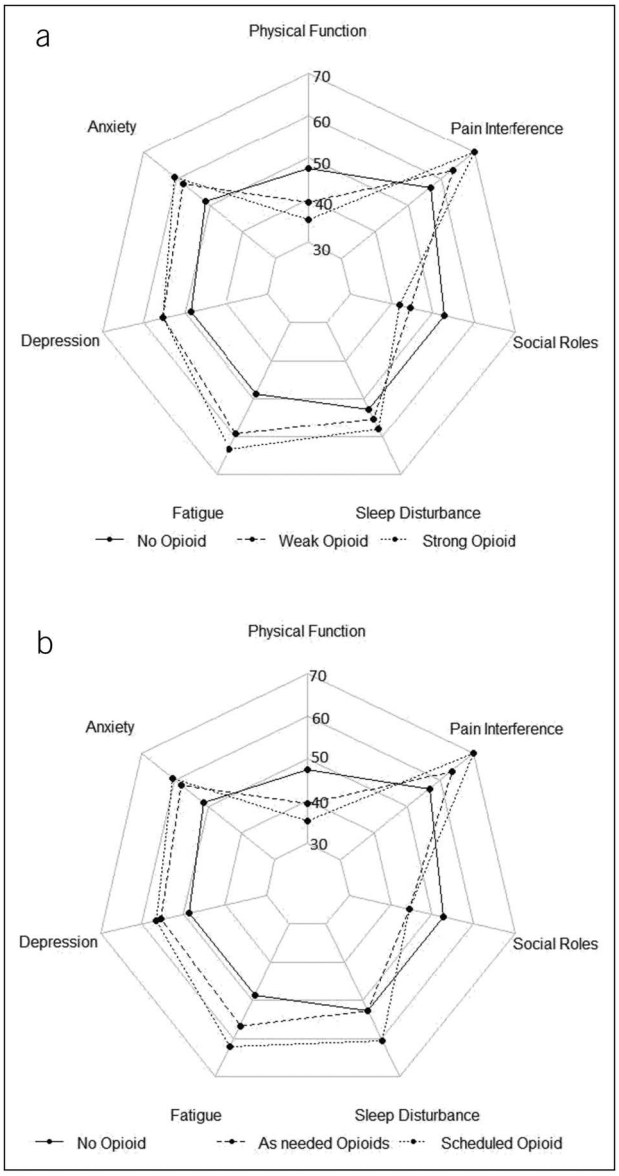

Figure 2. Radar chart of Patient-Reported Outcomes Measurement Information Systems from 29.0 quality-of-life domains in 681 adults with chronic pancreatitis according to opioid potency (**a**) and opioid dosing frequency (**b**). A higher number represents a less favorable outcome for all domains with the exception of physical function and social roles.

be prescribed opioids. Similarly, the duration of pancreatitis was not associated with the use of opioids, suggesting that a longer duration of disease does not necessarily lead to burn out of pain symptoms (11,26). Although many other covariates, such as age, sex, lower socioeconomic status, tobacco use, history of AP, imaging features, and prior endoscopic or surgical therapy, showed significant associations with opioid use in univariate analysis, they were not significant on multivariable analyses.

A previous analysis from the PROspective Evaluation of CP for EpidEmiologic and Translational StuDies study demonstrated that pain severity and pain constancy were the most important determinants of poor QOL in CP (9). In that analysis, we did not control for opioid use in the regression models. The rationale was that drawing causal association between opioid use with QOL would be difficult because patients with more severe pain symptoms tend to use opioids more often, and inclusion of both would lead to a confounding phenomenon. In the current analysis, we found opioid use to be associated with a higher prevalence of disability, healthcare utilization, and poorer QOL. As noted, rather than being causal, these associations are likely an indirect reflection of the increased burden of symptoms, especially pain in these patients.

Our study has many strengths including its large size and a careful in-depth analysis of the strength and frequency of opioid use in a carefully phenotyped CP study population. While the study results are not necessarily unexpected, the rigorous methodology of data collection and analysis provides confident estimates of opioid utilization rates in CP. However, there are limitations that should be acknowledged. A cross-sectional design limits assessment of temporal relationships that are important in clarifying the reasons behind associations (or lack thereof) between opioid use and different clinical and sociodemographic factors. Opioid use data are analyzed as an ordinal variable and could not be assessed as a continuous variable; further evaluation in future studies using oral morphine equivalents as a continuous variable may reveal additional associations. While this is a large study, most of the patients enrolled in the study are cared for clinically in tertiary care pancreatology specialty locations, resulting in likely higher rates of PERT use; more attention to underlying diabetes or exocrine pancreatic insufficiency (EPI); and higher rates of prior invasive interventions such as endotherapy, celiac plexus block, and surgery. Although data on celiac plexus block were recorded, information on other interventional procedures, e.g., transversus abdominal plan blocks, or other techniques that might also be used to treat pain were not collected. Finally, it is acknowledged that these associated risk factors have potential to contribute to a future prediction model for opioid use in CP, although care needs to be taken to identify the need for and purpose of such a model given the inherent complexities and challenge of trying to predict human behavior.

Opioid use in patients with CP is common and associated with increased severity and constancy of pain. Importantly, higher opioid potency and more frequent opioid dosing are associated with multiple unfavorable outcomes, including disability, increased healthcare utilization, and poor QOL. Although it is not possible to draw definitive conclusions on the impact of opioids mitigating or worsening these outcomes because of the cross-sectional study design, there are many important implications from the current observations. These findings first provide a clearer picture of analgesic use patterns in patients with CP that can be used by clinicians caring for these patients in both inpatient and outpatient settings. In addition, we provide rigorous and detailed estimates of analgesic use and their associations with important patient-reported outcomes, findings that emphasize the ongoing need for investigations to further understand the complex interactions between patient factors, disease factors, pain, and pain interventions. These results also provide helpful baseline estimates to guide the planning of future observational and interventional studies of pain in CP.

CONFLICTS OF INTEREST

Guarantor of the article: Anna Evans Phillips, MD, MS.
Specific author contributions: A.E.P.: drafting of manuscript, critical review of manuscript. D.L.C.: critical review of manuscript. S.L.: Statistical analysis and review of manuscript. J.L.S.: critical

review of manuscript. P.A.H.: data interpretation, critical review of manuscript. E.L.F.: critical review of manuscript. S.S.V.: data interpretation, critical review of manuscript. W.E.F.: critical review of manuscript. C.F.: critical review of manuscript. S.P.: critical review of manuscript. W.G.P.: critical review of manuscript. M.D.T.: critical review of manuscript. S.K.V: critical review of manuscript. J.S.: data interpretation, critical review of manuscript. L.L.: Statistical analysis, review of manuscript. D.Y.: Study design and conception, data interpretation, revision and critical review of manuscript.

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Study Highlights

WHAT IS KNOWN

- ✓ Opioids are a mainstay of treatment of chronic pain conditions in the United States, including chronic pancreatitis (CP).

WHAT IS NEW HERE

- ✓ Increasing frequency and severity of pain are associated with increased strength and frequency of opioid use.
- ✓ Patients with CP who are using opioids have higher rates of disability, healthcare utilization, and poorer quality of life compared with patients with CP who do not use opioids.

REFERENCES

1. Drewes AM, Bouwense SAW, Campbell CM, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology 2017;17(5):720–31.
2. Phillips AE, Faghih M, Drewes AM, et al. Psychiatric comorbidity in patients with chronic pancreatitis associates with pain and reduced quality of life. Am J Gastroenterol 2020;115(12):2077–85.
3. 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(10):1386–92.
4. Ramachandran S, Salkar M, Bentley JP, et al. Patterns of long-term prescription opioid use among older adults in the United States: A study of Medicare administrative claims data. Pain Physician 2021;24(1):31–40.
5. Nusrat S, Yadav D, Bielefeldt K. Pain and opioid use in chronic pancreatitis. Pancreas 2012;41(2):264–70.
6. Perito ER, Palermo TM, Pohl JF, et al. Factors associated with frequent opioid use in children with acute recurrent and chronic pancreatitis. J Pediatr Gastroenterol Nutr 2020;70(1):106–14.
7. Issa Y, Kempeneers MA, Bruno MJ, et al. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: The ESCAPE randomized clinical trial. JAMA 2020;323(3):237–47.
8. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med 2007;356(7):676–84.
9. Yadav D, Askew RL, Palermo T, et al. Association of chronic pancreatitis pain features with physical, mental, and social health. Clin Gastroenterol Hepatol 2023;21(7):1781–91.e4.
10. Kempeneers MA, Issa Y, Verdonk RC, et al. Pain patterns in chronic pancreatitis: A nationwide longitudinal cohort study. Gut 2021;70(9):1724–33.
11. Mullady DK, Yadav D, Amann ST, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: A prospective cohort study. Gut 2011;60(1):77–84.
12. 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(12):5493–9.
13. LeBrett WG, Chen FW, Yang L, et al. Increasing rates of opioid prescriptions for gastrointestinal diseases in the United States. Am J Gastroenterol 2021;116(4):796–807.
14. Olesen SS, Bouwense SA, Wilder-Smith OH, et al. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Gastroenterology 2011;141(2):536–43.
15. Griffin NE, Feldman R, Althouse AD, et al. Clinical diagnosis of psychiatric comorbidities, performance of screening tests and pattern of psychotropic medication use in patients with chronic pancreatitis. Pancreatology 2024;24(3):378–83.
16. Yadav D, Park WG, Fogel EL, et al. PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies: Rationale and study design for PROCEED from the consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer. Pancreas 2018;47(10):1229–38.
17. Tirkes T, Shah ZK, Takahashi N, et al. Reporting standards for chronic pancreatitis by using CT, MRI, and MR cholangiopancreatography: The consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer. Radiology 2019;290(1):207–15.
18. Approximate potency of opioids relative to morphine; PO and immediate-release formulations unless stated otherwise. Geneva, 2018. In: WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. Geneva: World Health Organization; Table A6.2. https://www.ncbi.nlm.nih.gov/books/NBK537482/table/appannex6.tab2/. Accessed February 14, 2025.
19. Health Measures. Transforming how health is measured. PROMIS Score cut points (https://www.healthmeasures.net/promis-scoring-manuals). Accessed October 10, 2023.
20. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician 2008;11(2 Suppl):S105–20.
21. Bedene A, Dahan A, Rosendaal FR, et al. Opioid epidemic: Lessons learned and updated recommendations for misuse involving prescription versus non-prescription opioids. Expert Rev Clin Pharmacol 2022;15(9):1081–94.
22. Schwarzenberg SJ, Uc A, Zimmerman B, et al. Chronic pancreatitis: Pediatric and adult cohorts show similarities in disease progress despite different risk factors. J Pediatr Gastroenterol Nutr 2019;68(4):566–73.
23. Sugumar K, Deshpande A. Outcomes of pain management in chronic pancreatitis: Experience from a tertiary care hospital in India. Turk J Surg 2020;36(4):359–67.
24. Shah I, Sheth SG, Kothari DJ. Pain management in chronic pancreatitis incorporating safe opioid practices: Challenge accepted. World J Gastroenterol 2021;27(23):3142–7.
25. Drewes AM, van Veldhuisen CL, Bellin MD, et al. Assessment of pain associated with chronic pancreatitis: An international consensus guideline. Pancreatology 2021;21(7):1256–84.
26. Vipperla K, Kanakis A, Slivka A, et al. Natural course of pain in chronic pancreatitis is independent of disease duration. Pancreatology 2021;21(3):649–57.