Pancreatology 22 (2022) 572–582

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Pain patterns in chronic pancreatitis and chronic primary pain

N.L. Tuck [a, b, c, *], K. Teo [d], L. Kuhlmann [e, f, g], S.S. Olesen [e, g], M. Johnson [h], D.J. Bean [a, c], U. Rashid [a], A.D. MacCormick [d, i], G. Srikumar [i], A.M. Drewes [e, g], J.A. Windsor [d]

[a] The Health and Rehabilitation Research Institute, School of Clinical Sciences, Faculty of Health and Environmental Sciences, Auckland University of Technology (AUT), Auckland, New Zealand
[b] The Auckland Regional Pain Service (TARPS), Auckland District Health Board (ADHB), Auckland, New Zealand
[c] The Pain Management Unit, Department of Anaesthesia and Perioperative Medicine, Waitematā District Health Board (WDHB), Auckland, New Zealand
[d] Department of Surgery, School of Medicine, Faculty of Medical and Health Science, University of Auckland, New Zealand
[e] Centre for Pancreatic Diseases & Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark
[f] Department of Internal Medicine, Randers Regional Hospital, Randers, Denmark
[g] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[h] Department of Psychological Medicine, Faculty of Medical and Health Science, University of Auckland, New Zealand
[i] Department of General Surgery, Counties Manukau District Health Board (CMDHB), Auckland, New Zealand

ARTICLE INFO

Article history:
Received 6 September 2021
Received in revised form
12 April 2022
Accepted 28 April 2022
Available online 2 May 2022

Keywords:
Biopsychosocial model
Chronic pain
Chronic pancreatitis
Pain assessment
Pain phenotypes

ABSTRACT

Background: Abdominal pain is the most distressing symptom of chronic pancreatitis (CP), and current treatments show limited benefit. Pain phenotypes may be more useful than diagnostic categories when planning treatments, and the presence or absence of constant pain in CP may be a useful prognostic indicator.
Aims: This cross-sectional study examined dimensions of pain in CP, compared pain in CP with chronic primary pain (CPP), and assessed whether constant pain in CP is associated with poorer outcomes.
Methods: Patients with CP (N = 91) and CPP (N = 127) completed the Comprehensive Pancreatitis Assessment Tool. Differences in clinical characteristics and pain dimensions were assessed between a) CP and CPP and b) CP patients with constant versus intermittent pain. Latent class regression analysis was performed (N = 192) to group participants based on pain dimensions and clinical characteristics.
Results: Compared to CPP, CP patients had higher quality of life ($p < 0.001$), lower pain severity ($p < 0.001$), and were more likely to use strong opioids ($p < 0.001$). Within CP, constant pain was associated with a stronger response to pain triggers ($p < 0.05$), greater pain spread ($p < 0.01$), greater pain severity, more features of central sensitization, greater pain catastrophising, and lower quality of life compared to intermittent pain (all p values ≤ 0.001). Latent class regression analysis identified three groups, that mapped onto the following patient groups 1) combined CPP and CP-constant, 2) majority CPP, and 3) majority CP-intermittent.
Conclusions: Within CP, constant pain may represent a pain phenotype that corresponds with poorer outcomes. CP patients with constant pain show similarities to some patients with CPP, potentially indicating shared mechanisms.

1. Introduction

Abdominal pain is the most common reason people with chronic pancreatitis (CP) seek medical attention [1]. Pain in CP is difficult to assess [2] and treat [3–5], and can be due to a combination of parenchymal and pancreatic nerve inflammation, ductal obstruction from stones and strictures, peripheral sensitization, and neuroplastic changes in central pain pathways [6–11]. Local pancreatic and extrapancreatic sources of pain, such as pseudocysts, may also contribute [12]. When central pain mechanisms such as sensitization of the central nervous system are involved, patients do not respond as well to endoscopic or surgical interventions [13–17]. Although direct testing for central pain mechanisms is not possible, other observable dimensions of pain,

* Corresponding author. The Health and Rehabilitation Research Institute, School of Clinical Sciencves, Faculty of Health and Environemtnal Sciences, Auckland University of Technology, 90 Akoranga Drive, Northcote, Auckland, 0627, New Zealand.
E-mail address: natalie.tuck@aut.ac.nz (N.L. Tuck).

https://doi.org/10.1016/j.pan.2022.04.016
1424-3903/

or pain phenotypes, may correspond with underlying mechanisms such as central sensitization [4,18–21]. Therefore, identifying pain phenotypes in CP should facilitate a mechanism-based approach to treatment and improve patient outcomes [19,22–24].

When considering pain phenotypes within CP, the typical fluctuations of pain, or the *pattern* of pain intensity has been examined, with studies differentiating between those with and without constant pain [4,25,26]. Compared to intermittent pain, constant pain is associated with poorer outcomes [4,26–29], including greater disability and healthcare utilization regardless of pain intensity [4], higher rates of pain medication use [4,16,26,29], poorer quality of life [4,26], and poorer surgical outcomes [27], and it has been suggested that constant pain in CP may indicate the involvement of central pain mechanisms [17,21].

In addition to pain patterns, pain-specific cognitive and emotional processes [30–33], and the descriptive characteristics of pain [20,23,34,35] also have links to pain mechanisms, and reliably predict outcomes [20,23,30–36]. For example, pain catastrophizing is associated with reduced top-down inhibition [37,38], greater pain intensity, and poorer functional outcomes [39]. Similarly, descriptive characteristics of pain, such as whether pain is described as 'burning' or 'squeezing' (among others) have been associated with distinct pain mechanisms [23] and treatment response [20,35]. Therefore, if constant pain in CP represents a phenotype that corresponds with underlying mechanisms [19,23], then those with and without constant pain are likely to also show systematic differences across other pain dimensions, such as the descriptive characteristics of pain, and pain-related catastrophising.

Another way of understanding pain in CP is to compare the features of CP pain, with chronic pain from other causes. The International Classification of Diseases 11th edition (ICD-11) differentiates between chronic primary pain (CPP), that is not accounted for by another condition, and chronic secondary pain, that is attributed to specific pathology (such as CP) [40,41]. Although both primary and secondary pain can involve overlapping nociplastic (from a sensitized nervous system), neuropathic (from nerve injury), and nociceptive (from tissue injury) processes [42–44], nociplastic pain mechanisms are particularly relevant in CPP [42]. Nociplastic mechanisms have also been implicated in CP [9,11,14,16,21,45,46]. If there are shared nociplastic mechanisms, then some patients with CP may display a similar pain phenotype to patients with CPP, however comparisons between these two patient groups have not been made.

Despite the importance of pain patterns and other pain dimensions in predicting outcomes [4,26,27] and the recognition that mechanism-based approaches to pain assessment and classification are needed [47,48], a review of published pain assessment tools for CP found that most assessed few pain dimensions, with little evidence for scale validity [2]. To address these limitations, the Comprehensive Pain Assessment Tool (COMPAT) was designed to assess a broad range of pain dimensions [2] and prospectively validated [29,49]. Work using the COMPAT has found that it can classify CP patients according to the presence or absence of constant pain, with approximately 40% reporting intermittent pain, and 60% reporting constant pain [2]. However, it is not known how these two patient groups differ across other pain dimensions, or how they compare to patients with CPP.

1.1. Hypotheses and aims

This study aimed to compare dimensions of pain between CP and CPP and assess differences between CP patients with constant pain (CP-constant), intermittent pain (CP-intermittent), and CPP. It was hypothesized that a) CP patients as a whole would differ from CPP across a range of pain dimensions, b) CP-constant and CP-intermittent would systematically differ across pain dimensions, and c) CP-constant would show some similarities to CPP.

2. Methods

2.1. Study design and setting

This three-centre cross-sectional study involved tertiary hospitals in New Zealand (Auckland City Hospital and Middlemore Hospital) and in Denmark (Aalborg University Hospital). In New Zealand ethical approval was obtained from the Health and Disability Ethics Committees, New Zealand (Ref: 16/NTA/27). In Denmark ethical approval was obtained from the local institutional review board (N-20090008).

2.2. Participants

Two patient groups were recruited in New Zealand. The first group were patients that were either a) discharged from Auckland City Hospital or Middlemore Hospital with CP as a diagnosis between 1 March 2010 and 29 February 2016. Other patients who were admitted as inpatients during the study period or who attended Pancreas Clinic appointments were also identified. Patients meeting the following criteria were invited to take part; a) diagnosis of CP based on Mayo criteria [50,51] with a score >4 indicating a high probability of chronic pancreatitis; or b) recurrent acute pancreatitis defined as more than one episode of acute pancreatitis, symptom-free in-between and with no evidence of underlying chronic pancreatitis [52–54]. Participants were excluded if they were under 18 years old or had any of the following co-morbidities; end-stage cancer, HIV, end-stage congestive heart failure, end-stage chronic obstructive pulmonary disease, cirrhosis or renal failure; or if they had acute pancreatitis (single episode); autoimmune pancreatitis; chronic pancreatitis secondary to malignancy; or were non-English speaking.

The second group were patients with CPP recruited from a tertiary-level, interdisciplinary, chronic pain treatment centre, The Auckland Regional Pain Service (TARPS), between June 2016 and March 2019. TARPS sees patients with persistent and disabling pain and delivers interdisciplinary pain self-management treatments. Most patients attending TARPS have pain in multiple sites, with common presentations including musculoskeletal pain conditions, complex regional pain syndrome, visceral pain, pelvic pain, and headaches among others. Patients attending either initial assessments or ongoing treatment at TARPS were approached in waiting areas or at the end of group sessions and invited to take part. Participants were included if they a) had pain for >6 months, b) were over 18 years old, c) were English speaking, and d) did not currently have CP. Although some people attending TARPS do have CP, in each instance these patients were identified through the CP recruitment strategy and were excluded from participating in the CPP arm of the study. Eligible participants from both groups provided informed consent before completing the COMPAT questionnaire.

For the Danish cohort eligible outpatients with CP meeting the above criteria were invited to participate in the study from the outpatient clinic at Aalborg University Hospital from 1st August 2016 to March 31, 2019. The COMPAT questionnaire was translated by a native Danish speaking translator who had in-depth knowledge of the English language, attested by an International English Language Testing System (IELTS) score of 8.5. The back-translation was reviewed to detect any linguistic loss. The Short-form McGill Pain Questionnaire-2 (SF-MPQ-2) forms part of the COMPAT questionnaire, for which a previously validated Danish translation was used [49,55].

2.3. Data collection

Demographics: Age, gender, country, and ethnicity data were extracted from clinical records.

Pain location: Participants in the CPP sample completed the Michigan Body Map (MBM) [56], a diagram of a human figure with 35 location sites marked by text labels (e.g., 'left upper leg') and tick boxes. Participants were instructed to *'check all areas of your body where you have felt persistent or recurrent pain for the past* 3 months *or longer (chronic pain)'*. Pain locations were then grouped into the following categories: 1) head, face, or jaw; 2) neck or shoulder, 3) chest, 4) upper limb, 5) lower limb, 6) pelvis/groin, 7) upper back, 8) lower back, 9) abdomen. See Table 1.

The Comprehensive Pancreatitis Pain Assessment Tool (COMPAT). All other variables were assessed using the COMPAT, an assessment tool developed to assess multidimensional aspects of pain in CP including; pain patterns, hospital admissions, pain duration, pain triggers, pain spread, pain related catastrophizing, quality of life, features of central sensitization, pain descriptors, and medication use [2,29]. The COMPAT was developed in accordance with recommendations from the American Gastroenterological Association, and items were based on a review of published pain assessment tools used in CP [29]. The Revised Short McGill Pain Questionnaire Version-2 (SF-MPQ-2) [57,58] and The Pancreatitis Quality of Life Instrument (PANQOLI) [59] are incorporated into the COMPAT in full. The face validity of the COMPAT was established via expert and patient consensus and CP patients have successfully used COMPAT to describe the dimensions of their pain [29]. Pain patterns assessed in the COMPAT are similar to those examined in previous work, including a recent longitudinal cohort study [26], and have been prospectively validated and associated with descriptive characteristics of pain, frequency of pain flares, and use of opioid medications [29,49]. For this study the COMPAT was adapted for the CPP sample by changing the phrasing from *'pancreatic pain'* or *'chronic pancreatitis'* to *'chronic pain'*. Additionally, subscales documenting surgical and endoscopic interventions for pancreatitis, alcohol, and cigarette use were omitted from the chronic pain version. All subscales in the COMPAT that were analyzed in this study are described below.

Pain patterns: Participants indicated which of the following four pain patterns best represented their experience of pain over the previous 12 months.

- Pattern A - pain flares with no pain in-between
- Pattern B - constant daily pain
- Pattern C - constant pain with added pain flares
- Pattern D - constant pain with episodes of reduced pain. See Fig. 1

Those reporting Pattern A were classified as having intermittent pain only (CP-intermittent), whereas those with patterns B, C, and D, were classified as having constant pain (CP-constant).

Hospital admissions: Participants indicated the number of times they had been admitted to hospital for pain relief in the previous 12 months.

Medication use: Participants listed all medications they were currently taking. These were categorized as strong opioids (fentanyl, methadone, morphine, oxycodone and pethidine) [60], weak opioids (codeine and tramadol) [60], adjuvants analgesics (gabapentinoids, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and anticonvulsants), non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen and scored as binary (yes/no) variables.

Pain triggers: Participants rated the degree to which 12 stimuli led to pain flares on scales from 0 ('Never/Not Applicable') to 5 (Always). Principal axis factoring was used to categorize items into meaningful subscales. Eigen values supported a two-factor solution with the first factor characterized by general triggers (temperature, pressure, touch, weather, exercise, socializing, stress), and the second factor primarily characterized by postprandial triggers (fatty food, any food, fluids, alcohol, smoking). Crohnbach's alpha for the two factors were in the 'good/very good' range (postprandial; $\alpha = 0.80$, general; $\alpha = 0.88$) [61]. Scores for each subscale were computed by adding the items, with total scores for the 'postprandial' subscale ranging from 0 to 18 with higher scores indicating greater sensitivity to postprandial triggers, and the 'general' subscale ranging from 0 to 28, with higher scores indicating greater sensitivity to general triggers.

Descriptive characteristics of pain: The Revised Short McGill Pain Questionnaire Version-2 (SF-MPQ-2) is a brief and well validated measure of pain quality [57,58]. Participants rated the degree to which they experienced 22 qualities of pain and pain related symptoms on Likert scales ranging from '0' ('none') to '10' ('worst possible') over the past 3–6 months. In addition to total scores, the SF-MPQ-2 includes the following subscales; [1]; *continuous pain* (throbbing, cramping, gnawing, aching, heavy, and tender pain); [2]; *intermittent pain* (shooting, stabbing, sharp pain, splitting pain, electric-shock, and piercing pain); [3]; *neuropathic pain* (hot-burning, cold-freezing, pain caused by light touch, itching, tingling or pins and needles, and numbness pain), and [4] *affective pain* (tiring-exhausting, sickening, fearful, and punishing-cruel). Total, and subscale scores are calculated using the mean of the relevant items. In the present study all alpha coefficients were in the 'good/acceptable' to 'very good' range ($\alpha = 0.76–0.91$).

Pain Spread: In addition to their 'typical pancreatic pain/chronic pain' participants indicated the frequency with which they experienced pain in other body sites such as 'head and/or facial pain', 'joint pain', or 'upper and/or lower limb pain'. Each site with at least weekly pain (i.e. 'always', 'more than once a day', 'daily', 'weekly') were given a score of 1, whereas those with less than weekly pain (i.e. 'monthly', 'yearly', 'never') were scored zero. Scores were summed to create a measure of pain spread. Scores ranged from 0 to 7 with higher scores indicating a greater number of body sites with at least weekly pain (in addition to their 'main pancreatic/chronic pain'). Internal consistency was in the good range ($a = 0.79$).

Characteristics of central sensitization: Six items assessed pain characteristics that often occur in the presence of central sensitization [62]. Participants indicated the degree to which they experienced 'stretching (pain)', 'squeezing (pain)', 'night pain', 'night sweats', 'widespread pain', and 'skin colour change at the location of pain' over the past 3–6 months on Likert scales ranging from '0' ('none') to '10' ('worst possible'). Mean scores were computed, with higher scores indicating the presence of more characteristics of central sensitization [62]. Internal consistency was in the moderate range ($\alpha = 0.67$).

Pain related catastrophizing: Participants rated the following 4 items indicative of pain-related catastrophizing on scales from 0 ('Not at all') to 5 ('All the time); 'I try to avoid things that bring on my pain or make it worse', 'It's awful and I feel it overwhelms me', 'I feel I can't stand it anymore', and 'I keep thinking about how much it hurts'. Mean scores were calculated with higher scores indicating greater pain-related catastrophizing. In the present sample Cronbach's alpha was 0.83 indicating 'very good' internal consistency.

Quality of life: The Pancreatitis Quality of Life Instrument (PANQOLI) is an 18 item scale measuring quality of life in CP [59]. Participants rated the degree to which statements assessing change in physical, social, economic, general, and emotional response to living with CP/CPP over the past 4 weeks, compared with the prior

Table 1
Demographics and clinical characteristics with comparisons between chronic pancreatitis (N = 91) and chronic primary pain (N = 127).

	Chronic Pancreatitis (N = 91)		Chronic Primary Pain (N = 127)			
	N*	%/mean (SD)	N	%/mean (SD)	t -test[a]	P value
Country (NZ) %	91	51.6	127	100		
Age in years (M, SD)	91	54.1 (14.7)	124	47.2 (12.6)	3.73	<0.001
Gender (% men)	91	57.1	126	40.5		0.019
Ethnicity (% white)	91	85.7	122	82.8		0.706
Pain Patterns (%)	85		127			
Intermittent		40.7		3.1		<0.001
Constant		59.3		96.9		<0.001
Duration of pain in years (M, SD)	72	10.7 (9.7)	90	7.5 (7.9)	2.26	0.025
Admissions past 12mths (M, SD)	77	1.5 (2.6)	124	0.8 (3.9)	1.53	0.128
Pain Triggers (M, SD)						
General	91	5.8 (5.2)	127	14.3 (6.0)	10.93	<0.001
Postprandial	91	5.9 (4.3)	127	1.6 (2.7)	8.58	<0.001
Pain Spread	88	2.2 (2.2)	125	3.4 (2.1)	3.89	<0.001
Medication Use %	91		127			
Acetaminophen		38.5		26.0		0.055
NSAIDs		16.5		16.5		0.999
Adjuvants		31.9		59.8		<0.001
Weak Opioids		25.3		27.6		0.757
Strong Opioids		38.5		12.6		<0.001
SF-MPQ-2 (M, SD)	91		127			
Continuous		3.6 (2.4)		4.7 (2.2)	3.41	<0.001
Intermittent		3.3 (2.4)		4.7 (2.4)	4.06	<0.001
Affective		4.5 (2.9)		4.5 (2.6)	0.07	0.948
Neuropathic		1.7 (1.4)		4.1 (2.2)	9.77	<0.001
Total		3.2 (1.8)		4.5 (2.0)	4.93	<0.001
Characteristics of sensitization (M, SD)	91	3.2 (2.0)	127	4.0 (2.1)	3.01	0.003
Catastrophizing (M, SD)	91	2.2 (1.2)	127	2.1 (1.0)	1.15	0.252
PANQOLI (M, SD)	66		96			
Physical		21.6 (6.4)		20.4 (3.6)	1.37	0.175
Role		14.5 (3.2)		13.5 (3.1)	2.01	0.046
Emotional		15.6 (6.4)		10.5 (3.7)	5.88	<0.001
Worth		17.0 (5.8)		14.9 (4.1)	2.51	0.014
Total		68.0 (18.3)		58.9 (9.9)	3.69	<0.001
Daily standard drinks (%)	91					
none		49.5				
1-2		15.4				
3-4		6.6				
>5		11.0				
Not stated		17.6				
Endoscopy Procedures (% Yes)	91	63.7				
Dilate		16.5				
Stent		37.4				
Clear Duct		22.0				
Other		25.3				
Lithotripsy		2.2				
Surgical Procedures (% Yes)	91	26.4				
Remove part of pancreas		9.9				
Open duct		5.5				
Open duct & remove part of pancreas		7.7				
Remove whole pancreas		1.1				
Other		8.8				
Pain Locations (% Yes)			127			
Head, face, or jaw				22.8		
Neck or shoulder				46.5		
Chest				10.2		
Upper limb (arm, elbow, wrist, hand)				41.7		
Lower limb (leg, knee, ankle, foot)				59.8		
Pelvis (pelvis, groin, hip, buttocks)				44.9		
Upper Back				23.6		
Lower Back				41.7		
Abdomen				15.0		

*SD; Standard Deviation; *N = number of participants with complete data; [a] Fishers exact test does not have a test statistic; NZ; New Zealand, SF-MPQ-2; Short Form McGill Pain Questionnaire Version 2, PANQOLI; Pancreatitis Quality of Life Instrument.*

4 weeks on scales ranging from '1' 'much less' to '5' 'much more' with scores of '3' indicating 'no change' and '0' for 'not applicable. Total scores range from 0 to 103 with higher scores representing greater quality of life. The PANQOLI has excellent internal reliability ($\alpha = 0.91$) and construct validity [59]. In the present study internal reliability was in the 'very good' range for the overall scale ($\alpha = 0.87$), 'moderate' to 'very good' for the subscales ($\alpha = 0.66–0.89$).

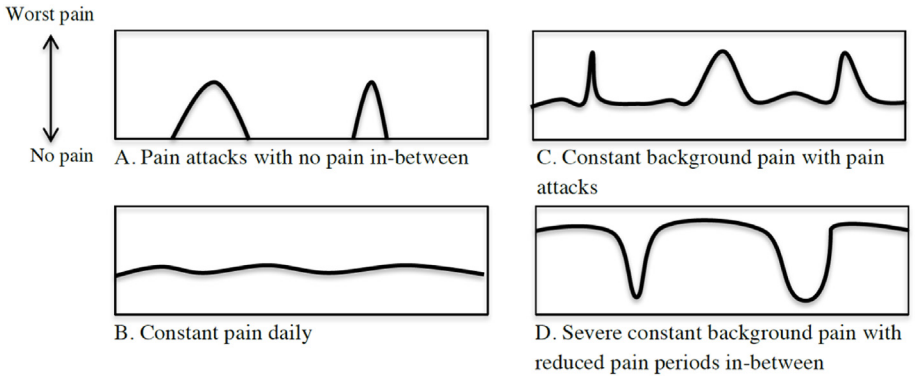

Fig. 1. Pain Patterns; Pattern A comprises the CP-intermittent group, and Patterns B, C, and D comprise the CP-constant group.

Medical Interventions: CP participants were given a list of endoscopic and surgical procedures commonly used to treat CP and were instructed to indicate the number of times they had undergone each procedure.

Alcohol use: CP participants were given details regarding what represents a 'standard drink' with examples, before indicating the number of standard drinks that they had on a typical day. Data were categorized as: 'none'; '1 to 2', '3 to 4', or '≥5'.

2.4. Statistical analyses

Statistical analyses were performed with SPSS Statistics version 27 (IBM Corporation, New York) and R environment for statistical computing version 4.1.1 using package *poLCA* version 1.4.1 [63,64]. Missing data were accounted for as follows. For single item measures missing data were excluded from analyses. For pain triggers missing data were imputed as the mean score for each of the two subscales, and for multi-item scales missing data were imputed as the mean score for each item. The PANQOLI was published in 2016 and was added to the COMPAT questionnaire partway through recruitment, therefore 56 participants (25 with CP and 31 with CPP) did not complete the PANQOLI, so were excluded from the PANQOLI analysis. Six people from the CP sample had missing data for pain patterns, so were excluded from between group analyses. Continuous data were screened for normality by examining histograms and estimates of skewness and kurtosis. Hospital admissions, pain duration, pain spread, and pain triggers were not normally distributed, however because the sample size is sufficiently large to account for deviations from normality [65–67], parametric test results are reported. Descriptive statistics with independent samples *t*-tests or Fisher's exact tests (for categorical variables) were used to examine demographics, pain patterns, clinical characteristics, and pain dimensions between the CP and CPP samples. General linear models controlling for age and/or gender, Fisher-Freeman-Halton Exact Tests (for categorical variables), and Welsh tests (for models that did not meet the homogeneity of variance assumption) were then used to examine differences between the following three groups: CP-constant, CP-intermittent, and CPP for pain duration, hospital admissions, pain dimensions, use of strong opioids, and pain related quality of life. To account for multiple tests, the false discovery rate was controlled at the $\alpha = 0.05$ level using the Benjamin-Hochberg method to calculate critical values using the formula (i/m)Q, where: i = the individual *p*-value's rank, m = total number of tests, Q = the false discovery rate ($\alpha = 0.05$). All *p* values below 0.05 that did not meet the above criteria are indicated (by ^{ns}) in tables. Differences between the CP and CPP groups are reported as percentages or mean ± standard deviation, and results for linear models are reported as percentages or mean ± standard error.

Using complete cases (N = 192), a post-hoc latent class regression analysis was then conducted to identify clusters of participants based on pain dimensions and clinical characteristics. Four models were fitted which allowed one to four latent categories. Akaike's information criterion (AIC) was used to choose the best model. Gender (male/female), race (non-white/white), constant pain (no/yes), pain patten (A, B, C, D), use of strong opioids (no/yes), acetaminophen (no/yes), NSAIDs (no/yes), adjuvant analgesics (no/yes), and any other opioid (no/yes) were included as categorical manifest variables. Age, hospital admissions, postprandial triggers, general triggers, sf-MPQ-2 subscales, features of central sensitization, pain catastrophising, and total number of surgical and endoscopy procedures were included as continuous covariates. Because only cases with complete data could be included, and 56 participants did not complete the PANQOLI, this scale was omitted from latent class analyses. Additionally, given similarities between the measure of pain spread, and the central sensitization metric (which includes an item assessing pain spread), only central sensitization was included in the latent class regression analysis. The relationship between latent classes and manifest variables is reported as conditional probabilities. For example, a probability of 0.54 for class 1 and female indicates that the probability of a class 1 member being female is 0.54. For continuous covariates, the relationship is reported as the change in log-odds of belonging to a latent class compared to the reference class for a unit change in the covariate. A conditional probability was deemed statistically significant if it differed by 2 standard errors from another probability. A continuous covariate was deemed statistically significant if the corresponding change in log odds was larger than 2 standard errors.

3. Results

3.1. Patients, demographics, and clinical features

There were 91 patients with CP (47 from New Zealand and 44 from Denmark) and 127 with CPP. The CP sample were older than the CPP sample (54.1 ± 14.7 vs. 47.2 ± 12.6; $p < 0.001$) and had a higher proportion of men (57.1% vs. 40.5%, $p = 0.019$). The CPP sample reported an average of 3.1 pain sites, with the most common being the lower limb (59.8%), neck or shoulder (46.5%), pelvis (44.9%), and lower back (41.7%). Within the CP group just over a quarter (26.4%) had undergone surgical procedures, and nearly two thirds (63.7%) had undergone endoscopic procedures. See Table 1.

Pain Patterns: There were significant differences in pain patterns between CP and CPP. The CP sample were more likely to have intermittent pain (Pattern A) compared to the CPP sample (40.7% vs 3.1% $p < 0.001$), whereas almost all of the CPP sample (96.9%) reported constant pain (patterns B, C, D) (Table 1 and Fig. 2).

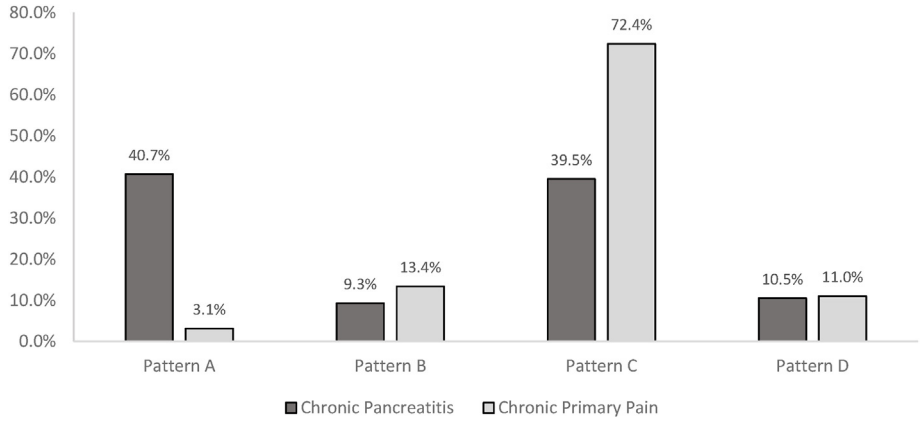

Fig. 2. Pain patterns in chronic pancreatitis and chronic primary pain. A; Pain attacks with no pain in-between, B; Constant daily pain, C; Constant background pain with pain attacks, D; Severe constant background pain with reduced pain periods in-between.

Pain duration: CP had longer pain duration than CPP (10.7 ± 9.7 vs 7.5 ± 7.9, $p = 0.025$) (Table 1). There was also a main effect between the three groups (CP-constant, CP-intermittent, CPP) ($p = 0.046$), with CP-constant having a longer pain duration than CPP (11.6 ± 1.4 vs 7.5 ± 0.9, $p = 0.013$) (Table 2 and Fig. 3).

Hospital admissions: There were no differences between CP and CPP for pain related hospital admissions (Table 1), however there was an overall difference between CP-constant, CP-intermittent and CPP ($p = 0.035$), with CP-constant reporting more pain-related admissions than CPP (2.3 ± 0.5 vs 0.8 ± 0.3, $p = 0.013$). (Table 2 and Fig. 3).

Pain Triggers: CP reported fewer general triggers than CPP (5.8 ± 5.2 vs 14.3 ± 6.0, $p < 0.001$) (Table 1). There was also a significant main effect for general triggers ($p < 0.001$), with CP-intermittent reporting fewer general triggers than CP-constant (4.5 ± 1.0 vs 7.4 ± 0.8, $p = 0.024$), and both CP groups reporting fewer general triggers than CPP (14.0 ± 0.5) both p values < 0.001). Conversely, CP reported more postprandial triggers than CPP (5.9 ± 4.3 vs 1.6 ± 2.7, $p < 0.001$) (Table 1). Again, there was a significant main effect ($p < 0.001$), with CP-constant reporting more postprandial triggers than both CP-intermittent (7.3 ± 0.6 vs 4.6 ± 0.6, $p = 0.007$) and chronic primary pain (1.6 ± 0.2, $p < 0.001$). Table 2, Fig. 3, and Fig. 4.

Pain Spread: CP had less pain spread than CPP (2.2 ± 2.2 vs 3.2 ± 2.1, $p < 0.001$) (Table 1). There was also a significant main effect ($p <$ 0,001), with CP-intermittent reporting less pain spread than both CP-constant (1.6 ± 1.8 vs 2.8 ± 2.3, $p = 0.008$), and CPP (3.4 ± 2.1, $p < 0.001$), whereas CP-constant and CPP did not differ. Table 2 and Fig. 3.

Table 2
Pain characteristics: Linear models comparing CP intermittent, CP constant, and chronic primary pain controlling for age and/or gender as applicable*.

	Main Effects Post Hoc Comparisons														
	CP-Intermittent		CP-Constant		Chronic Pain					CP-Int vs. CP-Constant		CP-Int vs. Chronic Pain		CP-Constant vs. Chronic Pain	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	Omnibus	P value	ES	Difference	P value	Difference	P value	Difference	P value
Age	35	57.5 (2.2)	51	50.5 (1.9)	124	47.2 (1.2)	8.30	<0.001	.07	7.0	0.018	10.3	<0.001	3.3	0.136
Gender (M)	35	60.0%	51	56.9%	126	40.5%	6.44	0.039	.18	3.1%	0.826	19.5%	0.054	16.4%	0.066
Duration (years)	28	9.0 (1.6)	40	11.6 (1.4)	90	7.5 (0.9)	3.15	0.046	.03	2.6	0.230	1.6	0.409	4.1	0.013
Admissions	32	0.6 (0.6)	42	2.3 (0.5)	124	0.8 (0.3)	3.42	0.035	.03	1.7	0.041[ns]	0.1	0.845	1.5	0.013
Pain Triggers															
General[ag]	35	4.5 (1.0)	51	7.4 (0.8)	124	14.0 (0.5)	47.80	<0.001	.32	2.8	0.024	9.5	<0.001	6.6	<0.001
Postprandial[w]	35	4.6 (0.6)	51	7.3 (0.6)	126	1.6 (0.2)	56.28	<0.001	.35	2.7	0.007	3.0	<0.001	5.7	<0.001
Pain Spread	34	1.6 (1.8)	50	2.8 (2.3)	125	3.4 (2.1)	9.89	<0.001	.09	1.3	0.008	1.8	<0.001	0.5	0.127
Strong Opioids (% yes)	35	25.7%	51	49.0%	124	12.6%	25.32	<0.001	.36	23.3%	0.043[ns]	13.1%	0.067	36.4%	<0.001
SF-MPQ-2	35		51		124										
Continuous[a]		2.6 (0.4)		4.5 (0.3)		4.6 (0.2)	10.82	<0.001	.10	1.8	<0.001	2.0	<0.001	0.1	0.668
Intermittent[a]		2.5 (0.4)		4.2 (0.3)		4.6 (0.2)	10.40	<0.001	.09	1.7	0.001	2.1	<0.001	0.4	0.290
Affective[a]		3.2 (0.5)		5.8 (0.4)		4.5 (0.2)	10.06	<0.001	.09	2.6	<0.001	1.3	0.015	1.3	0.003
Neuropathic[w]		1.5 (0.2)		1.8 (0.2)		4.1 (0.2)	40.30	<0.001	.28	0.4	0.434	2.6	<0.001	2.2	<0.001
Total[a]		2.4 (0.3)		3.9 (0.3)		4.4 (0.2)	15.68	<0.001	.13	1.5	<0.001	2.0	<0.001	0.5	0.091
Sensitization[ag]	35	2.3 (0.4)	51	3.9 (0.3)	124	4.0 (0.2)	9.12	<0.001	.08	1.6	<0.001	1.7	<0.001	0.0	0.896
Catastrophizing	35	1.8 (0.2)	51	2.5 (0.1)	127	2.1 (0.1)	6.21	0.002	.06	0.7	0.001	0.3	0.162	0.5	0.006
PANQOLI	26		37		95										
Physical[w]		24.5 (1.0)		18.9 (1.0)		20.5 (0.3)	12.25	<0.001	.14	5.6	<0.001	4.0	0.002	1.6	0.303
Role		15.0 (0.6)		14.1 (0.5)		13.5 (0.3)	2.48	0.087	.03	–	–	–	–	–	–
Emotional[w]		17.9 (1.1)		13.2 (1.0)		10.5 (0.4)	27.48	<0.001	.26	4.7	0.006	7.5	<0.001	2.8	0.035[ns]
Worth[a]		18.2 (0.9)		14.9 (0.7)		15.4 (0.4)	4.42	0.014	.06	4.3	0.008	4.2	0.002	0.1	0.996
Total[w]		76.1 (3.1)		60.5 (2.8)		58.9 (1.0)	18.67	<0.001	.19	15.6	0.001	17.2	<0.001	1.6	0.846

** Covariates are included when significantly associated with the outcome variable and adjusted means are presented; a = controlling for age; g = controlling for gender; w = Welch test with Games-Howell post hoc tests, N = Number of participants with complete data; CP = Chronic Pancreatitis; int = intermittent; SE = standard error; ES = effect size; Admissions = number of hospital admissions for pain in the previous 12 months; SF-MPQ-2 = Short Form McGill Pain Questionnaire Version 2; PANQOLI = Pancreatitis Quality of Life Instrument; ns = no longer significant when controlling for the false discovery rate; difference = mean or percentage difference between comparison groups.*

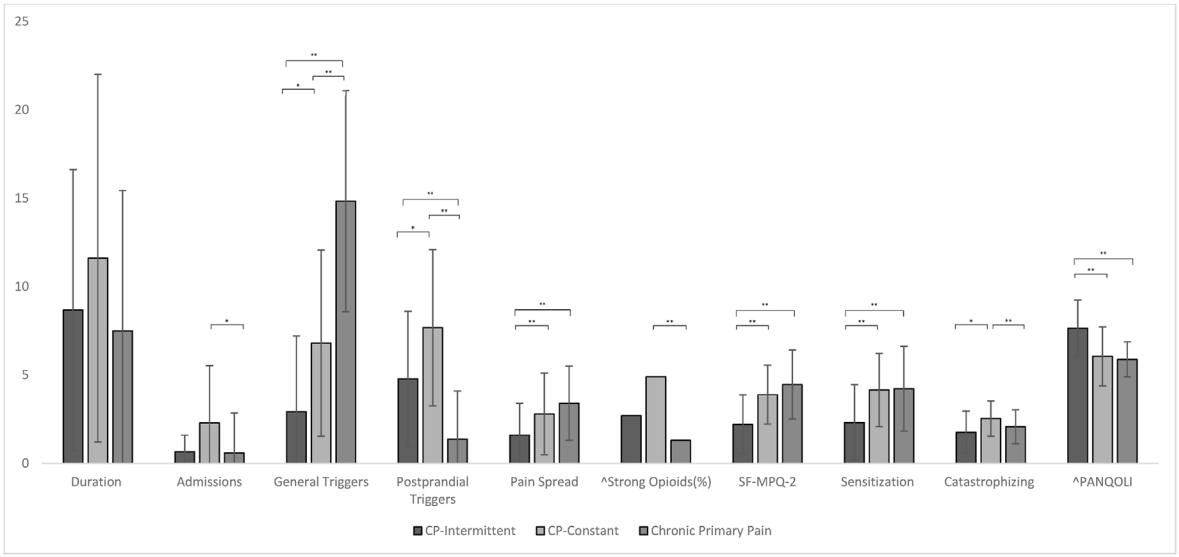

Fig. 3. Pain dimensions by pain patterns and diagnosis.
Note: Values presented are unadjusted mean or percentage scores with standard deviations; ^ percentages and scores are transformed to scores/10 for Opioids and PANQOLI so they can be represented on the same scale; *p < 0.05, **p < 0.01.

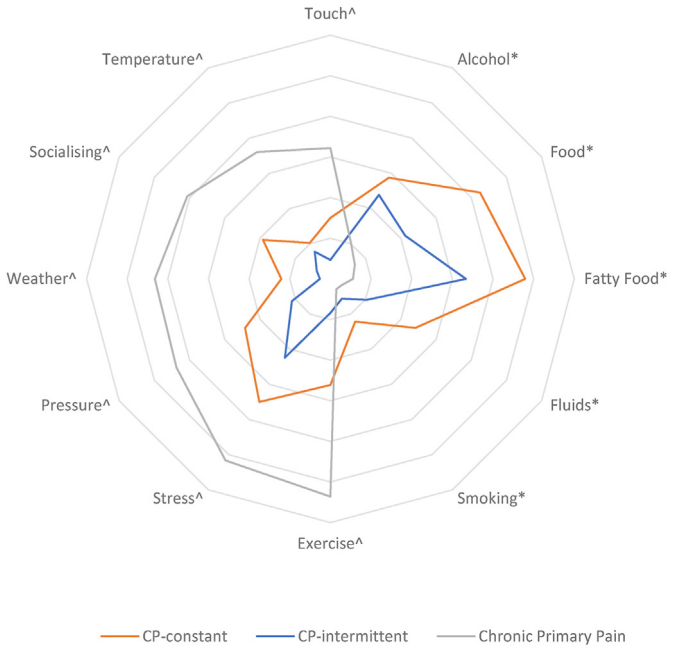

Fig. 4. Radar plots of pain triggering factors by pain phenotype (mean)
^ General triggers subscale; * Postprandial triggers subscale.

Strong Opioids: CP used more strong opioids than CPP (38.5% vs 12.6%, $p < 0.001$) (Table 1). There was also a significant main effect ($p < 0.001$), with CP-constant using more strong opioids than CPP (49.0% vs 12.6%, $p < 0.001$), whereas CP-intermittent and CP-constant did not differ once corrections for the false discovery rate were applied (25.7% vs 49.0%, $p = 0.043$) (Table 2 and Fig. 3).

SF-MPQ-2: The CP group had lower total SF-MPQ-2 scores than CPP (3.2 ± 1.8 vs 4.5 ± 1.9, $p < 0.001$) (Table 1). There was a significant main effect ($p < 0.001$), with CP-intermittent scoring lower than both CP-constant (2.4 ± 0.3 vs 3.9 ± 0.3, $p < 0.001$), and CPP (4.4 ± 0.2, $p < 0.001$), whereas CP-constant and CPP did not differ (Table 2 and Fig. 3).

Characteristics of sensitization: CP had lower self-reported central sensitization than CPP (3.2 ± 2.0 vs 4.0 ± 2.1, $p = 0.003$) (Table 1). There was also a significant main effect ($p < 0.001$), with CP-intermittent scoring lower than both CP-constant (2.3 ± 0.4 vs 3.9 ± 0.3, $p < 0.001$), and CPP (4.0 ± 0.2, $p < 0.001$), whereas CP-constant and CPP did not differ (Table 2 and Fig. 3).

Pain related catastrophizing: Scores for pain-related catastrophizing did not differ between CP and CPP (Table 1). However, there was a significant main effect ($p = 0.002$), with CP-constant scoring higher than both CP-intermittent (2.5 ± 0.1 vs 1.8 ± 0.2, $p = 0.001$) and CPP (2.1 ± 0.1, $p = 0.006$). See Table 2 and Fig. 3.

Quality of life: CP had higher total PANQOLI scores than CPP (68.0 ± 18.3 vs 58.9 ± 9.9, $p < 0.001$) (Table 1). There was also a significant main effect ($p < 0.001$), with CP-intermittent scoring higher than both CP-constant (76.1 ± 3.1 vs 60.5 ± 2.8, $p < 0.001$), and CPP (58.9 ± 1.0, $p < 0.001$), whereas CP-constant and CPP did not differ (Table 2 and Fig. 3).

Latent class model: Based on the minimum Akaike's information criterion, the latent class model with three classes had the best fit (AIC = 1922) compared to models with one (AIC = 2191), two (AIC = 1965) and four latent classes (AIC = 1965). The estimated class population shares were 30% for class 1, 52% for class 2 and 18% for class 3. The parameters obtained from the latent class model are shown in Table 3. Class 1 overlapped with both CPP and CP-constant (29 CPP, 28 CP-constant and 0 CP-intermittent participants), Class 2 overlapped with a diagnosis of CPP (85 CPP, 14 CP-constant and 0 CP-intermittent), and Class 3 overlapped with a diagnosis of CP-intermittent (4 CPP, 0 CP-constant and 32 CP-intermittent). Compared to Classes 2 and 3, Class 1 (combined CPP and CP-constant) were more likely to be using strong opioids, and had more hospital admissions, higher scores on the sf-MPQ-2 *continuous pain* scale and more features of central sensitization, but less postprandial pain, lower scores on the sf-MPQ-2 *neuropathic pain* scale, and lower pain-related catastrophising. See Table 3.

4. Discussion

This study compared the dimensions of pain in CP with CPP from non-pancreatic causes, examined whether pain dimensions

Table 3
Results of latent regression model (N = 192) showing three latent classes. For categorical covariates, conditional item response probabilities ± standard errors are shown, and for continuous covariates the log-odds standard errors for class membership with respect to class 1 are shown.

	Class 1 (30%)		Class 2 (52%)		Class 3 (18%)				
CP-intermittent	*0*		*0*		*32*				
CP-constant	*28*		*14*		*0*				
Chronic Primary Pain	*29*		*85*		*4*				
Manifest variable							**Significant**		
Categorical variables	***Probability***	***SE***	***Probability***	***SE***	***Probability***	***SE***	***1v2***	***1v3***	***2v3***
Sex (F)	0.54	0.08	0.54	0.06	0.44	0.10	ns	ns	ns
Race (White)	0.79	0.06	0.83	0.04	0.86	0.09	ns	ns	ns
Constant Pain	1.00	0.00	1.00	0.00	0.00	0.00	ns	✓	✓
Pattern									
A	0.00	0.00	0.00	0.00	1.00	0.00	ns	✓	✓
B	0.13	0.05	0.14	0.04	0.00	0.00	ns	✓	✓
C	0.66	0.07	0.75	0.05	0.00	0.00	ns	✓	✓
D	0.21	0.06	0.11	0.04	0.00	0.00	ns	✓	✓
Strong Opioids (Y)	0.54	0.08	0.06	0.03	0.25	0.10	✓	✓	ns
Acetaminophen (Y)	0.42	0.08	0.23	0.05	0.31	0.09	✓	ns	ns
NSAID (Y)	0.21	0.06	0.15	0.04	0.11	0.07	ns	ns	ns
Adjuvants (Y)	0.60	0.08	0.56	0.06	0.19	0.10	ns	✓	✓
Other Opioid (Y)	0.21	0.06	0.30	0.06	0.28	0.11	ns	ns	ns
Continuous Variables			***Log odds***	***SE***	***Log odds***	***SE***			
Age (years)			−0.24	0.81	−0.19	0.17	ns	ns	
Hospital admissions			−27.39	7.63	−26.76	7.66	✓	✓	
Triggers									
Postprandial			5.11	1.50	5.13	1.52	✓	✓	
General			1.45	1.32	1.13	1.34	ns	ns	
sf-MPQ-2									
Continuous			−18.33	4.50	−17.36	4.61	✓	✓	
Intermittent			−1.12	2.36	−0.93	2.37	ns	ns	
Affective			5.19	2.38	4.58	2.42	✓	ns	
Neuropathic			15.34	3.41	14.32	3.38	✓	✓	
Central sensitivity			−11.42	4.61	−11.12	4.56	✓	✓	
Pain catastrophising			13.51	5.41	13.20	5.38	✓	✓	
Surgeries			−7.69	10.06	−6.46	9.91	ns	ns	
Endoscopies			−0.20	1.62	0.09	1.57	ns	ns	
Constant			*47.64*	*9.34*	*46.81*	*8.61*	✓	✓	

Note: Log-odds and change in log-odds larger than 2 standard errors are considered statistically significant “ns” stands for not statistically significant.

differed between CP patients with constant versus intermittent pain, and compared pain dimensions in these two CP sub-groups, with a CPP sample. A post hoc latent class regression analysis then identified groups of patients based on pain dimensions and clinical characteristics, and examined whether these latent groups would map onto hypothesized CP phenotypes, characterized by constant versus intermittent pain. Findings revealed that compared to the CPP sample, CP patients were older, had a greater proportion of men, were more likely to report intermittent pain and a longer pain duration. CP patients also reported more postprandial triggers and fewer general triggers, and were more likely to be using strong opioids, but had less severe pain, less pain spread, fewer self-reported features of central sensitization, and higher quality of life than the CPP sample. Although this suggests better outcomes for CP compared to CPP, classifying CP patients according to the presence or absence of constant pain revealed important differences. Consistent with previous work [4,5,17,26–29], CP patients with constant pain had poorer outcomes than those with intermittent pain in terms of vulnerability to triggers, pain severity, pain spread, features of central sensitization, pain related catastrophizing, and quality of life, and did not differ from CPP for total sf-MPQ scores, pain spread, features of central sensitization, and quality of life. Finally, latent class regression analysis revealed three groups in which CPP and CP-intermittent patients formed largely separate clusters, whereas the third cluster contained the majority of CP-constant patients, with approximately 25% of the CPP patients. Compared to the other two groups, this combined class were more likely to be using strong opioids, had more hospitalizations for pain, higher scores for central sensitization and the continuous pain subscale of the sf-MPQ-2, but less postprandial pain, and lower scores on the neuropathic pain subscale of the sf-MPQ-2. Overall, these findings support the hypothesis that CP patients can be meaningfully grouped according to the presence or absence of constant pain, and that CP patients with constant pain may show a similar pain phenotype as some patients with CPP.

4.1. Links between pain patterns and pain mechanisms

Identifying observable pain phenotypes that correspond with underlying mechanisms may improve CP outcomes by facilitating precision medicine [19]. Although it is not possible to directly test for central sensitization, self-reported assessment tools [68,69], and pain descriptors assessed in this study (such as widespread pain and night pain) correspond with nociplastic processes [22,62,70], and findings that CP patients with constant pain scored higher on a self-reported measure of central sensitization than those with intermittent pain is consistent with prior work documenting links between constant pain in CP and nociplastic mechanisms [14,17,21]. Moreover, nociplastic mechanisms are central to CPP, and findings from latent cluster analysis that some CPP patients clustered into the same class as the CP-constant patients, and that these two patient groups did not differ across several important outcomes including quality of life, total sf-MPQ-2 scores, pain spread, and self-reported features of central sensitization, indicates that CPP and CP-constant may share some underlying mechanisms. Finally, evidence that the CP-constant group reported similar pain triggers as CP-intermittent, but a stronger pain response suggests greater allodynia and

hyperalgesia among these patients [6], both of which are hallmarks of central sensitization [22]. Overall, these findings add to the growing body of work indicating that the presence of constant pain in CP may represent an important prognostic indicator that potentially corresponds with nociplastic processes.

4.2. A mechanism-based approach to assessment and treatment of pain in CP

It is increasingly recognized that a mechanism-based approach to the assessment and treatment of pain has advantages over focusing on specific symptoms or disease states [19,71–74], and phenotypes, such as the presence of constant pain, may be more useful than disease-based diagnostic categories when planning treatments [19,23]. One example of a mechanism-based approach to pain assessment is the ACTTION-APS Pain Taxonomy (AAPT) developed by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Network (AACTION) and American Pain Society (APS). This pain taxonomy incorporates biopsychosocial pain mechanisms, and is applicable across disciplines and pain conditions [47,48]. Although AAPT criteria are yet to be developed for CP, tools that assess biopsychosocial dimensions, such as the recently developed COMPAT, enable a mechanism-based approach to classifying pain in CP in a manner that can guide treatment planning.

Although treatments for CP have traditionally focused on reducing pain severity, these have shown limited success [3–5], and it is increasingly evident that the temporal aspects of pain are more closely associated with outcomes. For example, a multicenter prospective study (N = 414) found that patients with constant pain had greater rates of disability, hospitalizations, and medication use, and poorer quality of life than those with intermittent pain, regardless of pain severity. Conversely, compared to those with mild/moderate pain, those with severe pain did not show greater rates of disability, hospitalizations, or medication use [4]. Importantly, constant pain in CP appears to be independent of morphological findings [15,16,26], so rather than treatments that focus on specific pathology, a mechanism-based approach to treating pain in CP is needed [47,48].

When considering treatments for pain in CP, current guidelines recommend behavioral interventions as part of a multidisciplinary approach [12], and similarities between CP-constant and CPP across descriptive characteristics of pain (sf-MPQ-2), pain spread, features of central sensitization, and quality of life suggest that these two patient groups may benefit from a similar therapeutic approach that targets these outcomes. Specifically, interventions that address pain-related catastrophising, general function, activities of daily living, and quality of life may be of benefit [17,19,22,43,75,76], and evidence indicates that cognitive behavioral therapy (CBT) may improve pain-related outcomes in CP [77,78]. Conversely, CP patients with intermittent pain may benefit from earlier and more aggressive treatments to prevent the development of nociplastic mechanisms [4,12,17].

Finally, given some similarities between the CP-constant and CPP groups, significant differences for hospital admissions and use of strong opioids are noteworthy, and likely reflect different treatment models and disease specific traditions. Nociplastic pain does not respond well to surgical interventions [42,79], and is a risk factor for opioid-induced hyperalgesia [80,81]. Current guidelines advise against the use of strong opioids in the treatment of both CPP [82], and chronic non-cancer pain [83]. Given the possibility of nociplastic mechanisms in the CP-constant group, high rates of opioid use in this population may be contributing to the poorer outcomes observed [26,80,83–85].

4.3. Limitations & future directions

The present study has several limitations. First, a priori power analyses were not conducted, instead, patients were recruited over given timeframes. Additionally, no objective tests of pain mechanisms were used, instead, symptoms consistent with central sensitization were self-reported, and because data are cross sectional, temporal inferences cannot be made. Future studies confirming the relationship between pain patterns and central sensitization using quantitative sensory testing as a proxy for nociceptive processing are needed to confirm the relationship between pain patterns and central pain mechanisms. Additionally, data regarding clinical features of the CP group such as dilated pancreatic duct, pancreatic stones, exocrine function were not collected, and although pain patterns have been shown to be independent of specific pathology [26] these details may have helped to further characterize the CP sample. Moreover, the exploratory nature of this study, and the comprehensiveness of the full COMPAT necessitated multiple analyses. To account for this, the false discovery rate was controlled at the $a = 0.05$ level using the Benjamin-Hochberg method, however, this approach may have obscured some between group differences. In particular, differences between CP-intermittent and CP-constant for the use of strong opioids may be clinically important but were no longer significant once corrections were applied. Confirmatory study designs with long term follow-up addressing specific hypotheses regarding the predictive validity of pain patterns, and how pain patterns and other dimensions relate to one another over time are needed. The recently developed short form COMPAT (sf-COMPAT) [49] measures pain patterns and other key outcomes that differed between these two groups and may be a useful tool for identifying pain phenotypes within CP. Finally, the CPP sample were recruited from a single, tertiary-level, hospital-based treatment center and may not represent people with CPP more broadly.

4.4. Conclusion

The present study supports the hypothesis that pain in CP can be considered in terms of pain phenotypes characterized by the presence or absence of constant pain, with constant pain corresponding with poorer outcomes. The single item measure of pain pattern in the COMPAT appears to be an effective way of capturing clinically meaningful information, that may correspond with underlying pain mechanisms and broader psychosocial characteristics. Latent class regression analysis supported the distinction between CP patients with constant versus intermittent pain and grouped the majority of CP-constant patients along with a subgroup of CPP patients into a single class. This, along with similarities between CP-constant and CPP groups in terms of pain characteristics, quality of life, and self-reported features of central sensitization suggest that for some CP patients, a transdiagnostic, biopsychosocial approach to the assessment and treatment of pain may improve outcomes.

Funding sources

None declared.

Conflict of interest

None declared.

References

[1] Olesen SS, Poulsen JL, Drewes AM, Frøkjær JB, Laukkarinen J, Parhiala M, et al. The Scandinavian Baltic Pancreatic Club (SBPC) database: design, rationale and

characterisation of the study cohort. Scand J Gastroenterol 2017;52(8):909–15.
[2] Teo K, Johnson MH, Truter S, Pandanaboyana S, Windsor JA. Pain assessment in chronic pancreatitis: a comparative review of methods. Pancreatology 2016;16(6):931–9.
[3] Olesen SS, Juel J, Nielsen AK, Frøkjær JB, Wilder-Smith OHG, Drewes AM. Pain severity reduces life quality in chronic pancreatitis: implications for design of future outcome trials. Pancreatology 2014;14(6):497–502.
[4] Mullady DK, Yadav D, Amann ST, O'Connell MR, Barmada MM, Elta GH, 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.
[5] Machicado JD, Amann ST, Anderson MA, Abberbock J, Sherman S, Conwell DL, 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(4):633–42.
[6] 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(11):1616–27.
[7] Demir IE, Friess H, Ceyhan GO. Neural plasticity in pancreatitis and pancreatic cancer. Nat Rev Gastroenterol Hepatol 2015;12(11):649–59.
[8] Drewes AM, Olesen AE, Farmer AD, Szigethy E, Rebours V, Olesen SS. Gastrointestinal pain. Nat Rev Dis Prim 2020;6(1).
[9] Olesen SS, Brock C, Krarup AL, Funch–Jensen P, Arendt–Nielsen L, Wilder–Smith OH, et al. Descending inhibitory pain modulation is impaired in patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2010;8(8):724–30.
[10] Frøkjær JB, Bouwense SAW, Olesen SS, Lundager FH, Eskildsen SF, van Goor H, et al. Reduced cortical thickness of brain areas involved in pain processing in patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2012;10(4):434–8.
[11] Olesen SS, Krauss T, Demir IE, Wilder-Smith OH, Ceyhan GO, Pasricha PJ, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: mechanisms and implications for treatment. Pain Reports 2017;2(6).
[12] Drewes AM, Bouwense SAW, Campbell CM, Ceyhan GO, Delhaye M, Demir IE, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology 2017;17(5):720–31.
[13] Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. United European gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J 2017;5(2):153–99.
[14] Poulsen JL, Olesen SS, Malver LP, Frøkjær JB, Drewes AM. Pain and chronic pancreatitis: a complex interplay of multiple mechanisms. World J Gastroenterol 2013;19(42):7282–91.
[15] Frøkjær JB, Olesen SS, Drewes AM. Fibrosis, atrophy, and ductal pathology in chronic pancreatitis are associated with pancreatic function but independent of symptoms. Pancreas 2013;42(7):1182–7.
[16] Wilcox CM, Yadav D, Ye T, Gardner TB, Gelrud A, Sandhu BS, et al. Chronic pancreatitis pain pattern and severity are independent of abdominal imaging findings. Clin Gastroenterol Hepatol 2015;13(3):552–60.
[17] Drewes AM, Kempeneers MA, Andersen DK, Arendt-Nielsen L, Besselink MG, Boermeester MA, et al. Controversies on the endoscopic and surgical management of pain in patients with chronic pancreatitis: pros and cons. Gut 2019;68(8):1343–51.
[18] Mahya F, P Anna E, Larsen I M, Asbjørn D, Vikesh S, Dhiraj Y, et al. Pain modulatory phenotypes differentiate chronic pancreatitis patients with distinct clinical pain profiles. Am J Gastroenterol 2019:s1043. 00.
[19] Edwards RR, Dworkin RH, Turk DC, Angst MS, Dionne R, Freeman R, et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations, vol. 157; 2018. p. 1851–71.
[20] Gammaitoni AR, Smugar SS, Jensen MP, Galer BS, Bolognese JA, Alon A, et al. Predicting response to pregabalin from pretreatment pain quality: clinical applications of the pain quality assessment scale. Pain Med 2013;14(4):526–32.
[21] Faghih M, Phillips AE, Kuhlmann LF, Afghani E, Drewes AM, Yadav D, et al. Pancreatic QST differentiates chronic pancreatitis patients into distinct pain phenotypes independent of psychiatric comorbidities. Clin Gastroenterol Hepatol 2020;(June):1–11.
[22] Nijs J, George SZ, Clauw DJ, Fernández-de-las-Peñas C, Kosek E, Ickmans K, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. Lancet Rheumatol 2021;3(5):e383–92.
[23] Freeman R, Baron R, Bouhassira D, Cabrera J, Emir B. Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs. PAIN® 2014;155(2):367–76.
[24] Attall N, Bouhassira D, Baron R, Dostrovsky J, Dworkin RH, Finnerup N, et al. Assessing symptom profiles in neuropathic pain clinical trials: can it improve outcome? Eur J Pain 2011;15(5):441–3.
[25] Ammann RW. The natural history of alcoholic chronic pancreatitis. Intern Med 2001;40(5):368–75.
[26] Kempeneers MA, Issa Y, Verdonk RC, Bruno M, Fockens P, Van Goor H, et al. Pain patterns in chronic pancreatitis: a nationwide longitudinal cohort study. Gut 2021;70(9):1724–33.
[27] Negi S, Singh A, Chaudhary A. Pain relief after Frey's procedure for chronic pancreatitis. Br J Surg 2010;97(7):1087–95.
[28] Olesen SS, Frandsen LK, Poulsen JL, Vestergaard P, Rasmussen HH, Drewes AM. The prevalence of underweight is increased in chronic pancreatitis outpatients and associates with reduced life quality. Nutrition 2017;43–44:1–7.
[29] Teo K, Johnson MH, Drewes AM, Windsor JA. A comprehensive pain assessment tool (COMPAT) for chronic pancreatitis: development, face validation and pilot evaluation. Pancreatology 2017;17(5):706–19.
[30] Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol 2011;7(4):216.
[31] Rice DA, Kluger MT, McNair PJ, Lewis GN, Somogyi AA, Borotkanics R, et al. Persistent postoperative pain after total knee arthroplasty: a prospective cohort study of potential risk factors. Br J Anaesth 2018;121(4):804–12.
[32] Lewis GN, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. Br J Anaesth 2015;114(4):551–61.
[33] Mankovsky T, Lynch ME, Clark AJ, Sawynok J, Sullivan MJL. Pain catastrophizing predicts poor response to topical analgesics in patients with neuropathic pain. Pain Res Manag 2012;17(1):10–4.
[34] Hochman JR, Davis AM, Elkayam J, Gagliese L, Hawker GA. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. Osteoarthr Cartil 2013;21(9):1236–42.
[35] Carroll IR, Younger JW, Mackey SC. Pain quality predicts lidocaine analgesia among patients with suspected neuropathic pain. Pain Med 2010;11(4):617–21.
[36] Edwards RR, Dworkin RH, Sullivan MD, Turk D, Ajay D. The role of psychosocial processes in the development and maintenance of chronic pain, vol. 17; 2017. p. 1–39.
[37] Galambos A, Szabó E, Nagy Z, Édes AE, Kocsel N, Juhász G, et al. A systematic review of structural and functional MRI studies on pain catastrophizing. J Pain Res 2019;12:1155–78.
[38] Malfliet A, Coppieters I, Van Wilgen P, Kregel J, De Pauw R, Dolphens M, et al. Brain changes associated with cognitive and emotional factors in chronic pain: a systematic review. Eur J Pain (United Kingdom) 2017;21(5):769–86.
[39] Martinez-Calderon J, Jensen MP, Morales-Asencio JM, Luque-Suarez A. Pain catastrophizing and function in individuals with chronic musculoskeletal pain. Clin J Pain 2019;35(3):279–93.
[40] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). Pain 2019;160(1):19–27.
[41] World Health Organisation. ICD-11: international classification of diseases for mortality and morbidity statistics 11th revision.
[42] Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet 2021;397(10289):2098–110.
[43] Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet 2021;397(10289):2082–97.
[44] Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice ASC, et al. Do we need a third mechanistic descriptor for chronic pain states? Pain 2016;157(7):1382–6.
[45] Kuhlmann L, Olesen SS, Grønlund D, Olesen AE, Phillips AE, Faghih M, et al. Patient and disease characteristics associated with sensory testing results in chronic pancreatitis. Clin J Pain 2019;35(9):786–93.
[46] Dimcevski G, Sami SAK, Funch-Jensen P, Le Pera D, Valeriani M, Arendt-Nielsen L, et al. Pain in chronic pancreatitis: the role of reorganization in the central nervous system. Gastroenterology 2007;132(4):1546–56.
[47] Fillingim RB, Bruehl S, Dworkin RH, Dworkin SF, Loeser JD, Turk DC, et al. The ACTTION-American Pain Society Pain Taxonomy (AAPT): an evidence-based and multidimensional approach to classifying chronic pain conditions. J Pain 2014;15(3):241–9.
[48] Dworkin RH, Bruehl S, Fillingim RB, Loeser JD, Terman GW, Turk DC. Multidimensional diagnostic criteria for chronic pain: introduction to the acttion–American pain society pain taxonomy (AAPT). J Pain 2016;17(9):T1–9.
[49] Kuhlmann L, Teo K, Søren O, Phillips AE, M F, Tuck N, et al. Development of the comprehensive pain assessment tool short form for chronic pancreatitis: validity and reliability. Clin Gastroenterol Hepatol 2021.
50 Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP, et al. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology November 1994 Nov;1(5):1481–7.
[51] Raimondo M, Imoto M, DiMagno EP. Rapid endoscopic secretin stimulation test and discrimination of chronic pancreatitis and pancreatic cancer from disease controls. Clin Gastroenterol Hepatol 2003;1(5):397–403.
[52] Testoni PA. Acute recurrent pancreatitis: etiopathogenesis, diagnosis and treatment. World J Gastroenterol 2014;20(45):16891–901.
[53] Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016;14(5):738–46.
[54] Levy MJ, Geenen JE. Idiopathic acute recurrent pancreatitis. Am J Gastroenterol 2001;96(9 SUPPL):2540–55.
[55] Drewes AM, Helweg-Larsen S, Petersen P, Brennum J, Andreasen A, Poulsen LH, et al. McGill Pain Questionnaire translated into Danish: experimental and clinical findings. Clin J Pain 1993;9(2):80–7.
[56] Brummett CM, Bakshi RR, Goesling J, Leung D, Moser SE, Zollars JW, et al. Preliminary validation of the Michigan body map. Pain 2016;157(6):1205–12.
[57] Dworkin RH, Turk DC, Revicki DA, Harding G, Coyne KS, Peirce-Sandner S,

et al. Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). PAIN® 2009;144(1–2):35–42.
[58] Lovejoy TI, Turk DC, Morasco BJ. Evaluation of the psychometric properties of the revised short-form McGill Pain Questionnaire. J Pain 2012;13(12):1250–7.
[59] Wassef W, Dewitt J, McGreevy K, Wilcox M, Whitcomb D, Yadav D, et al. Pancreatitis quality of life instrument: a psychometric evaluation. Am J Gastroenterol 2016;111(8):1177–86.
[60] Health Quality & Safety Commission New Zealand. Atlas of healthcare variation; opioids [Internet], [cited 2021 May 25]. pp. 1–5. Available from: https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/opioids/; 2021.
[61] Bland JM, Altman DG, Bland JM. Statistics notes : the odds ratio. Br Med J 1997;314(7080):572.
[62] Smart KM, Blake C, Staines A, Doody C. Clinical indicators of 'nociceptive','-peripheral neuropathic'and 'central'mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. Man Ther 2010;15(1):80–7.
[63] Linzer DA, Lewis JB. poLCA: an R package for polytomous variable latent class analysis. J Stat Softw 2011;42(10):1–29.
[64] R Core Team. R. A language and environment for statistical computing. 2013.
[65] Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Who is afraid of non-normal data? Choosing between parametric and non-parametric tests: a response. Eur J Endocrinol 2020;183(2):L1–3.
[66] Schmider E, Ziegler M, Danay E, Beyer L, Bühner M. Is it Really Robust?: reinvestigating the robustness of ANOVA against violations of the normal distribution assumption. Methodology 2010;6(4):147–51.
[67] Blanca MJ, Alarcón R, Arnau J, Bono R, Bendayan R. Datos no normales: ¿es el ANOVA una opción válida? Psicothema 2017;29(4):552–7.
[68] Scerbo T, Colasurdo J, Dunn S, Unger J, Nijs J, Cook C. Measurement properties of the central sensitization inventory: a systematic review. Pain Pract 2018;18(4):544–54.
[69] Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, et al. The development and psychometric validation of the Central Sensitization Inventory. Pain Pract 2012;12(4):276–85.
[70] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152(3):S2–15.
[71] Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, et al. Towards a mechanism-based classification of pain? Pain 1998;77(3):227–9.
[72] Vardeh D, Mannion RJ, Woolf CJ. Towards a mechanism-based approach to pain diagnosis, vol. 17; 2017. p. 1–36.
[73] Gewandter JS, Dworkin RH, Turk DC, Farrar JT, Fillingim RB, Gilron I, et al. Research design considerations for chronic pain prevention clinical trials: IMMPACT recommendations. Pain 2015;156(7):1184–97.
[74] Woolf CJ, Max MB. Mechanism-based pain diagnosis: issues for analgesic drug development. Anesthesiology 2001;95(1):241–9.
[75] Clauw DJ, Essex MN, Pitman V, Jones KD. Reframing chronic pain as a disease, not a symptom: rationale and implications for pain management. Postgrad Med 2019;131(3):185–98.
[76] Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, et al. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci 2011;31(20):7540–50.
[77] Yadav D, Palermo TM, Phillips AE, Bellin MD, Conwell DL. Painful chronic pancreatitis - new approaches for evaluation and management. Curr Opin Gastroenterol 2021;37(5):504–11.
[78] Palermo TM, Law EF, Topazian MD, Slack K, Dear BF, Ko YJ, et al. Internet cognitive-behavioral therapy for painful chronic pancreatitis: a pilot feasibility randomized controlled trial. Clin Transl Gastroenterol 2021;12(6):e00373.
[79] Genc H, Nacir B, Duyur Cakit B, Saracoglu M, Erdem HR. The effects of coexisting fibromyalgia syndrome on pain intensity, disability, and treatment outcome in patients with chronic lateral epicondylitis. Pain Med 2012;13(2):270–80.
[80] Ballantyne JC. Opioids for the treatment of chronic pain: mistakes made, lessons learned, and future directions. Anesth Analg 2017;125(5):1769–78.
[81] Goldenberg DL, Clauw DJ, Palmer RE, Clair AG. Opioid use in fibromyalgia A cautionary tale. Mayo Clin Proc 2016;91(5):640–8.
[82] NICE Guideline. Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. 2021.
[83] BPAC. Understanding the role of opioids in chronic non-malignant pain. Best Pract J 2018;(October):1–4.
[84] Drossman D, Szigethy E. The narcotic bowel syndrome: a recent update. Am J Gastroenterol Suppl 2014;2(1):22–30.
[85] Drewes AM, Munkholm P, Simrén M, Breivik H, Kongsgaard UE, Hatlebakk JG, et al. Definition, diagnosis and treatment strategies for opioid-induced bowel dysfunction - recommendations of the Nordic Working Group. Scand J Pain 2016;11:111–22. 2016.