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Natural course of pain in chronic pancreatitis is independent of disease duration

Kishore Vipperla [a], Allison Kanakis [b], Adam Slivka [a], Andrew D. Althouse [c], Randall E. Brand [a], Anna E. Phillips [a], Jennifer Chennat [a], Georgios I. Papachristou [d], Kenneth K. Lee [e], Amer H. Zureikat [e], David C. Whitcomb [a], Dhiraj Yadav [a, *]

[a] Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[b] Division of General Medicine, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[c] Center for Research on Health Care Data Center, Department of Medicine, University of Pittsburgh, PA, USA
[d] Division of Gastroenterology, Hepatology and Nutrition, Ohio State University Wexner Medical Center, Columbus, OH, USA
[e] Division of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

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ABSTRACT

Objectives: Pain *burn-out* during the course of chronic pancreatitis (CP), proposed in the 1980s, remains controversial, and has clinical implications. We aimed to describe the natural course of pain in a well-characterized cohort.

Methods: We constructed the clinical course of 279 C P patients enrolled from 2000 to 2014 in the North American Pancreatitis Studies from UPMC by retrospectively reviewing their medical records (median observation period, 12.4 years). We assessed abdominal pain at different time points, characterized pain pattern (Type A [short-lived pain episodes] or B [persistent pain and/or clusters of recurrent severe pain]) and recorded information on relevant covariates.

Results: Pain at any time, at the end of follow-up, Type A pain pattern or B pain pattern was reported by 89.6%, 46.6%, 34% and 66% patients, respectively. In multivariable analyses, disease duration (time from first diagnosis of pancreatitis to end of observation) did not associate with pain - at last clinical contact (OR, 1.0, 95% CI 0.96–1.03), at NAPS2 enrollment (OR 1.02, 95% CI 0.96–1.07) or Type B pain pattern (OR 1.01, 95% CI 0.97–1.04). Patients needing endoscopic or surgical therapy (97.8 vs. 75.2%, $p < 0.001$) and those with alcohol etiology (94.7 vs. 84.9%, $p = 0.007$) had a higher prevalence of pain. In multivariable analyses, invasive therapy associated with Type B pain and pain at last clinical contact.

Conclusions: Only a subset of CP patients achieve durable pain relief. There is urgent need to develop new strategies to evaluate and manage pain, and to identify predictors of response to pain therapies for CP.

Author contributions

K.V., A.D.A., and D.Y.: study design; A.K., and K.V.: data collection; A.D.A.: data analysis; A.S., G.I.P., R.E.B., D.Y.: patient ascertainment; All authors: data interpretation; K.V., A.D.A. and D.Y.: drafting manuscript; All authors: revising the manuscript and providing important intellectual input and final approval of the version to be published.

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* Corresponding author. Division of Gastroenterology, Hepatology & Nutrition University of Pittsburgh Medical Center, 200 Lothrop Street, M-2, C-wing, Pittsburgh, PA, 15213, USA.
E-mail address: yadavd@upmc.edu (D. Yadav).

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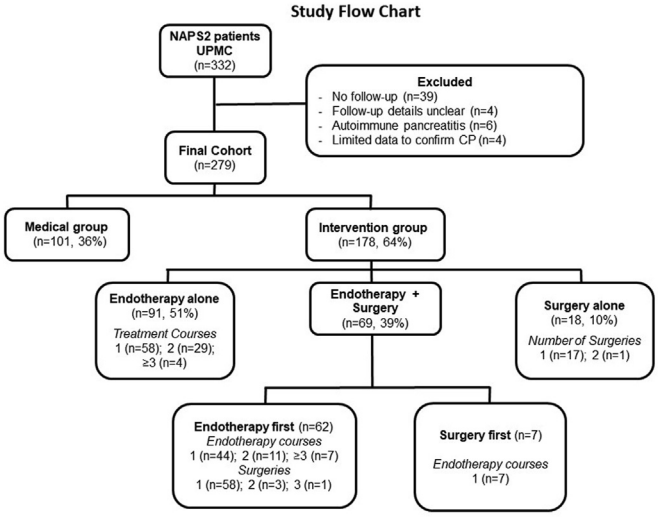

Fig. 1. Study flow chart.

Table 1
Demographics, risk factors, etiology and pancreatitis-related variables and follow-up duration in patients with Chronic Pancreatitis.

	All Patients (n = 279)	Medical Management (n = 101)	Intervention (Endoscopic or Surgical) (n = 178)	p-value
Male – n (%)	150 (53.8)	58 (57.4)	92 (51.7)	0.355
White – n (%)	233 (83.5)	83 (82.2)	150 (84.3)	0.651
Acute Pancreatitis (Ever)	208 (74.6)	64 (63.4)	144 (80.9)	<0.001
Recurrent Acute Pancreatitis	144 (51.6)	42 (41.6)	102 (57.3)	0.012
Age at: (mean ± sd) (yrs)				
First diagnosis of pancreatitis	40.7 ± 18.0	46.3 ± 18.9	37.5 ± 16.7	<0.001
CP diagnosis	45.2 ± 16.1	50.3 ± 16.1	42.4 ± 15.5	<0.001
Last clinical contact	54.3 ± 15.3	58.0 ± 15.4	52.2 ± 15.0	0.002
Smoking status at NAPS2 Enrollment – n (%)				0.034
Never	80 (28.7)	27 (26.7)	53 (29.8)	
Past	57 (20.4)	29 (28.7)	28 (15.7)	
Current	142 (50.9)	45 (44.6)	97 (54.5)	
Etiology – n (%)				0.920
Alcohol	133 (47.7)	48 (47.5)	85 (47.8)	
Idiopathic	89 (31.9)	34 (33.7)	55 (30.9)	
Genetic	31 (11.1)	11 (10.9)	20 (11.2)	
Other	26 (9.3)	8 (7.9)	18 (10.1)	
Present at NAPS2 enrollment – n (%)				
Diabetes	79 (28.3)	29 (28.7)	50 (28.1)	0.911
Exocrine insufficiency	97 (34.8)	37 (36.6)	60 (33.7)	0.621
Calcifications	198 (71.0)	70 (69.3)	128 (71.9)	0.645
Present at last clinical encounter – n (%)				
Diabetes	138 (49.5)	41 (40.6)	97 (54.5)	0.026
Exocrine insufficiency	205 (73.5)	63 (62.4)	142 (79.8)	0.002
Calcifications	209 (74.9)	73 (72.3)	136 (76.4)	0.444
Duration of observation: (median (IQR)) (yrs)				
First diagnosis of pancreatitis to NAPS-2 Enrollment	5.1(2.0–11.2)	3.0(1.3–7.5)	5.7(2.9–12.4)	<0.001
CP diagnosis to last clinical contact	8.8 (5.1–13.4)	7.7 (4.1–11.1)	9.9 (5.7–14.3)	0.002
First diagnosis of pancreatitis to last clinical contact	12.4 (7.8–20.8)	9.7 (5.5–15.7)	13.6 (8.9–21.3)	<0.001

Table 2
Pain, pain medication use and pancreatitis-related hospitalization during the clinical course of patients with Chronic Pancreatitis.

	All Patients (n = 279)	Medical Management (n = 101)	Any Intervention (n = 178)	p-value
Abdominal Pain at any time during clinical course – n (%)	250 (89.6)	76 (75.2)	174 (97.8)	<0.001
Pain at enrollment in NAPS2 – n (%)				0.011
No Pain	56 (20.1)	26 (25.7)	30 (16.9)	
Usually pain free, episodes of mild to moderate pain	27 (9.7)	16 (15.8)	11 (6.2)	
Constant mild to moderate pain	24 (8.6)	10 (9.9)	14 (7.9)	
Usually free of pain but have episodes of severe pain	64 (22.9)	21 (20.8)	43 (24.2)	
Constant mild to moderate pain plus episodes of severe pain	100 (35.8)	25 (24.8)	75 (42.1)	
Constant severe pain	8 (2.9)	3 (3.0)	5 (2.8)	
Pain Pattern during clinical course*				<0.001
- n (%)				
Type A	85 (34.0)	41 (53.9)	44 (25.3)	
Type B	165 (66.0)	35 (46.1)	130 (74.7)	
Ever used narcotics for pain as outpatient* - n (%)	189 (75.6)	46 (60.5)	143 (82.2)	<0.001
Pancreatitis-related hospitalizations during clinical course – median (IQR)	6 (1–15)	2 (0–9)	7 (3–20)	<0.001
Pain at last contact – n (%)	130 (46.6)	26 (25.7)	104 (58.4)	<0.001

* Calculated among those who had pain.

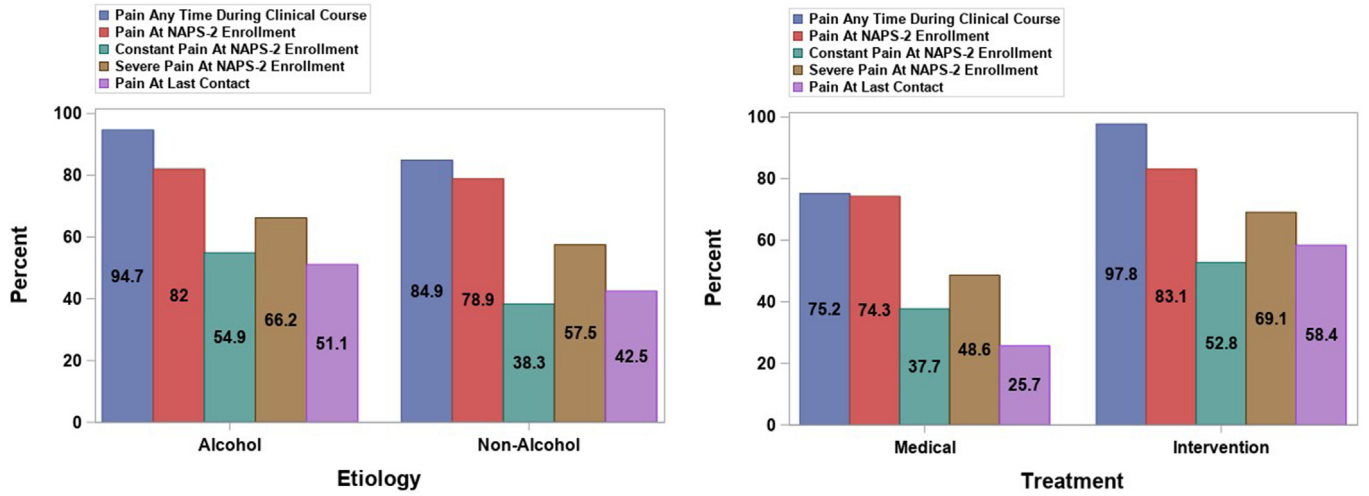

Fig. 2. Prevalence of pain at different time points during the disease course in patients with chronic pancreatitis, based on – a) etiology, b) receiving medical or invasive treatment.

Table 3
Primary indications for endoscopic therapy and surgeries during the clinical course of patients with Chronic Pancreatitis.

First Intervention		
Indication[b]	Endotherapy (n = 153)	Surgery (n = 25)
Pain	94 (61.4)	13 (52)
Drainage	2 (1.3)	5 (20)
Jaundice	20 (13)	3 (12)
RAP	16 (10.4)	2 (8)
Others (pancreatic duct leak, fistulas)	5 (3.3)	1 (4)
Unknown[a]	16 (10.4)	1 (4)
Second Intervention		
Indication[b]	Endotherapy (n = 49)	Surgery (n = 50)
Pain	31 (63.3)	38 (76)
Drainage	1 (2)	3 (6)
Jaundice	10 (20.4)	6 (12)
Recurrent acute pancreatitis	7 (14.3)	2 (4)
Others (high risk of cancer)	0 (0) or N/A	1 (2)

[a] Details of the procedure were 'unknown' when performed at some out-side facilities or prior to implementation of electronic health records.
[b] Primary indication.

Table 4
Details of endoscopic therapy and surgeries performed during the clinical course of patients with chronic pancreatitis.

Endotherapy		
	First Endotherapy course (n = 153)	Second Endotherapy course (n = 49)
Biliary		
Biliary sphincterotomy	28	7
Biliary Stent	30	10
Pancreatic		
PD sphincterotomy	97	4
PD stone extraction	54	18
PD stent	112	35
ESWL	8	1
Drainage		
Cystgastrostomy	2	2
Unknown[a]	24	3
Surgery		
	First Surgery (n = 25)	Second Surgery (n = 50)
Resection		
Whipple's	2	8
TPIAT	0	7
Distal Pancreatectomy	5	7
Drainage		
Peustow	5	5
Hepaticojejunostomy	5	8
Cystgastrostomy	2	2

(*continued on next page*)

Table 4 (*continued*)

Endotherapy		
	First Endotherapy course (n = 153)	Second Endotherapy course (n = 49)
Duval	1	0
Resection & Drainage		
Frey	4	6
Berne	0	5
Beger	0	1
Unknown[a]	1	1

PD- Pancreatic duct; ESWL- Extracorporeal shock wave lithotripsy, TPIAT- Total pancreatectomy and islet auto transplantation.
Endoscopic treatment often consisted of a combination of interventions over multiple sessions.
[a] Details of the procedure were 'unknown' when performed at some out-side facilities or before implementation of electronic health records.

Table 5
Multivariable associations with pain at different time points during the clinical course of patients with Chronic Pancreatitis.

	Events	At Risk	Odds Ratio	95% CI	p-Value
Pain at End of Study	130	279			
Age at first diagnosis of pancreatitis			0.97	(0.94, 0.99)	0.001
Duration of observation from first diagnosis of pancreatitis to last clinical contact			1.00	(0.96, 1.03)	0.871
Alcohol etiology (vs. other etiology)			1.75	(0.94, 3.21)	0.074
Intervention (vs. medical management)			3.23	(1.80, 5.75)	<.0001
Pain at NAPS-2 Enrollment	223	279			
Age at first diagnosis of pancreatitis			0.98	(0.96, 1.01)	0.148
Duration of observation from first diagnosis of pancreatitis to NAPS2 enrollment			1.02	(0.96, 1.07)	0.513
Alcohol etiology (vs. other etiology)			1.16	(0.58, 2.31)	0.663
Intervention (vs. medical management)			1.49	(0.78, 2.83)	0.222
Severe Pain at NAPS2 Enrollment	172	279			
Age at first diagnosis of pancreatitis			0.99	(0.97, 1.00)	0.145
Duration of observation from first diagnosis of pancreatitis to NAPS2 enrollment			1.03	(0.98, 1.07)	0.203
Alcohol etiology (vs. other etiology)			1.72	(0.95, 3.10)	0.071
Intervention (vs. medical management)			2.12	(1.23, 3.64)	0.007
Constant Pain at NAPS2 Enrollment	159	279			
Age at first diagnosis of pancreatitis			0.98	(0.96, 1.00)	0.059
Duration of observation from first diagnosis of pancreatitis to NAPS2 enrollment			0.99	(0.95, 1.03)	0.669
Alcohol etiology (vs. other etiology)			1.49	(0.85, 2.62)	0.161
Intervention (vs. medical management)			1.14	(0.67, 1.92)	0.637
Type B Pain Pattern	132	250			
Age at first diagnosis of pancreatitis			0.99	(0.96, 1.00)	0.147
Duration of observation from first diagnosis of pancreatitis to last clinical contact			1.01	(0.97, 1.04)	0.640
Alcohol etiology (vs. other etiology)			2.05	(1.11, 3.77)	0.021
Intervention (vs. medical management)			2.02	(1.10, 3.63)	0.020

Other covariates in regression analyses were sex, race, diabetes, exocrine insufficiency, calcifications.

Declaration of competing interest

DCW serves as a consultant for AbbVie, Regeneron, Ariel Precision Medicine, is a cofounder of Ariel Precision Medicine and may have equity. Other authors report no conflict.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.01.020.

Introduction

Chronic pancreatitis (CP) is defined as persistent, pathologic fibro-inflammatory response in the pancreas to injury or stress, occurring in subjects with an underlying predisposition. Patients have varying combination of clinical features, including abdominal pain, acute pancreatitis (AP), loss of function such as exocrine and endocrine insufficiency, morphological abnormalities such as atrophy, ductal abnormalities, and calcifications [1,2].

Abdominal pain is one of the cardinal features of chronic pancreatitis (CP) [3–6], and the primary driver of resource utilization and poor quality of life [6–8]. There is high degree of variability in the presence, severity and temporal nature of pain [6,9]. Patients may have periods of symptom exacerbation, interspersed between quiescent phases of no or little pain.

Abdominal pain in CP is attributed to multiple mechanisms, such as pancreatic ductal hypertension from obstructive stones and/or strictures, inflammation related to AP, local complications, e.g. pseudocysts, and sensitization of peripheral and/or central nociceptive pathways [10]. Endoscopic and/or surgical intervention is performed in patients with pain and evidence of ductal obstruction or local complications [11]. In a subset with debilitating symptoms, a total pancreatectomy with islet autotransplantation (TPIAT) is offered as the last resort [12]. However, response to therapies, including invasive treatments, remains unpredictable [13].

Ammann et al. described pain *burn-out* based on observations in

a prospectively followed cohort. In a study of 145 patients with alcoholic CP, they observed pain relief in 85% at a median of 4.5 years from disease onset. Pain relief correlated with disease duration, loss of pancreatic function and development of calcifications [3]. Reconstructing the clinical course in 207 patients with alcoholic CP in a follow-up study, they identified two distinct pain patterns [14]: type A (short-lived pain episodes with long pain-free intervals lasting months to years) or type B (prolonged periods of either persistent or clusters of recurrent severe pain episodes). Patients with type A pain were managed medically. Type B pain was attributed to the presence of local complications, needing a surgical intervention to achieve pain relief. Persistent pain relief, defined by pain-free interval of $\geq$2 years, was observed at a similar rate in both surgical and non-surgical groups, ~50% within 6 years and >80% within 10 year from disease onset. Subsequent studies, including our own, have questioned this *universal* phenomenon of pain burn out [4,6,15]. In addition to confirming these findings, a recent study from the Dutch Pancreatitis Study Group also documented the temporal nature of fluctuations in pain pattern during longitudinal follow-up [16].

A better understanding of the pain is critical to appropriately counsel patients and choose treatment strategies. In this study, we aim to describe the natural course of pain in a well-phenotyped cohort with specific attention to disease duration, effect of endoscopic or surgical interventions, and pancreatic function in the modern era of CP management. We accomplished this by retrospectively evaluating the clinical course of CP patients who were enrolled in the North American Pancreatitis Studies (NAPS2) from the University of Pittsburgh Medical Center (UPMC).

Materials and methods

NAPS2

NAPS2 is a series of three studies (NAPS2 Original, NAPS2-continuation and validation study [NAPS2-CV], and NAPS2 Ancillary Study [NAPS2-AS]) which recruited 1195 patients with CP from 27 U. S. sites from 2000 to 2014. The University of Pittsburgh was the coordinating center. The diagnosis of CP was based on presence of definitive changes on cross-sectional imaging, endoscopic ultrasound (EUS), or histology. Institutional Review Board at each of the participating institutions approved the protocol and all subjects signed an informed consent before any study procedures were performed. NAPS2 methodology has been published previously [2,9,17].

Study cohort

We limited the current study to NAPS2 patients enrolled from the UPMC. For the NAPS2-CV study, in addition to previously reported data [18], an additional 25 patients recruited from UPMC were included in the current analysis. In addition to d data data reported from the NAPS2 database, detailed review of medical records was performed as described below.

NAPS2 data

For the purposes of this study, information on demographics, self-reported smoking status and alcohol consumption, presence and pattern of pain, history of prior AP or RAP, age at first diagnosis of pancreatitis, pancreatitis-related hospitalizations, physician-determined etiology, presence of diabetes, exocrine insufficiency, calcifications on imaging, medical therapies (e.g. pancreatic enzyme replacement therapy [PERT]), and invasive treatment (endotherapy or surgery) until the time of enrollment was retrieved from the NAPS2 database. Patients who reported pain identified the pattern from one of five predefined categories – response to these were used to classify severity (mild-moderate vs. severe) and temporal nature (intermittent vs. constant) of pain [9,17].

Medical record review

UPMC has an electronic health record (EHR) system for both inpatient and outpatient care for hospitals and physician offices. UPMC also has a medical record data repository that began in 1989 and is used to populate the EHR with data that was electronically collected prior to the EHR implementation at each hospital. This type of integration allows for sufficient availability of medical records spanning ten, sometimes twenty years [19]. UPMC began using Epicare (EPIC Systems, Madison WI) for outpatient primary care clinics at UPMC Presbyterian in 2001 and has continued the rollout to all primary care and specialist physician offices throughout UPMC. The inpatient EHR system (Cerner Millennium, Cerner Corp, Kansas City, MO) was introduced in 2000. Both EHR systems permit the storage of digitized scans of paper medical records from outside facilities to ensure that all point of care documentation is available. Relevant to our study, most patients had longitudinal outpatient follow-up in the pancreas clinic of the Digestive Disorders Center, UPMC Presbyterian where Epicare was implemented in 2006.

A detailed review of available inpatient and outpatient EHRs in the UPMC system was performed by two investigators (KV, AK) under the guidance of the senior author (DY) to complement data collected at NAPS2 enrollment. This included relevant information that was not included in NAPS2 database, e.g. pain at any time prior to enrollment, details of endoscopic therapy or surgery, and information after NAPS2 enrollment.

We recorded information whether a patient had abdominal pain at any time during the clinical course prior to, at NAPS2 enrollment, during the follow-up period, and at the last clinical encounter until November 2017 from which information on the status of pain could be obtained. The duration of observation was calculated from the age at first diagnosis of AP or CP, and from the age at CP diagnosis to the age at last clinical encounter. For each patient, we recorded performance of endotherapy or surgery and their details, e.g. age, indication, and the type intervention. We recorded information on outpatient usage of narcotic and/or non-narcotic analgesic medications (e.g. pain modulators), and pain clinic visits, when available. Unlike the Ammann study, we did not exclude patients with narcotic dependence in this study, as making this determination was not possible in a retrospective study [14]. Finally, we collected information on RAP, pancreatitis-related hospitalizations (defined as admissions for AP, CP, pancreatitis-related pain or complications), diabetes, treatment with PERT, and calcifications on imaging studies during the observation period. Information on exocrine insufficiency at NAPS2 enrollment was obtained from the NAPS2 database. Since, few patients underwent formal testing during follow-up, presence of exocrine insufficiency during follow-up was often based on physician impression of clinical symptoms and/or signs.

For each patient with abdominal pain, we reviewed records to construct pattern of pain (type A or B) during the clinical course, using the same definitions as Ammann et al. [14]. Often, this information was based on review of physician notes from the pancreas clinic. Type A only pain category included patients who had one or more episodes of abdominal pain with intervening pain free intervals. Type B pain category included patients with constant pain lasting for weeks, months or years with or without intervening pain free intervals or episodes of Type A pain. Patients may have responded partially or completely to endoscopic or surgical

interventions, and a subset may have developed a new pain pattern during subsequent follow-up. We have previously reported on the efficacy of endoscopic and/or surgical in a subset of this cohort [20]. Since pain pattern during the clinical course was our primary aim, we did not record or present information on pain relief with individual courses of endotherapy or surgical interventions in our analysis.

Statistical analyses

Continuous variables are presented as mean (standard deviation, SD) or median (interquartile range, IQR) and compared between groups using Kruskal-Wallis test; categorical variables are presented as n (%) and compared between groups using chi-squared tests. Multivariable logistic regression was used to examine associations between covariates of interest and a selection of pain outcomes. Disease duration, etiology (alcohol vs. other) and treatment (medical vs. intervention) were covariates of specific interest. Other covariates included sex, race (white vs. others), presence of diabetes, exocrine insufficiency and calcifications. For analyses using pain outcomes at NAPS-2 enrollment (any pain, severe pain, or constant pain) only covariates available at the time of NAPS-2 enrollment were included; for analyses using pain outcomes through the last clinical contact (any pain, pain pattern), covariates were updated to reflect their final status (e.g. diabetes, calcifications, exocrine pancreatic insufficiency) at the last clinical contact. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Study cohort

Of the 332 patients enrolled from UPMC in the NAPS2 studies, 279 formed the final cohort for the current study (Fig. 1). The majority of patients were White (83.5%) and just over half were male (53.8%). About three-fourths (74.6%) had at least one attack of AP, and half had RAP (51.6%). Mean age at the first diagnosis of pancreatitis was 40.7 ± 18 years and for CP was 45.2 ± 16.1 years. Smoking was highly prevalent with 71.3% ever smokers, 50.9% current smokers at NAPS2 enrollment, and 35% heavy smokers (≥1 packs/day). Roughly half (47.7%) of patients had alcohol etiology, followed by idiopathic CP (31.9%). Diabetes was diagnosed in 49.5% and three-fourths (73.5%) had exocrine insufficiency at the time of last contact. The median observation period from the first diagnosis of pancreatitis to the last clinical encounter was close 12.4 years. About one-thirds (36.2%) were managed by medical therapy alone while 178 (63.8%) underwent one or more endoscopic and/or surgical interventions during the clinical course (Table 1 and Fig. 1).

Abdominal pain, pain pattern, pain medication use and hospitalizations

Overall, abdominal pain at some point during the clinical course was observed in 89.6% patients. At the time of NAPS2 enrollment, 20.1% patients reported no pain in the preceding year, 61.8% reported severe pain, and 47.3% constant pain. At the last clinical encounter, presence of pain was recorded in 46.6% patients (Table 2).

Overall, among the 250 patients who ever reported pain, about one-thirds (34%) had only Type A pain, while 66% reported Type B pain during their clinical course. Three-fourths (75.6%) of patients with pain received one or more prescription for narcotic medication during the clinical course. Documentation for the use of neuromodulating agents for pain management and pain clinic visits was recorded in at least 53 (21.1%) and 60 (24%) patients, respectively. There was a high burden of resource utilization as reflected by a median of 6 (IQR 1–15) pancreatitis-related hospital admissions during the clinical course.

Alcohol etiology and its relationship with pain-related variables

When compared with patients with non-alcohol etiology, those with alcoholic CP were more likely to be male, of non-white race and smokers. Alcoholic CP patients were also more likely to have AP and RAP, and were on an average 4–5 years older at first diagnosis of any pancreatitis and CP. The prevalence of calcifications in patients with alcoholic CP was higher than those with non-alcoholic etiologies, but the prevalence of diabetes, exocrine insufficiency and the duration of follow-up was similar in the two groups (Supplementary Table 1).

Patients with alcohol etiology (vs. other etiology) were significantly more likely to have pain ever (94.7% vs. 84.9%, 0.007) and Type B pain (69.2% vs. 50%, $p = 0.001$), but the prevalence of pain at the end of the observation period was similar irrespective of alcohol etiology (51.1% vs. 42.5%, $p = 0.53$) (Fig. 2a). Patients with alcoholic CP who ever had pain were significantly more likely to require narcotics (78.5% vs. 72.5%, $p = 0.022$), neuromodulating agent (27.8% vs. 15.3%, $p = 0.048$) and pain clinic appointment (29.4% vs. 18.5%, $p = 0.026$) (Supplementary Table 2).

Among 142 current smokers at the time of NAPS2 enrollment, at the end of the observation period, 122 (85.9%) were still smoking at the last clinical encounter (91/100 with alcohol etiology, 31/42 with non-alcohol etiology). Of the 51 current drinkers at the time of NAPS2 enrollment, 27 (52.9%) were still drinking at the last clinical encounter (21/30 with alcohol etiology, 6/21 with non-alcohol etiology).

Medical management versus intervention groups and its relationship to pain-related variables

Patients who were managed medically were similar in distribution for sex, race and etiology of CP, and the prevalence of calcifications when compared with those who needed one or more interventions (Table 1). Patients in the intervention group were significantly more like to have AP or RAP during their clinical course, and their diagnosis of AP or CP was made at a younger age (by almost 8 years). They were also significantly more likely to have diabetes or exocrine insufficiency during their clinical course. The duration of observation in the intervention group on average was 4 years longer than the medically managed group.

Virtually all patients who underwent an intervention had abdominal pain at some point of time during their clinical course; this was significantly greater when compared with patients managed medically (75.2%) (Table 2). At the time of enrollment into the NAPS2 study, patients in the intervention group were significantly more likely to report severe pain (69.1% vs. 48.6%) and constant pain (52.8% vs. 37.7%) when compared with the medically managed group. Similarly, a significantly greater proportion of patients in the intervention group had Type B pain (74.7% vs. 46.1%), while those medically managed had more Type A pain (53.9% vs. 25.3%). At the end of the observation period, over half (~60%) patients in the intervention group still had abdominal pain when compared with only one-fourths (25.7%) in the medically managed group (Fig. 2b).

Patients needing an intervention were significantly more likely to receive a prescription of narcotic medication (80.2% vs. 60.5%, $p < 0.001$), neuromodulating agent (23.6% vs. 11.9%, $p = 0.017$), pain clinic appointment (27.5% vs. 10.9%, $p = 0.001$) and pancreatitis-related hospitalizations (median 7 vs. 2) (Table 2).

Details of endoscopic therapy and surgery

Among 178 patients in the intervention group, 91 (51%) underwent endotherapy alone, 69 (39%) both endotherapy and surgery, and 18 (10%) only surgery. Among those who needed both interventions, 62 (90%) underwent endotherapy first followed by surgery (Fig. 1).

Abdominal pain was the primary indication for an intervention in the large majority of patients (Table 3). As an example, abdominal pain was the primary indication in 61.4% and 52% patients in whom endotherapy or surgery were the first intervention, and in 63.3% and 76% when endotherapy or surgery were the second intervention, respectively. During session(s) of endotherapy, pancreatic sphincterotomy, stone extraction and stent placement were the most common maneuvers performed. A subset of patients underwent biliary interventions such as biliary sphincterotomy and/or stent placement. A variety of surgical interventions were performed ranging including pure resections, drainage, or a combination (Table 4).

Multivariable analyses evaluating the association of pain with disease duration and other covariates

In multivariable analyses, the duration of disease, i.e. time from observation from first diagnosis of pancreatitis to the last clinical contact had no influence on the presence of pain at the end of study (OR 1.0, 95% CI 0.96–1.03) or the presence of Type B pain pattern during the disease course (OR 1.01, 95% CI 0.97–1.04). The duration of disease also was not significantly associated with the severity (OR 1.03, 95% CI 0.98–1.07) or constant pain (OR 0.99, 95% CI 0.95–1.03) at the time of NAPS2 enrollment (Table 5). With increasing age, there was less likelihood of having pain at the end of study (OR 0.97, 95% CI 0.94–0.99).

In these analyses, after controlling for covariates, the odds of being in pain at the end of study (OR 3.23, 95% CI 1.80–5.75), having Type B pain pattern during the clinical course (OR 2.02, 95% CI 1.10–3.63) and severe pain at NAPS2 enrollment (OR 2.12, 95% CI 1.23–3.64) were significantly higher in the intervention group when compared with medical group (Table 5). Patients with alcohol-related CP were significantly more likely to have Type B pain pattern (OR 2.05, 95% CI 1.10–3.63) and an increased tendency to have pain at the end of study, and severe pain at NAPS2 enrollment ($p = 0.07$). Patients with exocrine insufficiency were also more likely to have pain at the end of study (OR 2.13, 95% CY 1.12–4.03) and constant pain at the time of NAPS2 enrollment (OR 1.90, 95% CI 1.10–3.28). Other covariates included in the regression model were not significantly associated with pain experience.

Discussion

In one of the largest studies of its kind in the modern era, we confirm that ~90% of patients with CP experience abdominal pain during their clinical course [3–5]. Abdominal pain was independent of disease duration. The prevalence decreased over time, in part because of therapeutic interventions, but roughly half of the patients continued to have abdominal pain at the end of observation. The need for invasive intervention was not limited to patients with Type B pain pattern, and roughly one-third of patients managed medically also suffered from Type B pain. As expected, patients with ongoing pain were more likely to have invasive therapies, receive narcotic medications for pain management, and have pancreatitis-related hospitalizations. Pain experience was also influenced by age and etiology.

We did not observe the degree of pain *burn-out* observed by Ammann et al. i.e. >80% within 10 year from disease onset [14]. In their experience, Type B pain pattern was limited to patients who underwent surgical intervention, which helped in achieving pain relief. However, in their series, pain *burn-out* was no different in medically and surgically managed patients, and lasted for several years in each group. In contrast, in the most comprehensive study to evaluate this question since then, during a median observation period of 12.4 years, we noted that 46.6% patients still complained of abdominal pain at the end of observation. Overall, the prevalence of Type A pain was lower (~34% vs. 44%) in our cohort. In contrast to Ammann et al. patients who were medically managed also reported Type B. Moreover, the need for invasive intervention was not universal in patients with Type B pain (130/165, 78%), and more than half (44/85, 52%) patients with Type A pain also needed such treatments. The prevalence of pain was greater at all time points among patients who needed an intervention.

While Ammann et al. study focused on patients with alcoholic CP [14], we extend observations to patients with etiologies other than alcohol. Patients with alcoholic CP were more likely to have pain at any time, and when compared with non-alcohol etiology, were more likely to suffer from Type B pain pattern, constant pain and use narcotic medications. However, the proportion of patients with non-alcohol etiology who continued to have pain at the end of the study was similar to those with alcohol etiology (42.5% vs. 51.1%, 0.53). We noted that the lack of association for the duration of disease with pain experience was independent of etiology, suggesting that patients with etiology other than alcohol also suffer from significant pain burden.

Why do patients not achieve durable pain relief, even after invasive therapies? It is recognized that pain in CP is multifactorial, and pain in an individual patient may be related to more than one mechanism [10]. Thus, performance of specific interventions, e.g. pseudocyst drainage or pancreatic ductal decompression by removal of stones and/or stent placement, results in resolution of symptoms in some but not all patients. This was illustrated in a recent rigorous randomized clinical trial comparing endoscopic therapy first vs. surgery, where only 25% patients achieved complete pain relief, and only 48% achieved complete or partial pain relief during 18 months of follow-up [21]. With increasing duration of symptoms, there is sensitization of nociceptive pathways, resulting in neuronal abnormalities at the level of spinal cord and the central nervous system. These neuropathic changes, termed as central sensitization, may be one explanation for the lack of efficacy of therapies directed at pancreatic inflammation or morphologic abnormalities [13]. Patient-related factors, such as continuing exposure to alcohol and/or tobacco, psychologic factors such as anxiety and/or depression, dependence on and side-effects of narcotic medications, etc. may also affect response to therapies [22–24]. The choice and timing of invasive therapy is another consideration. A meta-analysis suggested that early surgical intervention may increase the likelihood of achieving partial or complete pain relief [25]. While endoscopic approach in suitable candidates is recommended as the initial strategy [11], this has been challenged by results of randomized trials comparing endoscopic versus surgical approaches [21,26]. Finally, data on efficacy of TPIAT in achieving pain relief is rapidly evolving [27]. However, this operation is limited to select patients, countries, and specialized centers, and long-term outcomes of a rigorous, multicenter, prospective study are eagerly awaited [28].

Critical gaps remain in translating the above concepts into clinical practice - these include objective ways to define patient's pain experience, tests to guide and predict response to therapies, and more effective therapies for pain management. Efforts in recent years have attempted to address these gaps. Examples of standardizing patient evaluation include development of the comprehensive pain assessment (COMPAT) score, use of behavioral and

quality of life measures [29–31]. Assessment of nociceptive system through quantitative sensory testing has a potential to classify patients into distinct phenotypic groups that can direct therapies [32]. Behavioral approaches, such as cognitive behavioral therapy show promise as an adjunct to treatment for pain [33]. Use of neuromodulating agents hold promise in patients with central sensitization [34].

Our study has several strengths. Patients were prospectively recruited to the NAPS2 studies using strict entry criteria. They were managed by a multidisciplinary team with expertise in pancreatic disease at a large tertiary care institution. Although the assessment of pain was retrospectively performed, this correlated well with patient's self-report at the time of NAPS2 enrollment. As stated previously, we extended observations to CP of all etiologies. Finally, longitudinal care received in our specialty clinics and the UPMC system resulted in a long duration of observation to accurately characterize clinical events. This enabled us to perform robust multivariable analyses to evaluate the association of pain with the duration of disease after controlling for important confounders such as demographics, age at disease onset, etiology, type of treatment, morphologic and functional abnormalities. Invasive therapies in our study consisted of endotherapy as an initial strategy in the majority of patients, which reflects the practice pattern in the modern era.

Limitations of our study are primarily related to retrospective study design. We could not perform a systematic evaluation for time to achieve pain relief and its relationship to other co-variates, such as time to diabetes diagnosis or detection of calcifications, as prospective assessment at prespecified time intervals is needed for such analyses. However, we do not believe that these limitations impact our primary conclusions. We recorded a point estimate for pain status at the end of observation, which may be an overestimation when compared with the stricter criteria for *burn-out* used by Ammann et al. i.e. no pain for $\geq$2 years [14]. Assessment for functional abnormalities was not systematic, which may have led to underestimation of diabetes and possibly overestimation of exocrine insufficiency. Our cohort consists of patients receiving care at a US tertiary care center, which may differ from community patients [35] or other geographic regions. An example of the latter in terms of practice patterns is more frequent use of narcotic medications in patients with AP [36].

In conclusion, a careful, longitudinal evaluation in a well-characterized cohort of CP patients revealed that ~50% of patients continued to report abdominal pain at the end of a long observation period which was independent of the duration of disease. Patients needing invasive therapies had a more aggressive phenotype, but performance of such therapies did not ensure durable pain relief. Etiology of CP also influences pain experience, although a similar fraction of patients irrespective of etiology continue to report pain symptoms. These data highlight an urgent need to develop new strategies for evaluation and management of pain in CP patients. Specifically, approaches to identify patients with abdominal pain who will benefit from endoscopic therapy or surgery will help to maximize pain relief and improve quality of life while minimizing morbidity from unnecessary procedures. In patients considered to be candidates for medical management, the goal should be to identify non-invasive approaches that will be most effective to achieve pain relief.

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