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ORIGINAL ARTICLE

Evaluating Outcomes and Misuse in Opioid-Dependent Chronic Pancreatitis Using a State-Mandated Monitoring System

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Abstract

Introduction Patients with chronic pancreatitis (CP) often require opioids for pain control. The goal of our study was to characterize opioid use in patients with CP in a real-life practice using a state-mandated online monitoring program and to assess outcomes compared to CP patients without opioid dependency.

Methods CP patients seen in our Pancreas Center from 2016 to 2021 were divided into two groups—with and without chronic opioid use. Details of opioids and other controlled prescriptions were obtained by review of the Massachusetts Prescription Awareness Tool (MassPat).

Results Of the 442 CP outpatients, 216 used chronic opioids. Patients with opioid use had significantly more recurrent acute pancreatitis (76.6% vs. 52.7%), concurrent alcohol use (11.2% vs. 5.8%), tobacco use (37.8% vs. 19.7%), anxiety (22.4% vs. 16.6%), depression (43.5% vs. 23.5%) and daily pain (59.8% vs. 24.8%) ($p < 0.001$). They also concurrently used more benzodiazepines (43.7% vs. 12.4%), gabapentinoids (66.4% vs. 31.1%) and medical marijuana (14.9% vs. 4.19%) ($p < 0.001$). They had more celiac plexus blocks (22.0% vs. 6.67%), surgery (18.3% vs. 8.89%) and more hospitalizations for CP flares (3.6 vs. 1.0 visits) ($p < 0.001$). Less than 13% patients received opioids by means of ED visits; 81.7% patients received their prescriptions from one facility and 75% received them at regular intervals.

Conclusion Opioid-dependent CP patients exhibit polypharmacy and have worse outcomes with higher resource utilization. The state-monitoring program ensures that the majority of patients receive opioids from a single facility, thereby minimizing misuse.

Keywords Chronic pancreatitis · Opioid use disorder · Polypharmacy

Introduction

Chronic pancreatitis (CP) is an inflammatory condition characterized by ductal destruction resulting in gland fibrosis [1]. The etiology of CP ranges from toxic ingestion (i.e., alcohol) to genetic predisposition, with a large cohort of patients without a clear etiology identified. Regardless of etiology, the hallmark of CP is gastrointestinal distress including abdominal pain, nausea, and weight loss. In advanced cases, patients can also develop exocrine and endocrine insufficiency resulting in steatorrhea and type 3c diabetes. The mainstay of management is supportive care including mitigation of symptoms and use of preventative strategies aimed at reducing complications [1, 2].

As abdominal pain is the most common manifestation of CP, analgesia is a key component of disease management and typically requires a multimodal approach [3–6]. In this model, providers target lifestyle modifications such as tobacco and alcohol cessation and use of non-controlled medications (i.e., acetaminophen and ibuprofen) as the initial strategy [3, 7]. However, these efforts often do not provide adequate pain relief. In many cases, patients are referred to

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pain clinics for co-management where additional analgesics may be considered including opioids and neuromodulation. While neuromodulators including tricyclic antidepressants and gabapentinoids are often preferred, opioids remain a powerful class of medications that are central to pain management and utilized in up to 66% of patients with CP [8, 9].

At the same time, opioid over-prescription and subsequent opioid use disorder (OUD) have become a key issue in modern medicine. Some studies estimate that OUD contributed to more than 600,000 deaths alone in the USA [10]. As a result, state and federal programs mandate prescribers to use monitoring platforms in an effort to prevent opioid misuse and over-prescription [11]. Massachusetts developed such a platform called Massachusetts Prescription Awareness Tool (MassPat) which queries prescription databases across 35 states to provide prescribers with accurate information and more transparency when prescribing opioids. [12].

Until now, opioid use in CP has been estimated either using large databases or via patient- and provider- recollection which may provide inaccurate data [9, 13]. Thus, we sought to characterize opioid use in patients with CP in a real-life practice using the MassPat monitoring platform. We also assessed patient characteristics and outcomes including the presence of polypharmacy, complications and resource utilization in CP patients using chronic opioids and compared them to those without chronic opioid use.

Methods

Patient Selection and Study Design

We performed a retrospective review of all adult patients with a diagnosis of CP followed at our outpatient Pancreas Center in our tertiary care hospital, between January 1st, 2016, and April 30th, 2021. The diagnosis of CP was made based on the presence of a clinical and radiologic (CT or MRCP) and/or endosonographic features. Patients diagnosed with CP via endoscopic ultrasound were only included if they met the Rosemont criteria for definitive diagnosis of CP [14]. We then identified patients who received chronic opioid medications for the treatment of abdominal pain associated with CP using MassPat. Chronic opioid use was defined as 10 or more prescriptions or > 120-day supply of an opioid in a year [14]. Patients receiving opioids for other concurrent painful conditions, such as fibromyalgia, malignancy, and chronic back pain, were excluded. We routinely adjusted opioid and non-opioid analgesics at the time of the office visit based on the patient's level of pain. We then divided our cohort of CP patients into two groups: those with chronic opioid use and those without.

Data Source

The information about opioid prescriptions in our patients with chronic opioid use was obtained via review of the MassPat for each patient. MassPat is a state-mandated online program that tracks prescriptions of Schedules II-V controlled substances from 35 states [12]. It monitors the dates of filled prescriptions, name and dose of the drug, quantity, duration and daily dose in morphine milliequivalents (MME), refills, prescribing providers, and dispensing pharmacy information. This information was collected for each eligible patient for the most recent 24 months.

Data Collection, Study Groups and Outcomes of Interest

Clinical data were collected for all patients. These included demographic characteristics such as age, gender, body mass index (BMI), as well as clinical characteristics such as comorbidity profile (Charlson Comorbidity Index) and active gastrointestinal symptoms including abdominal pain pattern. We also collected data on complications of CP such as pancreatic pseudocyst, splanchnic vein thrombosis, biliary obstruction, vitamin D deficiency, as well as information on concurrent use of other controlled and non-controlled medications such as benzodiazepines, neurostimulants, neuromodulators and medical marijuana. Neuromodulators included gabapentin, pregabalin, amitriptyline and nortriptyline. Lastly, we obtained data on the average number of CP flares requiring hospitalization in the preceding 24 months, endoscopic procedures and surgeries for CP, average number of imaging studies such as CT and MRCP, and recurrent emergency department (ED) visits for abdominal pain resulting in an opioid prescription. We then compared these characteristics between those with opioid use and those without opioid use.

Statistical Analysis

All outcomes were evaluated for normality. Categorical variables were presented as proportions and continuous variables as means with range, standard deviations (SD) and 95% confidence interval (CI). All analyses were performed using the R software (version 3.6.1, R Core Team 2018a) within RStudio (version 1.1463, RStudio, Inc.) using the Tidyverse (Wickham, 2017) package. [15].

Results

In the study period, 650 patients were evaluated for CP in our pancreas center of which 442 patients had radiographic and/or echo-endosonographic evidence of CP. Of the 442 CP

patients, there were 216 (49%) with chronic opioid use and 226 patients without chronic opioid use. Baseline characteristics for these groups are summarized in Table 1. Patients on chronic opioids were significantly younger (56.8 vs. 60.0 years, $p=0.03$). Further, a significantly greater proportion of patients on chronic opioids had alcoholic CP (39.8% vs. 24.6%; $p<0.001$) and endorsed active smoking (37.4% vs. 19.7%; $p<0.001$) and recreational marijuana use (27.1% vs. 11.7%; $p<0.001$). Of those patients on chronic opioids, the majority of patients were on oxycodone followed by a combination regimen (Fig. 1).

Table 2 summarizes the data on patient-reported symptoms and CP-associated complications. Patients on chronic opioids reported significantly more chronic abdominal pain, changes in bowel habits, nausea, appetite loss and weight loss compared to those not prescribed opioids ($p<0.001$). Also, patients on chronic opioids had a greater number of flares requiring hospitalization in the preceding 2 years compared to those not on opioids (3.6 vs. 1 visit, $p<0.001$). Furthermore, more patients on opioids had comorbid psychiatric illness such as anxiety and depression ($p<0.001$). Patients on chronic opioids also had more biliary obstruction, splanchnic vein thrombosis and pseudocysts than those without opioids; however, only pseudocysts met statistical significance (46.0% vs. 26.0%, $p<0.001$).

Patients with chronic opioid use had greater utilization of other pain modalities and non-opioid controlled substances (Table 3). Specifically, a significantly greater proportion of patients were concurrently taking benzodiazepines and/or neuromodulators (43.7% vs. 12.4% and 66.4% vs. 31.1%, $p<0.001$, respectively). Moreover, more patients on chronic opioids underwent celiac plexus blocks and pancreatic resection surgery than those not on opioids (22.0% vs. 6.67% and 18.3% vs. 8.89% $p<0.001$, respectively). Also, patients on chronic opioids were more likely to present to the ED for a CP flare that resulted in an opioid prescription (12.7% vs 1.3%; $p<0.001$).

As shown in Table 4, 126 patients (58.9%) within the chronic opioid group received their opioid prescription from a pain management specialist. One-hundred-seventy patients (81.7%) received their opioid prescription from the same prescribing facility, with the average number of prescribers being 4.63. The average number of opioid prescriptions over the two-year period was 24.2, and the average daily MME was 55.8 units/day. About 75% patients received their opioid prescriptions at regular intervals.

Table 1 Demographic characteristics and comorbidities in patients with and without chronic opioid use

	Not on chronic opioids ($N=226$)	On chronic opioids ($N=216$)	*P* value
Mean Age, years (SD)	60.0 (16.0)	56.8 (13.8)	0.025
Age Groups, *n* (%)			0.221
18–35 years	17 (7.5%)	15 (6.9%)	
36–50 years	45 (19.9%)	54 (25%)	
51–65 years	76 (33.6%)	82 (38%)	
> 65 years	88 (38.9%)	65 (30.1%)	
Mean BMI, kg/m^2 (SD)	26.0 (5.64)	25.5 (5.07)	0.385
Mean CCI (SD)	1.01 (1.09)	1.67 (1.19)	0.07
Female gender, *n* (%)	111 (49.1%)	100 (46.3%)	0.619
Race, *n* (%)			0.220
Caucasian	169 (75.4%)	157 (72.7%)	
African American	21 (9.4%)	26 (12%)	
Hispanic	8 (3.6%)	15 (6.9%)	
Other	26 (11.6%)	18 (8.3%)	
Etiology of CP, *n* (%)			0.004
Alcohol	58 (24.6%)	90 (39.8%)	
Idiopathic	110 (49.1%)	85 (38.4%)	
Other	56 (24.7%)	41 (18.9%)	
Current smoker, *n* (%)	44 (19.7%)	80 (37.4%)	< 0.001
Current alcohol use, *n* (%)	13 (5.8%)	24 (11.2%)	0.001
Recreational marijuana use, *n* (%)	26 (11.7%)	58 (27.1%)	< 0.001
Other recreational drug use, *n* (%)	1 (0.45%)	1 (0.47%)	0.642

SD standard deviation; *BMI* body mass index; *CCI* Charlson Comorbidity index; *CP* chronic pancreatitis

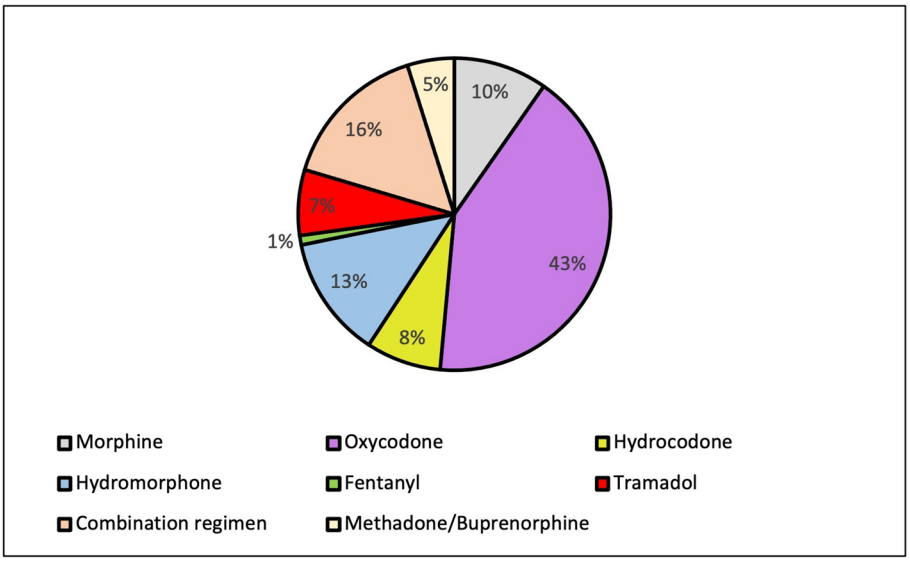

Fig. 1 Types of opioid prescriptions derived from the Massachusetts Prescription Awareness Tool (MassPat)

Table 2 Symptoms and complications associated with chronic pancreatitis in patients with and without chronic opioid use

	Not on chronic opioids ($N=226$)	On chronic opioids ($N=216$)	P value
Chronic abdominal pain, n (%)	126 (56.8%)	194 (90.7%)	<0.001
Type of abdominal pain, n (%)			<0.001
Daily	33 (24.8%)	119 (59.8%)	
Intermittent	98 (73.7%)	80 (40.2%)	
Abnormal bowel movements, n (%)			<0.001
Diarrhea	34 (15.3%)	50 (23.5%)	
Constipation	20 (9.01%)	40 (18.8%)	
Nausea, n (%)	57 (25.7%)	107 (50.0%)	<0.001
Loss of appetite, n (%)	49 (22.0%)	100 (46.9%)	<0.001
Loss of weight, n (%)	48 (21.5%)	88 (41.1%)	<0.001
History of recurrent acute pancreatitis, n (%)	117 (52.7%)	164 (76.6%)	<0.001
Psychiatric illness, n (%)			<0.001
Anxiety	37 (16.6%)	48 (22.4%)	
Depression	52 (23.3%)	93 (43.5%)	
Splanchnic vein thrombosis, n (%)	20 (8.97%)	32 (14.9%)	0.077
Pancreatic pseudocyst, n (%)	58 (26.0%)	99 (46.0%)	<0.001
Biliary obstruction, n (%)	28 (12.6%)	39 (18.6%)	0.115
Vitamin D deficiency, n (%) ($N=301$)	69 (34.0%)	97 (49.2%)	0.003

Discussion

In this study, we report on patterns of chronic opioid use in a large cohort of CP patients seen at a multi-disciplinary Pancreas Center at an urban tertiary care hospital. Our study shows that nearly 50% patients with CP required chronic opioids for management of their abdominal pain. Patients using chronic opioids were found to have a higher prevalence of polypharmacy with more use of concurrent neuromodulators, benzodiazepines and medical marijuana. These patients were also more likely to undergo procedural interventions for pain control such as celiac plexus blocks and pancreatic resection surgeries. Using the MassPat system, we were able to accurately characterize opioid use in this modern era of pain management for CP. Importantly, there were minimal overlapping prescriptions including prescriptions obtained from emergency visits during this period, which may indicate that current practice patterns limit opioid overuse, perhaps, attributed to monitoring platforms such as MassPat.

In our cohort of CP patients, those with chronic opioid use did not have more severe pain at baseline compared to

Table 3 Polypharmacy and resource utilization in patients with and without chronic opioid use

	Not on chronic opioids ($N=226$)	On chronic opioids ($N=216$)	P value
Patients receiving non-opioid controlled medications, *n* (%)	28 (12.4%)	94 (43.7%)	< 0.001
Type of non-opioid controlled medications, n (%)			0.115
Methylphenidate	1 (3.57%)	4 (4.08%)	
Alprazolam	6 (21.4%)	14 (14.3%)	
Clonazepam	4 (14.3%)	28 (27.6%)	
Diazepam	3 (10.7%)	3 (3.06%)	
Lorazepam	11 (28.6%)	42 (40.8%)	
Zolpidem	3 (10.7%)	7 (7.14%)	
Patients on medical marijuana, *n* (%)	9 (4.19%)	30 (14.9%)	< 0.001
Neuromodulators, *n* (%)	70 (31.1%)	142 (66.4%)	< 0.001
Type of neuromodulator, *n* (%)			0.215
Gabapentin	51 (22.5%)	94 (43.5%)	
Pregabalin	12 (5%)	38 (17.5%)	
Nortriptyline	5 (2.2%)	5 (2.3%)	
Amitriptyline	3 (1%)	6 (2.7%)	
NSAIDs or acetaminophen, *n* (%)	27 (12%)	30 (14%)	0.652
Patients with celiac plexus block, *n* (%)	15 (6.67%)	47 (22.0%)	< 0.001
Patients with pancreatic surgery for pain, *n* (%)	20 (8.89%)	39 (18.3%)	0.006
Number of flares requiring hospitalization in the last two years, *n* (%)	0.96 (1.66)	3.63 (4.07)	< 0.001
Patients with recurrent ED visits resulting in opioid prescriptions, *n* (%)	3 (1.33%)	27 (12.7%)	< 0.001

SD standard deviation; *NSAID* non-steroidal anti-inflammatory drug; *ED* emergency department

Table 4 Details of opioid prescriptions from the Massachusetts Prescription Awareness Tool (MassPat)

Patterns of opioid use	$N=216$
Average MME per day (SD)	55.8 (53.2)
Average number of opioid prescribers (SD)	4.63 (3.77)
Average number of opioid prescriptions in 24 months (SD)	24.2 (21.2)
Patients receiving prescription from a pain management specialist, *n* (%)	126 (58.9%)
Patients with regular intervals between opioid prescriptions, *n* (%)	162 (75%)
Patients with recurrent ED visits resulting in opioid prescriptions, *n* (%)	27 (12.7%)
Patients receiving opioids at the same clinic, *n* (%)	170 (81.7%)

SD standard deviation; *MME* morphine milliequivalents

those not using opioids. However, our study demonstrates that patients with CP who received chronic opioids were more likely to report daily abdominal pain, nausea, irregular bowel movements and loss of appetite and weight. Although most of these symptoms may overlap with underlying CP itself, it has been well documented that opioid use is associated with varying degrees of nausea and vomiting by stimulating the mu-receptor signaling pathway [16]. Similarly, chronic opioid use has also been associated with opioid-hyperalgesia syndrome [17]. Given these findings, it may be possible that CP patients using opioids who report persistent GI symptoms may be experiencing symptoms due to the opioid medication itself rather than from CP. Another important interpretation of these results is that these patients reported persistent abdominal pain despite being on chronic opioids and had a significantly higher number of CP flares requiring hospitalization, which may question the efficacy of use of opioids in treating their chronic abdominal pain [18]. This is particularly relevant in the case of CP, as abdominal pain in CP has been known to be of a complex nature, comprising of several visceral and neural pathways. [19].

Our patients on chronic opioids also had a greater prevalence of comorbid psychiatric illnesses such as anxiety and depression. Increased prevalence of both these conditions has been well documented in the CP population in recent years [20]. One multi-center study showed the prevalence of anxiety to be 46.8% and that of depression to be 36.8% in patients with CP [21]. Chronic opioid use has also been

independently associated with mental health disorders, with one study showing that 9–11% patients who used prescription opioids for more than 30 days, had new-onset depression [22]. Given these findings and the significantly higher prevalence of anxiety and depression in our opioid-using CP group, it is possible that use of opioids may have contributed to worsening of pre-existing anxiety and depression in these patients.

In our study, patients using chronic opioids were also found to have a higher prevalence of polypharmacy, demonstrated by higher usage of a variety of controlled medications including benzodiazepines, gabapentinoids and tricyclic antidepressants. While gabapentinoids and tricyclic antidepressants were primarily used for the treatment of CP-related abdominal pain as an adjunct to opioids, benzodiazepines were primarily used for anxiety, and methylphenidate was primarily used for attention deficit hyperactivity disorder. Such centrally acting medications when used in conjunction with opioids have been associated with detrimental adverse events such as cardiorespiratory decompensation, encephalopathy and even death [23]. This is particularly important when concurrent alcohol use is also present, which is frequently the case in patients with CP [24]. We also show that interventional and surgical procedures on the pancreas were more common in the opioid-dependent group. However, it is important to note that despite undergoing surgery, patients in the opioid group were more likely to report daily pain. This is in keeping with several other studies that have established that preoperative opioid use has been associated with increased risk of failure to achieve long-term pain relief after an endoscopic or surgical intervention. [25–27].

Lastly, our study utilized a state-monitoring tool created to monitor opioid abuse or misuse and showed that most patients received opioids from the same facility and there were no overlapping prescriptions in our data set. This was demonstrated by a high proportion of patients receiving opioids from the same prescribing facility at regular intervals. While we do not have data prior to the implementation of the monitoring tool, the low incidence of multiple prescriptions and providers in opioid group might suggest that the monitoring program provided details of prior prescriptions and their frequency to providers at the time of prescription, thereby, reducing the likelihood of opioid over-prescription and misuse.

While our data provide insight into prescription patterns in the era of monitoring platforms, there are several limitations including the retrospective nature of the study design. Furthermore, as we do not have data for all 50 states in the monitoring platform it is possible that patients could have received opioids from other sources, although that seems less likely as all the neighboring states and the entire New England region participate in data sharing for opioid prescriptions. Finally, our study does not provide specific data on endpoints of misuse, in that, we do not have confirmatory data (i.e., urine toxicology screens) to know whether the patients were indeed using opioids themselves and not distributing them.

In conclusion, we report that CP patients with opioid use are more likely to exhibit persistent abdominal pain, have a higher rate of polypharmacy including other controlled medications, and have increased resource utilization in the form of more hospitalizations for CP flares and procedural interventions for pain control. We also report on utilization of MassPat as an important tool in an effort to streamline opioid prescription practices among providers caring for patients with CP. In order to prevent opioid dependence in CP, patients are to consider adoption of the World Health Organization (WHO) analgesia model which has predominantly been used for management of cancer pain [28]. Several pancreatologists have recommended using this model in CP patients as well and involve a stepwise approach toward pain management ranging from non-opioid analgesics such as acetaminophen and NSAIDs to neuromodulators and antispasmodics to potential endoscopic or surgical intervention [4, 29, 30]. Opioids should finally be used only if all other strategies fail. Further research is needed to study the endpoints of opioid use disorder among CP patients using chronic opioids as well to devise strategies to further streamline opioid prescription practices.

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Declarations

Conflict of interest None of the authors have any conflicts of interest pertaining to this manuscript.

Ethical approval Our Institutional Review Board (IRB) approved this study.

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