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Original Research Article

A Two-Year Prospective Multicenter Study of Opioid Therapy for Chronic Noncancer Pain: Prescription Trends and Predictors

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Abstract

Objectives. Opioid use in chronic pain has increased worldwide in recent years. The aims of this study were to describe the trends and patterns of opioid therapy over two years of follow-up in a cohort of chronic noncancer pain (CNCP) patients and to assess predictors of long-term opioid use and clinical outcomes. **Methods.** A prospective cohort study with two years of follow-up was undertaken in four multidisciplinary chronic pain clinics. Demographic data, pain characteristics, and opioid prescriptions were recorded at baseline, three, six, 12, and 24 months. **Results.** Six hundred seventy-four CNCP patients were recruited. The prevalence of opioid prescriptions at baseline was 59.6% (N = 402), and 13% (N = 86) were strong opioid prescriptions. At 24 months, opioid prescription prevalence was as high as 74.3% (N = 501), and strong opioid prescription was 31% (N = 207). Most opioid users (71%, N = 479) maintained their prescription during the two years of follow-up. Our opioid discontinuation was very low (1%, N = 5). Opioid users reported higher severity and interference pain scores, both at baseline and after two years of follow-up. Opioid use was independently associated with continuous pain, pain location in the lower limbs, and higher pain interference scores. **Conclusions.** This study describes a pattern of increasing opioid prescription in chronic pain patients. Despite the limited improvement of clinical outcomes, most patients keep their long-term opioid prescriptions. Our results underscore the need for changes in clinical practice and further research into the effectiveness and safety of chronic opioid therapy for CNPC.

Key Words: Opioids; Chronic Pain; Trends; Outcome Assessment; Predictors

Introduction

Chronic noncancer pain (CNCP) is highly prevalent and has significant repercussions on the individual (reduced quality of life and functional disability) and society (health care resources, loss of productivity) [1,2]. Estimates of chronic pain (CP) prevalence are highly variable in the literature, ranging from 8.7% to 64.4%, with a mean of 31%, which may be explained by differences in CP definition and data collection methods [3]. Despite variability in estimated prevalence, CP is a very important public health issue that deserves to be prioritized, similar to cardiovascular diseases or cancer [4], as proposed

by Breivik et al. According to the Institute of Medicine, in 2011 chronic pain affected 116 million Americans, with associated costs of $560–$635 billion per year in health care and loss of productivity [5]. The estimated costs of musculoskeletal pain and low back pain in Europe represent 2% of the annual GDP [1,5]. In 2012, a cross-sectional epidemiological study estimated the Portuguese chronic pain prevalence to be as high as 37% [6]. Moreover, CP patients had a very high rate of health services utilization, and the estimated direct and indirect costs related to CP represented 2.71% of the Portuguese annual GDP [7,8]. In summary, chronic pain is a prevalent condition, and there is an urgent need to improve its management and to reduce its associated costs [4,5]. Opioid analgesics have an important role in acute and chronic cancer pain treatment. Although opioid use is recommended on several treatment guidelines for CNCP [2,5,9–11], there is still a lack of robust evidence to support such recommendations. Long-term opioid use is associated with the risk of neuroendocrine dysfunctions, osteoporosis, immunosuppression, cognitive disorders, opioid-induced hyperalgesia, and addiction. Long-term exposure and higher doses seem to increase the risk of the above [12–15], although no clear dose-effect relationship has been established. Moreover, there is still controversy related to the effectiveness of long-term opioid use in the management of CNCP [16,17]. Most of the available studies, and particularly the clinical trials, present some limitations such as short follow-up periods (less than one year), high rates of patient dropout, and variability of study designs. Therefore, there is no robust evidence concerning this subject [15,18,19].

In spite of this, prescription of opioids for CNCP has increased worldwide in recent years [20–23]. According to data from the Centers for Disease Control and Prevention (CDC), the presciption of opioids has quadrupled in the past decade, with an associated increase of overdose deaths related to opioid prescription [12,24]. The same trend of increasing opioid prescription has been observed in European countries, albeit at a lower magnitude than in the United States [25,26]. Possible reasons to explain this exponential growth in opioid prescription include inadequate undergraduate and postgraduate training on pain management, paucity of research-based evidence on long-term opioid use, increased public awareness of pain, limited availability of pharmacological options for CNCP treatment, and the recognized efficacy of opioids in acute and cancer pain management [2,20].

Most available studies on opioid therapy for CNCP are limited to a short follow-up period of three to six months and are generally not based on real-world data. Moreover, only a few studies have described the patterns and determinants of opioid use in multidisciplinary pain clinics (MPCs).

In this study, we aimed to describe the trends and patterns of opioid therapy over two years of follow-up in a cohort of CNCP patients and to assess predictors of opioid long-term use and clinical outcomes.

Methods

A prospective cohort study with 24 months of follow-up was performed in four MPCs. This study was conducted in accordance with the Guideline for Good Clinical Practice of the International Conference on Harmonization and the ethical principles of the Declaration of Helsinki and subsequent updates. The study was approved by the National Committee for Data Protection and by the local ethics committees of participating institutions. All patients enrolled in the study were informed of the study details and provided informed consent.

Patient Selection

A consecutive sample of CNCP patients aged 18 years old or older with pain duration of at least three months were recruited at their first consultation in one of the four participating MPCs from the Oporto region in a face-to-face interview with a trained interviewer. Clinical assessment was performed by the MPC attending physician. The exclusion criteria were psychiatric or cognitive impairment that could interfere with data collection, inability to communicate verbally, not fluent in the Portuguese language, and absence of informed consent. Follow-up contacts were performed by telephone by trained interviewers at six, 12, and 24 months, complemented by analysis of hospital records.

Data Collection

Demographic data collected included age, gender, professional status, education level, and prior diagnosis of depression. Data concerning patterns of pain persistence, pain location, and pain frequency were assessed through patient questionnaires. Pain severity and pain interference were measured using the Brief Pain Inventory (BPI), adapted and validated for the Portuguese language [27]. The severity scale comprises four items: 1) worst, 2) least, and 3) average pain in the previous week and 4) current pain. Each item was scored from 0 (“no pain”) to 10 (“worst imaginable pain”). The severity score subscale was calculated as a mean severity score of the four pain items. The interference scale encompasses seven items of quality of life: 1) general activity, 2) mood, 3) walking, 4) work, 5) relation with other people, 6) sleep, and 7) enjoyment of life. Each item is scored from 0 (“does not interfere”) to 10 (“interferes completely”). The interference score subscale was calculated as the mean of the seven interference scores [28].

Pain classification was performed according to the International Association for the Study of Pain Taskforce on Pain Classification for ICD-11 [29]. Data on psychiatric comorbidities were collected based on clinical records,

patient self-report, and validated instruments. The Portuguese version of the Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression. The HADS is a 14-item scale with two subscales of seven items each, measuring anxiety (HADS-A) and depression (HADS-D) symptoms. Each item is measured on a four-point (0–3) Likert scale. The scores for each subscale range from 0 to 21. A score of ≥8 on the HADS-A/HADS-D indicates the presence of clinically significant anxiety and depression symptoms [30]. The Current Opioid Misuse Measure (COMM) is a self-report assessment scale with 17 items designed to identify aberrant drug-related behaviors and the development of substance use disorders in patients with chronic pain taking opioids. Each item is measured on a five-point (0–4) Likert scale. A score ≥9 is a positive indicator that the patient is misusing his/her medication and is at increased risk of abuse [31].

Opioid Medication

Opioid drug prescription was registered according to self-reported data and clinical records. Opioid classification was based on the World Health Organization three-step analgesic ladder: "Weak opioids" include tramadol and codeine. "Strong opioids" include morphine, oxycodone, tapentadol, hydromorphone, buprenorphine, and fentanyl [32–34]. Morphine-equivalent daily doses (MEDD) were estimated using available references. High opioid use was defined as MEDD >200 mg [25,35,36].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 24.0 (SPSS, USA).

Descriptive statistics are presented as frequencies for categorical variables and as medians and interquartile ranges for continuous variables, taking into account the variables considered and assessments of the normality assumption. A primary analysis stratified in two groups was performed: opioid nonusers and opioid users at baseline and at 24-month follow-up. Subgroup analysis was performed to assess patterns of use and clinical outcomes among strong and weak opioids users. Patterns of opioid therapy and/or withdrawal at baseline, three, six, 12, and 24 months are described.

Subgroup analysis among opioid users at two years of follow-up was performed to assess differences between those users who have reported clinical improvement and those who have not reported clinical improvement. In accordance with Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations, clinical improvement was considered when there was a reduction in pain intensity of at least 10–20% on the BPI severity score and at least a one-point reduction on the BPI interference score at 24 months of follow-up in comparison with baseline [37].

To characterize predictors of opioid use, univariate and multivariate logistic regression models were performed. We evaluated the goodness of fit of the logistic regression model using the Hosmer-Lemeshow test and receiver operating characteristic (ROC) curve to evaluate its predictive and discriminative power. A value of statistical significance of 0.05 was adopted.

Results

Eight hundred eight patients with a CNCP diagnosis were recruited, but only 674 patients had completed the two years of follow-up and were included in our study. The general characteristics of the sample are described in Table 1. At their first consultation, a higher proportion of opioid users were 60–75 years old (N = 148, 36.8%), female (N = 300, 74.6%), retired (N = 208, 51.7%), with low levels of education (one to four years of basic school; N = 227, 56.6%), and with a higher association with depressive (N = 94, 25.0%) and anxiety disorders (N = 274, 40.6%) (Table1).

Pain characteristics are described in Table 2. At baseline, opioid users presented mostly a continuous pain pattern (N = 309, 76.9%). In opioid users, pain was predominantly localized to the lumbar region (N = 253, 62.9%, vs N = 143, 52.6%, $P = 0.008$) and lower limbs (N = 288, 71.6%, vs N = 145, 53.3%, $P < 0.001$). The most common pain etiology in opioid users was chronic musculoskeletal pain (N = 267, 66.4%, vs N = 153, 56.3%, $P < 0.001$). Opioid users reported higher pain severity scores (6.3, P25-P75 4.8–7.5, vs 5.7, P25-P75 4.7–7.5, $P < 0.001$) and pain interference scores (6.7, P25-P75 5.1–8.3, vs 5.9, P25-P75 4.0–7.3, $P < 0.001$). There were no differences between opioid and nonopioid users regarding sex, pain duration, or self-reported medication efficacy.

At 24 months of follow-up, similar to baseline, opioid users often presented a continuous pain pattern (N = 309, 76.9%, vs N = 163, 59.9%, $P \leq 0.001$), lower limb pain (N = 288, 71.6%, vs N = 145, 53.3%, $P < 0.001$), and chronic musculoskeletal pain (N = 267, 64.4%, vs N = 153, 56.3%, $P = 0.009$). Opioid users also presented higher severity (6.1, P25-P75 3.5–7.5, vs 4.2, P25-P75 2.4–6.3, $P < 0.001$) and higher interference scores (5.0, P25-P75 2.0–15.0, vs 3.7, P25-P75 0.9–6.4, $P < 0.001$). Contrary to what happened at baseline, at 24 months, opioid users and nonusers were significantly different with respect to self-reported medication efficacy; most opioid users reported none (N = 126, 27.1%, vs N = 25, 17.5%, $P = 0.012$) or only modest self-reported efficacy (N = 126, 26.9%, vs N = 28, 19.6%, $P = 0.012$) of their analgesic therapy.

Opioid prescription and/or withdrawal were recorded at baseline, three months, six months, 12 months, and 24 months (Figure 1). For this purpose, patients were subdivided into four different groups: no opioid prescription, beginning opioid, continuing opioid, or opioid

Table 1. Sample characterization at baseline and at 24-month follow-up

Variable	Baseline				24 mo		
	All (N = 674)	Opioid Nonusers (N = 272)	Opioid Users (N = 402)	*P* Value	Opioid Nonusers (N = 173)	Opioid Users (N = 501)	*P* Value
Age, y							
18–45	151	84	67	<0.001*	57	94	<0.001*
	22.4%	30.9%	16.7%	<0.001†	32.9%	18.8%	<0.001†
45–60	214	88	126		60	154	
	31.8%	32.4%	31.3%		34.7%	30.7%	
60–75	221	73	148		41	180	
	32.8%	26.8%	36.8%		23.7%	35.9%	
>75	88	27	61		15	73	
	13.1%	9.9%	15.2%		8.7%	14.6%	
Sex							
Female	498	188	300	0.070	115	373	0.049*
	72.4%	69.1%	74.6%		66.5%	74.5%	
Male	186	84	102		58	128	
	27.6%	30.9%	25.4%		33.5%	25.5%	
Professional status							
Full or part-time worker	222	120	102	<0.001‡	89	133	<0.001‡
	32.9%	44.1%	25.4%	<0.001†	51.4%	26.5%	<0.001†
Student	6	3	3		2	4	
	0.9%	1.1%	0.7%		1.2%	0.8%	
Unemployed	91	37	54		23	68	
	13.5%	13.6%	13.4%		13.3%	13.6%	
House worker or domestic worker	27	9	18		3	24	
	4.0%	3.3%	4.5%		1.7%	4.8%	
Retired	309	101	208		56	253	
	45.8%	37.1%	51.7%		32.4%	50.5%	
Other	19	2	17		0	19	
	2.8%	0.7%	4.2%		0.0%	3.8%	
Education level							
No education	19	6	13	<0.001*	4	15	<0.001‡
	2.8%	2.2%	3.2%	<0.001†	2.3%	3.0%	<0.001†
1–4 y (basic school)	340	113	227		65	275	
	50.5%	41.5%	56.6%		37.6%	55.0%	
5–9 y	163	71	92		46	117	
	24.2%	26.1%	22.9%		26.6%	23.4%	
10–12 y (secondary school)	78	46	32		35	43	
	11.6%	16.9%	8.0%		20.2%	8.6%	
>12 y (higher school)	73	36	37		23	50	
	10.8%	13.2%	9.2%		13.3%	10.0%	
HADS depression ≥8	139	45	94	0.032*	24	115	0.011*
	22.1%	17.7%	25.0%	<0.001*	14.8%	24.6%	<0.001*
HADS anxiety ≥8	378	104	274		80	210	
	56.0%	15.4%	40.6%		11.9%	31.1%	
COMM ≥9	0	0	0	–	0	10	–
	0%	0%	0%		0%	1.5%	

Data are presented as No. above %. Proportions are calculated as column proportions. A score ≥8 on the HADS-A/HADS-D indicates the presence of clinically significant anxiety and depression symptoms. A score ≥ 9 on the COMM is indicative of an increased risk of opioid misuse.

COMM = Current Opioid Misuse Measure; HADS = Hospital Anxiety and Depression Scale.

*X^2 test.

†Linear by linear test.

‡Fisher exact test.

withdrawal. At baseline, 60% (N = 402) of the cohort was prescribed opioid analgesics: 316 patients (47%) were prescribed weak opioids, and 86 patients (13%) were prescribed strong opioids at their first consultation at the MPC. At six months of follow-up, 58% (N = 394) of our sample continued their opioid prescription; at 12 and 24 months of follow-up, this number increased to 67% (N = 453) and 71% (N = 479), respectively. Most new opioid prescriptions occurred between the period of three to six months of follow-up (10%, N = 70). The opioid discontinuation rate was minimal over the two years of follow-up (Figure 2).

Most patients were on weak opioid prescriptions during follow-up (Figure 2). However, a progressive increase

Table 2. Pain characteristics at baseline and at 24-month follow-up

		Baseline				24 mo		
		Total	Opioid Nonusers (N = 402)	Opioid Users (N = 272)	*P* Value	Opioid Nonusers (N = 173)	Opioid Users (N = 501)	*P* Value
Pain duration, y		4.0 (2.0–12.0)	4.0 (2.0–10.0)	5.0 (1.7–14.0)	0.275*	3.0 (1.3–9.0)	5.0 (2.0–15.0)	0.023*
Pain persistence pattern	Continuous	472, 70.0%	163, 59.9%	309, 76.9%	<0.001† <0.001‡	88, 50.9%	384, 76.6%	0.001† 0.001‡
	Noncontinuous	202, 30.0%	109, 40.1%	93, 23.1%		85, 49.1%	117, 23.4%	
Pain location	Head	103, 14.8%	43, 41.7%	60, 58.3%	0.633†	24, 23.8%	77, 76.2%	0.897†
	Face	42, 6.2%	19, 7.0%	23, 5.7%	0.519†	12, 28.6%	30, 71.4%	0.447†
	Cervical region	251, 37.2%	97, 35.7%	154, 38.3%	0.516†	46, 19.3%	192, 80.7%	0.097†
	Dorsal region	64, 9.5%	19, 7.0%	45, 11.2%	0.081†	13, 20.3%	51, 79.7%	0.642†
	Lumbar region	396, 58.8%	143, 52.6%	253, 62.9%	0.008†	76, 20.3%	298, 61.6%	0.066†
	Abdominal region	42, 6.2%	16, 38.1%	26, 61.9%	0.758†	9, 22.0%	32, 78.0%	0.527†
	Upper limb	341, 50.6%	130, 47.8%	211, 52.5%	0.240†	67, 20.4%	261, 79.7%	0.066†
	Lower limb	433, 64.2%	145, 53.3%	288, 71.6%	<0.001†	71, 17.4%	338, 82.6%	<0.001†
Pain etiology	Chronic primary pain	50, 7.4%	20, 7.4%	30, 7.5%	1.000†	12, 6.9%	38, 37.2%	0.305†
	Chronic postsurgical and post-traumatic pain	92, 13.6%	42, 15.4%	50, 12.4%	0.303†	31, 23.6%	61, 12.2%	0.867†
	Chronic neuropathic pain	170, 25.2%	61, 22.4%	109, 27.1%	0.176†	36, 20.8%	134, 26.7%	0.129†
	Chronic headache and orofacial pain	15, 2.2%	6, 2.2%	9, 2.2%	1.000†	4, 2.3%	11, 2.2%	0.929†
	Chronic visceral pain	26, 3.9%	14, 5.1%	12, 3.0%	0.159	12, 6.9%	14, 2.8%	0.021†
	Chronic musculoskeletal pain	420, 62.3%	153, 56.3%	267, 66.4%	0.009†	92, 53.2%	328, 65.5%	0.005† 0.004‡
Pain severity	Pain severity score (0–10 NRS)	6.0 (4.5–7.3)	5.7 (4.7–7.5)	6.3 (4.8–7.5)	<0.001‡	4.2 (2.4–6.3)	5.7 (3.5–7.3)	<0.001*
	Pain on average (0–10 NRS)	6.0 (5.0–8.0)	6.0 (5.0–7.0)	6.0 (5.0–8.0)	<0.001‡	5.0 (2.7–7.0)	6.0 (4.0–8.0)	<0.001‡
	Pain at its least (0–10 NRS)	4.0 (2.0–5.0)	3.0 (2.0–5.0)	4.0 (2.0–6.0)	0.015‡	2.0 (0.0–5.0)	4.0 (2.0–5.0)	0.013‡
	Pain at its worst (0–10 NRS)	8.0 (7.0–10.0)	8.0 (6.0–10.0)	9.0 (7.0–10.0)	<0.001‡	6.0 (4.0–8.0)	8.0 (5.0–9.0)	<0.001‡
	Pain right now (0–10 NRS)	5.0 (3.0–8.0)	5.0 (3.0–7.0)	5.0 (3.0–8.0)	0.074‡	3.0 (0.0–6.0)	5.0 (2.3–8.0)	<0.001‡
Pain interference	Pain interference score (0–10 NRS)	6.3 (4.6–7.9)	5.9 (4.0–7.3)	6.7 (5.1–8.3)	<0.001‡	3.7 (0.9–6.4	6.1 (3.5–7.5)	<0.001‡
	General activity (0–10 NRS)	8.0 (5.0–9.0)	7.0 (4.0–9.0)	8.0 (5.0–10.0)	<0.001*	5.0 (0.0–7.0)	7.0 (5.0–9.0)	<0.001*
	Mood (0–10 NRS)	7.0 (5.0–9.0)	7.0 (4.0–9.0)	8.0 (5.0–10.0)	0.016*	4.0 (0.0–7.0)	6.0 (2.0–8.0)	<0.001*
	Walking ability (0–10 NRS)	8.0 (5.0–10.0)	6.0 (2.0–9.0)	8.0 (6.0–10.0)	<0.001*	3.0 (0.0–7.0)	7.0 (4.0–9.0)	<0.001*
	Normal work (0–10 NRS)	8.0 5.0–10.0)	7.5 (5.0–9.0)	8.0 (6.0–10.0)	<0.001*	5.0 (0.0–8.0)	7.0 (5.0–9.0)	<0.001*
	Relations with other people (0–10 NRS)	5.0 (0.0–7.0)	4.0 (0.0–7.0)	5.0 (0.0–8.0)	0.042*	1.0 (0.0–6.0)	5.0 (0.0–7.0)	<0.001*
	Sleep (0–10 NRS)	7.0 (2.0–9.0)	6.0 (1.7–9.0)	7.0 (3.0–10.0)	0.032*	3.0 (0.0–7.0)	5.0 (0.0–8.0)	0.002
	Enjoyment of life (0–10 NRS)	6.0 (1.0–9.0)	5.0 (0.0–8.0)	7.0 (3.0–9.0)	<0.001*	1.5 (0.0–7.0)	5.0 (0.0–8.0)	<0.001*
Pain medication efficacy	None	152, 24.8%	52, 22.2%	100, 26.5%	0.107†	25, 17.5%	126, 27.1%	0.012†
	A little	154, 25.2%	50, 21.4%	104, 27.5%		28, 19.6%	126, 26.9%	
	Moderate	179, 29.2%	81, 34.6%	98, 25.9%		51, 35.7%	128, 27.3%	
	Quite a bit	117, 19.1%	48, 20.5%	69, 18.3%		36, 25.2%	81, 17.3%	
	Completely	10, 1.6%	3, 1.3%	7, 1.9%		3, 2.1%	7, 1.5%	

Data are presented as No., %, except pain duration, pain intensity, and pain interference, which are presented as median (interquartile range). Proportions were calculated as column proportions.

NRS = numerical rating scale.

*Mann-Whitney *U* test.

†X^2 comparisons.

‡*t* test.

in strong opioid prescription from baseline (N = 86, 13%) to 24 months of follow-up (N = 207, 26%) was observed. The most prevalent strong opioid prescriptions were buprenorphine and tapentadol.

The median MEDD in our population at baseline and six months was 60.0 (30.0–90.0) mg/d; it increased to 90.0 (60.0–90.0) mg/d at one and two years of follow-up (Supplementary Data). Over the two-year follow-up period, there was a significant increase of the proportion of patients in the rank of 50–120 mg MEDD (N = 296, 59.08% at two-year follow-up; N = 13, 3.23% at baseline). Despite this, no significant clinical improvement in pain outcomes was observed. A small number of patients were on high opioid doses (>200 mg MEDD) during the whole duration of the study (N = 5, 1.24% at baseline; N = 3, 0.6% at two years) (Figure 3). In our cohort, a

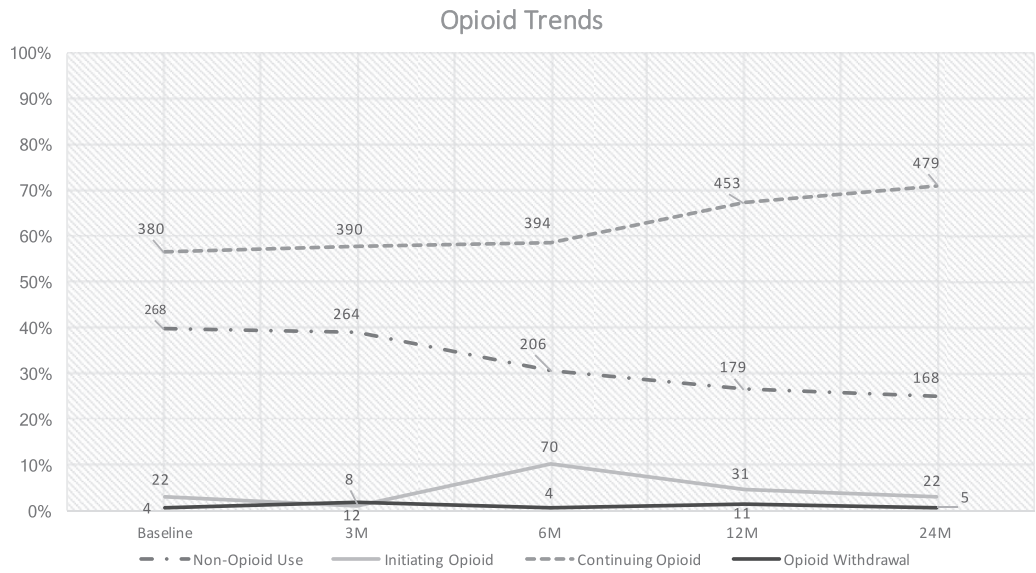

Figure 1. Opioid prescription trends of two years of follow-up. Data are presented as No. and %.

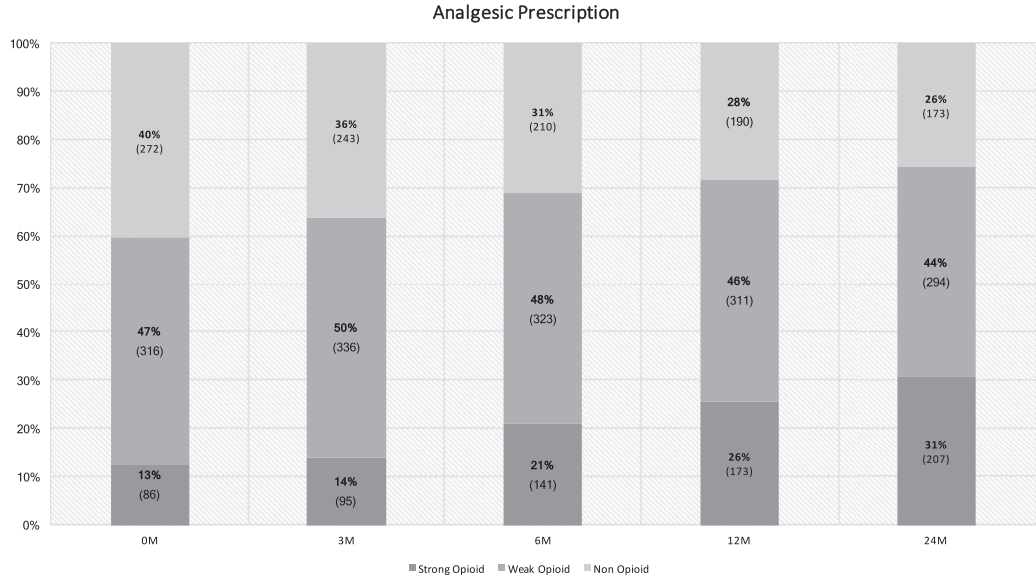

Figure 2. Analgesic prescription. Data are presented as % and (No.).

small proportion of patients developed aberrant opioid-related behaviors: 0.7% (N = 5) at 12 months and 1.5% (N = 10) at 24 months of follow-up.

A comparison of pain clinical outcomes assessment in strong opioid vs weak opioid users was performed in a subgroup analysis of our cohort. Both at baseline and at two years of follow-up, there were no significant differences in the pain interference or severity subscale scores of the BPI questionnaire. At baseline, strong opioid users reported significantly higher disability concerning mood, walking, and normal work items. Regarding self-reported efficacy of medication, at two years of follow-up, 34.5% of strong opioid users reported no effect of their medication (N = 68), and 30.6% of weak opioid users reported only a little benefit of their medication (N = 83) (Table 3).

In accordance with our subgroup analysis concerning opioid users at two years of follow-up, those users who reported clinical improvement did not present significant sociodemographic differences compared with the other opioid users (without clinical improvement), except for professional status, wherein the first (with clinical improvement) were more often active workers ($P = 0.012$). Moreover, there were also no significant differences concerning depressive or anxiety disorders in these subgroups. Concerning pain characterization, there were no significant differences among these subgroups except for pain location: opioid users with clinical improvement more often presented with pain at the cervical region ($P = 0.022$), lumbar region ($P = 0.027$), and in the lower limbs ($P = 0.019$) (Supplementary Data).

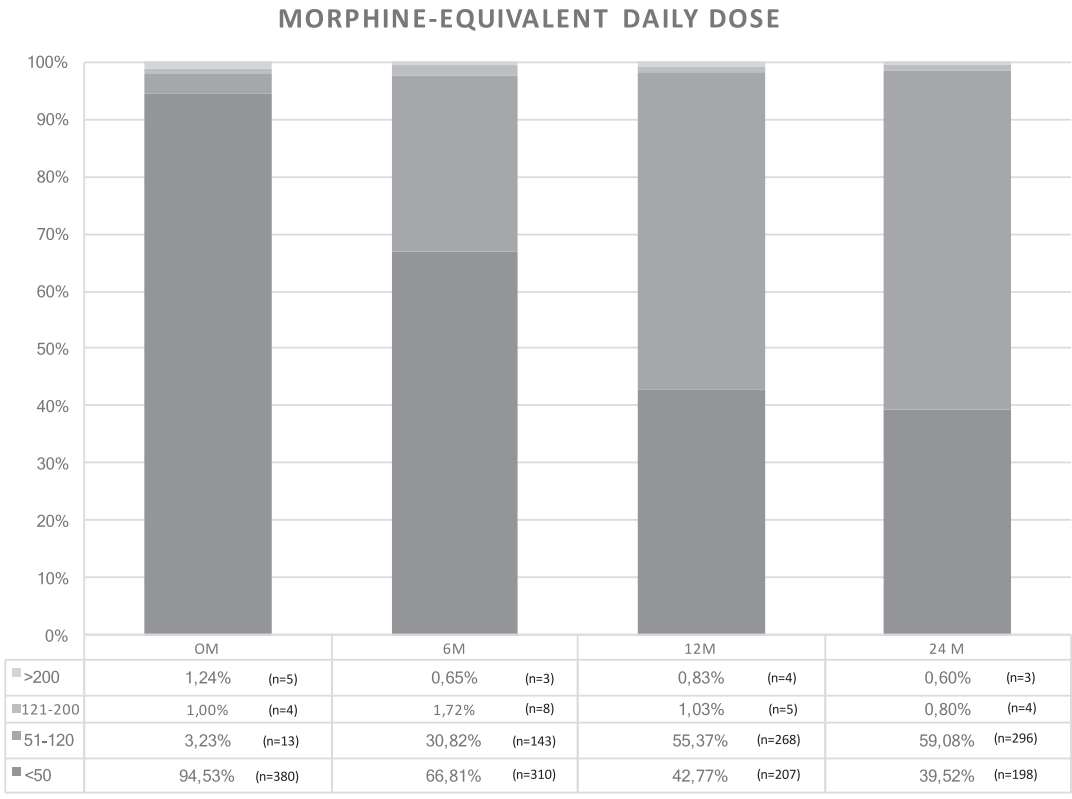

Figure 3. Morphine-equivalent daily doses. Data are presented as % and (No.).

Table 3. Subgroup analysis of pain characteristics of opioid users

		Baseline			24 mo		
		Weak Opioids (N = 316)	Strong Opioids (N = 86)	*P* Value	Weak Opioids (N = 294)	Strong Opioids (N = 207)	*P* Value
Pain intensity	Pain severity score (0–10 NRS)	6.3 (4.7–7.5)	6.5 (4.8–7.5)	0.863*	5.6 (3.3–7.3)	5.7 (4.3–7.3)	0.491†
	Pain on average (0–10 NRS)	6.0 (5.0–7.0)	6.0 (5.0–8.0)	0.462*	6.0 (4.0–8.0)	6.0 (5.0–8.0)	0.271*
	Pain at its least (0–10 NRS)	4.0 (2.0–5.0)	5.0 (3.0–6.0)	0.503*	4.0 (1.0–5.0)	4.0 (2.0–6.0)	0.885*
	Pain at its worst (0–10 NRS)	9.0 (7.0–10.0)	9.0 (7.0–10.0)	0.897*	8.0 (5.0–9.0)	8.0 (6.0–9.0)	0.428*
	Pain right now (0–10 NRS)	5.0 (3.0–8.0)	5.0 (3.0–8.0)	0.814*	5.0 (2.0–8.0)	5.0 (3.0–8.0)	0.142*
Pain interference	Pain interference score (0–10 NRS)	6.7 (5.0–8.3)	7.2 (5.6–8.3)	0.127*	6.0 (3.7–7.6)	5.9 (4.0–7.4)	0.094*
	General activity (0–10 NRS)	8.0 (6.0–9.0)	8.0 (7.0–10.0)	0.112†	7.0 (4.0–8.0)	7.0 (5.0–9.0)	0.238†
	Mood (0–10 NRS)	7.0 (5.0–9.0)	8.0 (5.0–10.0)	0.026†	6.0 (1.0 –8.0)	7.0 (3.0–8.0)	0.116†
	Walking ability (0–10 NRS)	8.0 (6.0–10.0)	9.0 (6.0–10.0)	0.031†	7.0 (3.0–9.0)	8.0 (5.0–9.0)	0.185†
	Normal work (0–10 NRS)	8.0 (6.0–10.0)	9.0 (7.0–10.0)	0.007†	7.0 (4.0–9.0)	7.0 (6.0–9.0)	0.195†
	Relations with other people (0–10 NRS)	5.0 (0.0–8.0)	5.0 (0.0–8.0)	0.882†	4.0 (0.0–8.0)	5.0 (0.0–7.0)	0.439†
	Sleep (0–10 NRS)	7.0 (3.0–9.0)	8.0 (5.0–10.0)	0.312†	5.0 (0.0–8.0)	5.0 (0.0–9.0)	0.246
	Enjoyment of life (0–10 NRS)	7.0 (4.0–9.0)	8.0 (3.0–9.0)	0.987†	5.0 (0.0–8.0)	5.0 (0.0–8.0)	0.378†
Pain medication efficacy	None	71, 23.9%	29, 35.8%	0.192‡	59, 21.7%	68, 34.5%	0.007‡
	A little	85, 27.3%	19, 21.0%		83, 30.6%	43, 21.8%	
	Moderate	55, 18.5%	14, 17.3%		76, 27.9%	52, 26.4%	
	Quite a bit	5, 1.7%	2, 2.5%		52, 19.1%	29, 14.7%	
	Completely	3, 1.3%	7, 1.9%		2, 0.7%	5, 2.5%	

Data are presented as median (interquartile range) for pain intensity and pain interference. Pain medication efficacy data are presented as No., %. Proportions are calculated as column proportions.

NRS = numerical rating scale.

*t test.

†Mann-Whitney U test.

‡X^2 comparisons.

Finally, factors associated with opioid prescription were analyzed (Table 4). Age, gender, professional status, education level, depression, the pattern of pain persistence, pain location (cervical region, lumbar region, upper or lower limb), pain etiology (chronic musculoskeletal pain), and BPI severity and interference scales had a statistically significant association with opioid use. In the multivariate model, only continuous pain (odds ratio [OR] = 2.66, 95% confidence interval = 1.66–4.25), lower limb pain location (OR = 1.77, $P = 0.012$), and BPI interference scale score (OR = 1.17, $P = 0.006$) were independent predictors of opioid use. Our model had an adequate goodness of fit (Hosmer and Lemeshow test: $P = 0.404$) and a satisfactory predictive and discriminative power (area under the curve = 0.776).

Table 4. Predictors of prescription opioid use in CNCP

	Crude OR (95% CI)	Adjusted OR (95% CI)
Age, y	$P \leq 0.001$*	$P = 0.809$
18–45	1	1
45–60	1.56 (1.00–2.43)	1.26 (0.71–2.26)
60–75	2.66 (1.66–4.27)	1.35 (0.61–3.00)
>75	2.95 (1.55–5.63)	1.54 (0.58–4.11)
Sex	$P = 0.044$	$P = 0.684$
Female	1.47 (1.01–2.14)	1.10 (0.69–1.75)
Male	1	1
Professional/occupational status	$P < 0.001$*	$P = 0.090$
Full- or part-time worker	1	1
Student	1.34 (0.24–7.46)	1.59 (0.14–18.10)
Unemployed	1.98 (1.15–3.41)	1.57 (0.83–2.95)
House worker or domestic worker	5.35 (1.56–18.31)	3.98 (1.05–15.13)
Retired	3.02 (2.04–4.49)	2.38 (1.25–4.53)
Education level	$P = 0.001$*	$P = 0.461$
No education	1	1
1–4 y (basic 1st cycle)	1.13 (0.36–3.51)	1.07 (0.29–3.94)
5–9 y (basic 2nd and 3rd cycles)	0.68 (0.21–2.15)	0.97 (0.25–3.79)
10–12 y (secondary)	0.33 (0.10–1.08)	0.61 (0.15–2.57)
>12 y (higher)	0.58 (0.17–1.94)	1.28 (0.30–5.44)
Current depressive disorders	$P = 0.011$*	$P = 0.083$
	1.87 (1.15–3.03)	1.62 (0.94–2.79)
Pain persistent pattern	$P \leq 0.001$*	$P \leq 0.001$*
Noncontinuous	1	1
Continuous	3.17 (2.20–4.55)	2.66 (1.66–4.25)
Pain location		
Cervical region	$P = 0.024$*	$P = 0.898$
	1.53 (1.06–2.22)	1.03 (0.63–1.71)
Lumbar region	$P = 0.001$*	$P = 0.937$
	1.80 (1.27–2.56)	1.02 (0.64–1.61)
Upper limb	$P = 0.002$*	$P = 0.203$
	1.73 (1.22–2.46)	1.36 (0.85–2.17)
Lower limb	$P < 0.001$*	$P = 0.012$*
	2.51 (1.76–3.58)	1.77 (1.13–2.75)
Pain etiology		
Chronic musculoskeletal pain	$P = 0.004$*	$P = 0.994$
	1.67 (1.17–2.37)	1.00 (0.64–1.58)
Severity scale	$P < 0.001$*	$P = 0.966$
	1.27(1.16–1.40)	0.97 (0.84–1.11)
Interference scale	$P < 0.001$*	$P = 0.006$*
	1.32 (1.22–1.43)	1.17 (1.05–1.31)

Predictors of opioid analgesics use were defined by simple and multiple logistic regression.

CI = confidence interval; CNCP = chronic noncancer pain; OR = odds ratio.

*Adjusted ORs were calculated using multivariate logistic regression models. The multivariate model included adjustment for all variables with crude association measures with P values <0.1 in the univariate analysis. P values for the omnibus tests evaluated the significance of each predictor variable.

Discussion

Opioid use in chronic noncancer pain is still a controversial topic regarding long-term effectiveness and safety. However, most of the available systematic reviews have been limited to studies with short follow-up periods (three to six months) [10,11,15,38]. Tayeb et al. examined the duration of studies concerning chronic pain drug trials and concluded that most of these studies have limited follow-up periods due to the difficulty of extending their duration (>12 months) for ethical, practical, and regulatory reasons [18].

In the last decades, there has been a worldwide increase of opioid prescriptions and opioid-related adverse events, raising epidemiological concerns in countries like the United States, Canada, and Australia [21,23,25,26,36,39,40]. A recent cross-sectional survey in the Danish population reported a 30% increase of strong opioid prescriptions from 2001 to 2013, making Denmark the country with the third highest legal opioid use in the world [23].

Portugal seems to be an exception, taking into account the results of an epidemiological population-based study published in 2013 in which the national estimated opioid prescription prevalence in subjects reporting chronic pain was only 4.37%, in comparison with other Western countries where the reported rates of prescription are as high as 15–30% [41].

In the present study, the prevalence of opioid prescription at baseline was 59.6% (N = 402), and 13.0% (N = 86) were strong opioids. At 24 months, the overall opioid prescription rate increased to 74.0% (N = 501), with strong opioid prescription increasing to 31.0% (N = 207). This can be explained by the fact that patients were recruited at highly specialized centers for pain management. Thus, although this may not be assumed to represent the pattern of opioid prescription in the general population of CNCP patients, it certainly raises concerns about possible increasing trends in opioid use. In fact, current opioid use in our country may be substantially higher than in 2013, and it would be advisable to perform new population-based studies on this subject.

Similar to other studies, opioid users in our cohort were older, had lower levels of education, and were retired. The increased prevalence of osteoarthritis in older age may explain the higher rate of opioid prescription in this population [23,36,42–49].

Most opioid users report a pain location of the lumbar region and lower limbs, which is in line with previous studies [50–52]. Chronic musculoskeletal pain was the most prevalent pain etiology, which is also in accordance with previous epidemiological data published on CNCP [45,53,54].

In our study, continuous pain, pain in the lower limbs, and higher BPI interference score were independent predictors of opioid use. Taking into account the high prevalence of knee and hip osteoarthritis pain in the older population, this association with opioid use is not surprising [51,55]. The association of higher interference pain scores with opioid use seems a paradox but could be explained by reverse association. Indeed, opioids are often used in patients with more complex pain (not responding to other treatments) and higher interference scores, and they may induce an increase in pain interference levels.

There are several reports about the controversial results of long-term opioid use in CNCP, namely regarding functional outcomes. The available systematic reviews have failed to find robust evidence to support opioid use in CNCP [10,11,15,19,56]. Therefore, the need to promote adequate and high-quality real-world prospective studies evaluating opioid effectiveness in these patients, namely concerning pain intensity and functional outcomes, has been highlighted [37,57,58]. Despite the paucity of solid evidence, opioids are still formally recommended for CNCP management in several guidelines. Indeed, opioids are essential therapeutic options in CNCP treatment, as long as they are used correctly and in appropriately selected patients [2,11,59,60].

Opioid users at 24 months of follow-up report significantly higher pain intensity scores and pain interference scores on functional outcomes, as compared with nonusers. On self-reported pain questionnaires, opioid users reported that they had no pain relief or only a little/moderate pain relief with their pain medications. The analysis of a subgroup of patients comparing strong opioid users with weak opioid users did not reveal differences in pain interference or severity subscale scores from the BPI questionnaire. Again, in self-reported pain questionnaires, 34.5% of strong opioid users reported no pain relief, and 30.6% of weak opioid users reported only little/moderate pain relief. Also, among opioid users at two years of follow-up, we did not find significant differences among those who reported clinical improvement and those who did not, concerning most sociodemographic and pain characteristics. It is important to note that, as our sample includes patients attending multidisciplinary pain clinics, their pain management includes a wide variety of treatment options, such as pharmacological therapy, psychological assessment, invasive procedures, occupational therapy, and rehabilitation medicine, depending on pain etiology and response to each treatment. Moreover, strong opioids are often prescribed in more complex pain situations when other therapies have failed.

These findings, although not surprising, raise additional doubts about the long-term effectiveness of opioid therapy in CNCP [39,61]. Another important observation was the progressive increase of opioid prescription during all periods of follow-up, despite the reduced analgesic efficacy reported by opioid users, including those on strong opioid prescriptions and at higher doses. Moreover, we registered an increase in MEDD over the two years of follow-up. At baseline, most opioid users (94.5%, N = 383) were on low-dose MEDD rank (<50 mg/d); whereas at 24-month follow-up 59, 1% (N = 296) of opioid users were on 51–120 mg MEDD rank. Furthermore, there was a progressive increase in the proportion of patients who were prescribed opioids over the two years of follow-up. Despite these changes, there was no significant improvement in clinical outcomes.

Once again, these results are in line with the conflicting evidence reported by the available systematic reviews on the topic of the effectiveness of long-term opioid use [10,15,62,63].

Opioids are associated with side effects, such as nausea or vomiting, obstipation, sedation, itching, or respiratory depression. The complete and thorough monitoring of adverse effects was outside the scope of our study. However, it is important to note that the opioid discontinuation rate was very low (1.6%, N = 11 at 12 months of follow-up; 0.7%, N = 5 at 24 months of follow-up).

It must be noted that only the COMM questionnaire was used as a screening tool to identify aberrant drug-related behaviors and the development of substance use disorders, which is an important limitation that may contribute to the very low rate of opioid-related aberrant behaviors observed. Although other more reliable methods for the detection of aberrant drug-related behaviors, such as urine drug screening or pill counts, are recommended in guidelines in the United States and Canada, they are not included in guidelines from other countries or in the recent position paper of the European Pain Federation [2,25]. Consequently, they are not routinely used in the clinical setting in Portugal, or in most European countries, and were not implemented in this observational study aiming to depict the "real-world" context of opioid prescription without changing the usual routines of care. On the other hand, in Portugal, there is strict control of opioid prescription based on an electronic drug prescription system and a monitoring program that includes the supply of the drugs by pharmacies under national identity card control. In clinical practice, physicians actually use this system to assess all the prescriptions made for each patient, allowing for the implementation of adequate control measures whenever opioid-related aberrant behaviors are suspected. In general, patients' signs, symptoms, and behaviors reported to or observed by the physicians prompt the suspicion, but there is no algorithm or common strict protocol triggering these electronic queries. It must be noted that the present study was carried out in the context of tertiary

pain clinics, with highly specialized physicians fully aware of the problem of the misuse and abuse of opioids. Although this may also contribute to the low rate of aberrant opioid-related behaviors observed, though using only COMM as a self-report measure, it also prevents generalization to other clinical contexts. Finally, rates of problematic use of opioids reported in a recent systematic review were quite broad, ranging from 1% to 81% [64], and although the situation concerning opioid misuse and abuse in Europe is substantially different from in the United States and Canada [26], further studies addressing this particular topic are needed to evaluate the current situation in different settings.

It is important to raise physicians' awareness about the safety and effectiveness of long-term opioid use, especially regarding patient-centered outcomes—pain score evaluation and functional outcomes [58,65–67]. Moreover, all physicians must be aware of the potential risk of the development of physical dependence, misuse, tolerance, and addiction with this class of drugs [68–70]. There is a strong case for the development of suitable guidelines on opioid prescription and adequate under- and postgraduate training on pain management as part of all physicians' curricula [2,4].

A recent survey in the United Kingdom, to assess primary care physicians' practices and approaches to opioid prescription showed that despite concerns about opioid use, most physicians believe in opioid effectiveness for CNCP management and consider themselves sufficiently educated on this topic. However, they also stated that one of the main reasons to prescribe opioids in CNCP was the absence of available alternatives [40]. Recently published guidelines by the European Pain Federation aim to provide expert recommendations on safe and appropriate opioid prescribing in chronic pain management. In these guidelines, opioids are recognized as valuable therapeutic options in pain treatment, assuming that physicians have adequate education on this topic and are aware of the importance of clinical surveillance and outcome evaluation for these patients [2,71].

Some limitations of this study must be addressed. Our opioid prescription rates are higher compared with other rates described in CNCP patients [42,49]. As mentioned above, these rates are high because the cohort sample includes only patients who were referred to specialized centers (MPCs) for pain management, presumably because they had failed nonspecialty treatment. Therefore, care must be taken when considering generalization of these results to the general population or to primary care settings. Another limitation of our study is the fact that we were unable, for practical reasons, to use urine drug testing protocols to detect aberrant use and misuse of opioids. However, we used the Current Opioid Misuse Measure as a screening tool, which has been shown to have good validity, reliability, and predictive ability to detect aberrant use and misuse of opioids [31,72]. Additionally, in Portugal, we have an electronic prescription drug program that allows clinicians to monitor patients' prescriptions and routinely check for abnormal patterns of use, which is particularly useful, for example, in the case of opioid drugs. Moreover, as the study design is not a randomized controlled trial, rigorous and unbiased causal comparisons between opioid and nonopioid users regarding pain outcomes are not warranted. However, our study design (observational prospective cohort study) allowed us to describe chronic opioid therapy and outcomes in CNCP patients under real-life and real clinical practice conditions, which we consider a major strength of our study. Additionally, the long follow-up of two years addressed the limitations of many previous studies with shorter follow-up periods [10,25]. Also, effective patient retention strategies were implemented to overcome the risk of loss of patients during follow-up.

Conclusions

In our cohort of prospectively studied CNCP patients, we reported high opioid use in CNCP. Initiation of opioid therapy and increasing doses were not associated with significant improvement in patients' long-term outcomes. Moreover, although 43% of opioid users reported some degree of pain relief, opioids were continued even in those patients who reported little or no benefit with their therapy.

Further evidence must rely on epidemiological real-world longitudinal studies to assess the effectiveness and safety of long-term opioid use, dose-related risk, and benefit profiles in CNCP patients.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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