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Original Reports

Effectiveness of Opioids for Chronic Noncancer Pain: A Two-Year Multicenter, Prospective Cohort Study With Propensity Score Matching

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Abstract: **Opioid use in chronic non cancer pain (CNCP) is still controversial regarding their effectiveness and safety. We conducted a 2-year prospective cohort study in 4 multidisciplinary chronic pain clinics to assess long-term opioid effectiveness in CNCP patients. All adult CNCP patients consecutively admitted to their first consultation were recruited. Demographic and clinical data were collected, and propensity score matching was used to adjust for differences between opioid users and nonusers. The Brief Pain Inventory and the Short version of Treatment Outcomes in Pain Survey were used to measure pain outcomes and quality of life. A total of 529 subjects were matched and included in our analysis. Rate of prescription opioid use was 59.7% at baseline, which increased to 70.3% over 2 years, of which 42.7% of the prescriptions were for strong opioids. Opioid users reported no improvement regarding pain symptoms, physical function, emotional function, and social/familiar disability. Opioid users reported higher satisfaction with care and outcomes at 1 year of follow-up, but at 2 years, they only reported improvement in satisfaction with outcomes. Opioids have shown limited effectiveness in long-term CNCP management, as opioid users presented no improvements regarding functional outcomes and quality of life. These findings emphasize the need for proper selection and outcome assessment of CNCP patients prescribed opioids.**

Perspective: ***This study adds important additional evidence concerning the controversial use of opioids in CNCP management. Opioid users presented no improvement regarding pain relief, functional outcomes and quality of life over 2 years of follow-up. Therefore, our results support and highlight the limited effectiveness of opioids in long-term CNCP management.***

Key words: *Opioids, chronic noncancer pain, propensity score, effectiveness, quality of life.*

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Chronic pain (CP) is a major and debilitating health problem.[9] It has an estimated prevalence of 20% in the European population and is an important cause of direct and indirect healthcare costs, quality of life impairment, and has a significant impact on patients' and their families' lives.[8,51]

In 2012, a cross-sectional epidemiological study estimated the Portuguese CP prevalence to be as high as 14.3%.[4] Despite its high prevalence and substantial burden in healthcare systems,[5] chronic noncancer pain (CNCP) remains an underdiagnosed and undertreated problem.[51,71]

Opioids have been used for centuries in pain treatment. They may be considered for CNCP management, especially when nonopioid and adjuvant therapies have failed or are not clinically appropriate. In recent decades, there has been an exponential increase in opioid prescriptions in Western countries such as the United States, some European countries, and Australia.[7,27–29,41,44,51,58] Portugal seems to be an exception, because its estimated opioid prescription rate in CP patients is only 4%; in contrast, the available estimates of prescription rates in other Western countries are 15% to 30%.[6,48]

Long-term use of opioids is associated with the risk of adverse event development, such as gastrointestinal disorders (nausea, constipation), neuroendocrine dysfunction, osteoporosis, immunosuppression, cognitive disorders, somnolence, respiratory depression, physical dependence, opioid-induced hyperalgesia, and addiction.[23,48,53,54] Therefore, opioid prescriptions should be administered by adequately trained professionals and require regular clinical supervision, education, and empowerment of these patients.[14,51]

Although current evidence remains conflicting regarding the long-term effectiveness of opioids in CNCP treatment, they are still recommended by several guidelines.[13,16,51] The available systematic reviews of randomized controlled trials and open-label studies only support their short-term use in CNCP (3 months) and report a high incidence of associated adverse effects and opioid withdrawal with long-term use. Moreover, most of the studies present methodological insufficiencies such as small sample sizes, a considerable number of dropouts, opioid discontinuation, low levels of statistical power, and a limited evaluation of functional outcomes and quality of life of the included patients.[17,23,39,50] Therefore, more adequately designed prospective observational cohort studies are needed to evaluate the real-world clinical practice conditions of long-term (>6 months) opioid use effectiveness, with an adequately long follow-up duration, as well as quality of life and functional outcomes assessment.[24,32]

Our study aimed to assess the effectiveness of opioid therapy for the long-term management of CNCP, focusing on an adequate set of patient-centered outcomes in accordance with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations,[24] a real-world clinical practice perspective and an adequately long follow-up period.

Methods

Type of Study and Selection of Participants

An observational, prospective, multicenter, cohort study was performed, including consecutive CNCP patients from four multidisciplinary chronic pain clinics (MCPCs) in the Porto metropolitan area, Portugal (Centro Hospitalar de S. João, Centro Hospitalar do Porto, Hospital Pedro Hispano, and Centro Hospitalar Vila Nova de Gaia/Espinho), with 2 years of follow-up.

Participants were recruited during their first appointment in one of the MCPCs and were included if they provided consent to participate, were 18 years or older, and were CNCP patients with a pain duration ≥3 months.

Patients with psychiatric or cognitive disorders that could interfere with data collection, those physically or psychologically unable to communicate, and those unable to speak Portuguese were excluded.

Pain etiology classification was performed according to the International Association for the Study of Pain Task Force on Pain Classification for the International Classification of Diseases, 11th revision.[64]

Formal sample size calculations were performed to detect minimal clinically important differences (MCIDs) between opioid users and nonusers of at least 5 points in the mean scores for the Short version of Treatment Outcomes in Pain Survey (S-TOPS) dimensions, assuming a population standard deviation of the primary outcomes of 20 points, a confidence level of 95%, and power of 80%. Therefore, we decided to recruit at least 252 patients in each group,[24,25,32] and assuming (based on historical data from the MCPCs) 40% of patients were opioid users, a total of 674 CNCP patients were recruited. This sample size is also adequate to identify MCIDs for secondary outcomes, namely, pain intensity (measured by a 0–10 numerical rating scale, with an MCID of 3 points).[2]

Data Collection Methods

Recruitment and initial assessment contact was performed in a face-to-face interview by a trained interviewer, and clinical assessment was performed by the attending physician. Patients' follow-up contacts were performed by telephone by trained interviewers at 6, 12, and 24 months and complemented with consultation and analysis of clinical records.

Opioid users were defined as patients taking opioids for 6 or more months during the 2-year period of follow-up.

The primary outcome measures, taking into account the IMMPACT Consensus Recommendations,[24,32] were the 7 main dimensions of the S-TOPS questionnaire (Pain Symptom, Physical Function–Lower Body, Physical Function –Upper Body, Family/Social Disability, Role of Emotional Disability, Satisfaction with Outcome, Satisfaction with Care)[36,47] and the pain interference and pain severity subscales of the Brief Pain Inventory (BPI) questionnaire.[2,40]

S-TOPS is composed of 7 validated independent subscales with a total of 29 items: 1) Pain Symptom, 2)

Physical Disability−Lower Body, 3) Physical Disability −Upper Body, 4) Family/Social Disability, 5) Role Emotional Disability, 6) Patient Satisfaction with Care, and 7) Patient satisfaction with Outcomes. Each subscale score from S-TOPS is expressed from 0 ("no pain/disability") to 100 ("maximum pain/disability"). The satisfaction with care and satisfaction with outcomes subscales are inverted, with 0 representing "no satisfaction" and 100 representing "maximum satisfaction". The mean of the answers in each subscale was calculated.[32]

The BPI questionnaire is composed of 2 independent subscales: the severity scale and the interference scale. 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 subscale score 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 7 interference scores.[40,60]

Clinical improvement was considered when there was a decrease at 12 and 24 months of follow-up in the scores of the S-TOPS dimensions (except for satisfaction with outcome and care) and in the interference and severity scores of the BPI questionnaire (difference between the score of each variable at 12 or 24 months and the score at baseline <0). In the case of the S-TOPS dimensions of satisfaction with outcome and satisfaction with care, clinical improvement was considered when an increase was observed (difference between the score at 12 or 24 months and the score at baseline >0).

The standardized median differences between 12 months of follow-up versus baseline and 24 months of follow-up versus baseline, comparing opioid users and nonusers, are also provided as supplemental data. The differences in the median scores between opioid and nonopioid users were calculated. Clinical improvement was considered when a negative difference was observed for each S-TOPS dimension (except for satisfaction with outcome and care) and for interference and severity scores of the BPI questionnaire (difference between opioid users and nonusers <0). In the case of the S-TOPS dimensions of satisfaction with outcome and satisfaction with care, it was considered clinical improvement when a positive difference was observed (difference between opioid users and nonusers >0).

Ethical Concerns

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 reformulations.

Approval from the National Committee for Data Protection and from the local Ethical Committees was obtained. All patients were informed of the study details and signed an informed consent form.

Propensity Score Matching

The aim of this study was to assess the long-term effectiveness of opioid therapy in chronic noncancer pain patients. Because the assignment of treatment depends on patients' characteristics in observational studies, simple effect measures are not appropriate to estimate treatment effects because of confounding biases caused by systematic differences in observed characteristics between the compared groups.[10,35] The creation of a propensity score allows the generation of a balancing score such that the conditional distribution of the pretreatment characteristics is the same for the treated (opioid users) and untreated groups (opioid nonusers) and provides unbiased estimates of the effectiveness measures of opioid therapy in CNCP patients.[10,55–57,70] Propensity scores and propensity score matching are methods that have evolved within the framework of modern counterfactual theories of causal inference; they are alternatives to classic regression model adjustments for controlling for confounds and have been shown to perform better.[19,45,57,59] The propensity score (PS) was first proposed by Rosenbaum and Rubin,[56] and it is defined as the estimate of the probability of a given subject receiving a treatment (or exposure) conditional on the observed baseline covariates. The main assumption on which PS analysis is based is that subjects with an equal (or similar enough) PS will have similar baseline covariate values and thus be comparable. In propensity score matching, subjects are matched using their estimated PS to create a balanced comparable sample.[19,59]

Variables for the propensity score model were selected based on measured baseline covariates and on clinical judgement of all covariates that could interfere with outcomes. The following variables were included in the PS model: sex; age; pain duration (in years); educational status, professional activity; musculoskeletal pain, neuropathic pain, postsurgical pain; anxiety; depression; diabetes mellitus; dyslipidemia; cardiac disease; chronic respiratory disease; hypertension; obesity; alcohol and drug consumption; S-TOPS questionnaire dimensions at baseline; and BPI interference and severity scores at baseline.

The resulting predicted probabilities (propensity scores) were used to match nonopioid users (controls) to opioid users with similar baseline characteristics. Matching was performed using a nearest-neighbor matching algorithm with a match ratio of 1:2 with replacement within a .2 caliper (width equal to .2 of the pooled standard deviation of the logit of PS).[3,56] For this purpose, we used the PS matching custom dialog for SPSS,[62,63] using R version 3.1.2[61] plug-ins. For the matching within defined calipers, the matched control was chosen within a preset distance (or caliper) between its propensity score and the one from the selected subject under treatment. Because there is no defined optimal caliper to be used, we have used a distance of 0.2, which is suggested

and recommended by many authors.[3,35] A very small caliper may result in a better balance but at the expense of finding fewer subjects that could be successfully matched. Therefore, to make this decision, as recommended, we initially tested several different calipers (.05; .10; .20; .25; .30) and chose the one that allowed a better balance between group comparability and effective sample size.

Statistical Analysis

Descriptive statistics of patient characteristics and clinical variables were expressed as frequencies with percentages (%), medians with interquartile ranges, or means with standard deviations when appropriate. Before and after sample matching, nonparametric and parametric tests were performed for testing hypotheses regarding numerical variables, according to their distribution and tested normality assumptions; chi-square tests were used for categorical variables. A P value of .05 was considered significant for all tests.

The software packages that were used for statistical analysis were SPSS version 24 (IBM, Armonk, NY) using R version 3.1.2 plug-ins.[61]

Results

Sample Characterization

We recruited 808 CNCPs, but only 674 subjects completed the 2-year follow-up assessment and were included in our study. Moreover, 145 subjects were excluded from our analysis because they had missing values for some of the variables included in the propensity score matching, resulting in a final sample of 529 subjects. To assess the potential selection bias associated with those exclusions, we compared included and excluded subjects and concluded that no major or significant differences existed between them (Supplementary Table 1).

Before matching, the opioid users at baseline were older, less educated (education level 1−4 years) and retired. Most opioid users presented chronic musculoskeletal pain and a higher prevalence of diabetes mellitus and hypertension. Table 1 provides descriptive statistics for patient sociodemographic and clinical characteristics, and bivariate comparisons among the opioid users and nonusers were performed.

Opioid Prescription Patterns

At baseline, opioid prescription prevalence was 59.7% (n = 316), and 16.2% (n = 86) of the prescriptions were for strong opioids. The opioid prescription rate increased at 6 months (60.3%, n = 319) and at 12 months of follow-up (72.6%, n = 384). At 24 months of follow-up, opioid prescriptions decreased slightly to 70.3% (n = 372), and the proportion of strong opioid prescriptions substantially increased (42.7%, n = 226) (Table 2). The most prescribed strong opioids were buprenorphine and Tapentadol during the follow-up period, and the rate of high-dose opioid prescription (>200 mg/d morphine equivalence) was <.5%.

Propensity Score Assessment

A total of 371 opioid users and 117 propensity score-matched nonopioid users were included in the analysis. After using the propensity score for matching subjects using opioids at baseline with those who did not, differences between both groups could be effectively removed (Table 1).

Opioid Effectiveness

All results regarding opioid effectiveness are presented after the propensity score matching. Clinical improvement with opioids was defined for each participant if there was a decreased difference in score values at 24 and 12 months of follow-up compared with baseline for the S-TOPS dimensions (except for satisfaction with outcome and care) and for the severity and interference scores of the BPI. In the case of the S-TOPS dimensions of satisfaction with outcome and satisfaction with care, clinical improvement was defined by an increased difference of the respective score values.

At 12 months, the opioid nonusers presented a significantly higher rate of clinical improvement in pain symptoms ($P = .014$), physical function of the lower body ($P = .014$) and severity score on the BPI ($P = .001$). In contrast, at this time point, the opioid users reported a significantly higher rate of improvement in satisfaction with outcome ($P = .030$) and satisfaction with care ($P = .044$; Table 3).

At 24 months, the opioid nonusers reported a significantly higher rate of clinical improvement in pain symptoms only ($P = .004$; Table 4). There were no significant differences in the improvement rates of all other S-TOPS domains. However, the opioid users reported a significantly higher rate of clinical improvement in their satisfaction with outcomes ($P = .004$). There were no differences between the opioid users and nonusers regarding the BPI severity and interference scores at 24 months (Table 4).

An analysis of the change from baseline in the seven dimensions of the S-TOPS and the interference and severity scores of the BPI was also performed (a continuous variable was calculated for each subject as the difference between the scores at 12 or 24 months and the scores at baseline). These additional comparisons based on changes from baseline as continuous variables were consistent with the results based on the analysis of the rates of improvement described above. At 12 months, the opioid users only presented significantly lower (better) values in physical function (upper and lower body). At 24 months, the opioid users presented significantly lower (better) values in physical function (lower and upper body). During the entire follow-up period, there were no significant differences regarding emotional functioning and family/social functioning in the patients on opioid therapy. At 24 months, the opioid

Table 1. Sample Characterization at Baseline Without and With Propensity Score Matching

		Without PS Matching			With PS Matching		
Variables	Total (N = 529)	Opioid users (n = 401)	Opioid non-users (n = 128)	P value	Opioid users (n = 371)	Opioid non-users (n = 117)	P value
Sociodemographic							
Age, y				.026*/.170†			.480*/.170†
18–45	111 (21.0)	76 (19.0)	35 (27.3)		73 (18.9)	17 (14.1)	
45–60	171 (32.3)	124 (30.9)	47 (36.7)		121 (31.3)	37 (31.7)	
60–75	179 (33.8)	143 (35.7)	36 (28.1)		137 (35.4)	41 (34.6)	
>75	68 (12.9)	58 (14.5)	10 (7.8)		56 (14.5)	23 (19.6)	
Female gender	379 (71.6)	296 (73.8)	83 (64.8)	.056*	287 (74.2)	84 (71.1)	.522*
Education level				.004*/.159†			.366*/.159†
No education, y	15 (2.8)	13 (3.2)	2 (1.6)		12 (3.1)	2 (1.3)	
1–4 (basic 1st cycle)	277 (52.4)	224 (55.9)	53 (41.4)		214 (55.3)	63 (53.5)	
5–9 (basic 2nd and 3rd cycles)	130 (24.6)	94 (23.4)	36 (28.1)		93 (23.8)	14 (12.0)	
10–12 (secondary)	52 (9.8)	30 (7.5)	22 (17.2)		29 (7.5)	14 (12.0)	
More than 12 (higher)	55 (10.4)	40 (10.0)	15 (11.7)		40 (10.3)	16 (14.0)	
Professional/ occupational status				<.001*/.756†			.252*/.756†
Full or part-time worker	167 (31.6)	106 (26.4)	61 (47.7)		104 (26.9)	31 (26.0)	
Unemployed	73 (13.8)	55 (13.7)	18 (14.1)		54 (14.0)	15 (13.0)	
Retired	251 (47.4)	205 (51.1)	46 (35.9)		196 (50.6)	69 (58.1)	
Other	38 (7.2)	90 (22.4)	21 (16.4)		33 (8.5)	3 (2.9)	
Pain characterization							
Pain duration, y	4.0 (2.0–12.0)	3.0 (1.5–6.8)	5.0 (2.0–15.0)	.003‡	4.0 (2.0–10)	5.0 (2.0–14.0)	.953‡
Pain classification							
Chronic musculoskeletal pain	331 (62.6)	263 (65.6)	68 (53.1)	.012*	254 (65.6)	77 (65.5)	.511*
Chronic neuropathic pain	140 (26.5)	109 (27.2)	31 (24.2)	.566*	103 (26.6)	36 (30.7)	.412*
Chronic postsurgical and posttraumatic pain	70 (13.2)	47 (11.7)	23 (18.0)	.074*	45 (11.6)	14 (12.0)	.528*
Comorbidities							
Dyslipidemia	140 (26.5)	112 (27.9)	28 (21.9)	.206*	108 (27.9)	31 (26.4)	.814*,[a]
Hypertension	217 (41.0)	176 (43.9)	41 (32.0)	.018*	169 (43.7)	59 (49.7)	.246*
Ischemic cardiac disease	33 (6.2)	28 (7.0)	5 (3.9)	.293*	27 (7.0)	13 (11.0)	.173*
Diabetes mellitus	76 (14.4)	65 (16.2)	11 (8.6)	.042*	59 (15.2)	14 (12.3)	.455*
Obesity	66 (12.5)	54 (13.5)	12 (9.4)	.282*	53 (13.7)	15 (12.4)	.878*
Respiratory disease	47 (8.9)	33 (8.2)	14 (10.9)	.373*	32 (8.3)	11 (9.0)	.708*
Alcohol	5 (0.9)	5 (1.2)	0 (0.0)	.343§	0 (0.0)	0 (0.0)	—
Drugs	2 (0.4)	1 (0.2)	1 (0.8)	.426§	0 (0.0)	0 (0.0)	—
Anxiety disorder	37 (7.0)	24 (6.0)	13 (10.2)	.114*	22 (5.7)	7 (5.8)	.535*
Depressive disorder	100 (18.9)	81 (20.2)	19 (14.8)	.196*	74 (19.1)	22 (18.3)	.513*

Abbreviations: PS, propensity score.
Note. Data are presented as n (%) except for pain duration, which is presented as the median (P25–P75). Proportions are calculated as row proportions.
*χ^2 test.
†Linear by linear test.
‡Mann–Whitney *U* test.
§Fisher's exact test.

users reported significantly higher (better) values in satisfaction with care (Supplementary Tables 2 and 3).

Discussion

In the past decade, opioid prescriptions for CNCP has increased worldwide, raising epidemiological concerns.[22,34,66] In spite of opioid widespread use and guidelines recommendations, the available literature on this subject has not been conclusive regarding opioid effectiveness and safety for their long-term use.[17,37,39,50,67] Kalso et al.[39] supported the short-term efficacy (3 months) of opioids in neuropathic and musculoskeletal pain treatment. However, they also reported a high incidence of adverse effects (80%) and associated opioid withdrawal. Moreover, only 3 studies have reported improvement in function and quality of life, but these studies presented significant heterogeneity in their methodologies.[42,68,69] Therefore, no firm conclusions can be made regarding this subject.[39] Noble et al.[49] also supported that there is insufficient evidence concerning the long-term effectiveness of opioids for CNCP and identified the limited analgesic efficacy and the high incidence of adverse effects as the main causes for opioid withdrawal. Chou et al[15] found no differences regarding analgesic efficacy and safety when comparing long-acting opioids to each other and short-acting opioids.

Table 2. Prescription of Opioids at Each Evaluation Point

Using opioids	Baseline, n (%)	6 mo, n (%)	12 mo, n (%)	24 mo, n (%)
Yes	316 (59.7)	319 (60.3)	384 (72.6)	372 (70.3)
Weak opioids	230 (43.5)	178 (33.6)	209 (39.5)	146 (27.6)
Strong opioids	86 (16.2)	141 (26.7)	175 (33.1)	226 (42.7)
Buprenorphine	28 (32.6)	49 (34.8)	51 (29.1)	68 (30.1)
Fentanyl	18 (20.9)	20 (14.2)	38 (21.7)	42 (18.6)
Methadone	1 (1.2)	1 (.7)	1 (.6)	1 (.4)
Morphine	12 (14.0)	16 (11.3)	19 (10.9)	21 (9.3)
Oxycodone	2 (2.3)	4 (2.8)	7 (4.0)	14 (6.2)
Tapentadol	25 (29.1)	45 (31.9)	57 (32.6)	55 (24.3)
Hydromorphone	0 (0)	6 (4.3)	2 (1.1)	25 (11.1)
No	213 (40.3)	210 (39.7)	145 (27.4)	157 (29.7)

Note. Data are presented as n (%).

Table 3. Effectiveness of Opioids for CNCP Treatment at 12 Months, Assessed by the Rates of Clinical Improvement From Baseline in the Seven Dimensions of S-Tops and the Interference and Severity Scores of BPI, Using Propensity Score Matching

Variables		Opioid users (N = 371), n (%)	Opioid non-users (N = 117), n (%)	Differences in Proportions (95% CI)	P value
Pain symptom		248 (66.8)	90 (76.9)	.101 (.005; .197)	.014
Physical function	Lower body	144 (38.8)	59 (50.4)	.166 (.065; .267)	.014
	Upper body	70 (47.9)	23 (60.9)	.008 (−.074; −.090)	.786
Family/social disability		176 (45.5)	63 (53.2)	.111 (.010; .212)	.081
Role emotional disability		157 (42.3)	48 (41.0)	.013 (−.090; −.116)	.533
Satisfaction with	Outcome	251 (67.6)	63 (53.8)	.139 (.040; .238)	.030
	Care	226 (60.9)	56 (47.9)	.130 (.027; .233)	.044
BPI	Interference	231(62.3)	79 (67.5)	.052 (−.048; −.152)	.162
	Severity	228 (61.5)	89 (76.1)	.146 (.047; .245)	.001

Abbreviations: BPI, Brief Pain Inventory; S-TOPS, Shortened Treatment Outcomes in Pain Survey.
Note. Data are presented as n (%). Proportions are calculated as row proportions. Differences in proportions were calculated as the difference between the proportions (n/N) of opioid users and nonusers for each subscale (95% CI). Statistical analysis was conducted using the χ^2 test.

Table 4. Effectiveness of Opioids for CNCP Treatment at 24 Months, Assessed by the Rates of Clinical Improvement From Baseline in the Seven Dimensions of S-Tops and the Interference and Severity Scores of BPI, Using Propensity Score Matching

Variables		Opioid users (N = 371), [n (%)]	Opioid non-users (N = 117), [n (%)]	Differences in Proportions (95% CI)	P value
Pain symptom		221 (57.1)	85 (71.7)	.130 (.030,.230)	.004
Physical function	Lower body	169 (45.5)	43 (36.7)	.088 (−.015,.191)	.168
	Upper body	75 (20.2)	17 (14.5)	.057 (−.024, −.138)	.276
Family/social disability		169 (46.0)	55 (47.0)	.014 (−.090, −.118)	.598
Role emotional disability		125 (33.7)	49 (41.9)	.082 (−.018, −.182)	.077
Satisfaction with	Outcome	239 (64.4)	55 (47.0)	.174 (.072, .276)	.004
	Care	209 (56.3)	54 (46.1)	.101 (−.003, −.205)	.140
BPI	Interference	222 (57.4)	73 (62.3)	.026 (−.076, −.128)	.396
	Severity	198 (53.4)	69 (59.0)	.056 (−.047, −.159)	.172

Abbreviations: BPI, Brief Pain Inventory; S-TOPS, Shortened Treatment Outcomes in Pain Survey.
Note: Data are presented as n (%). Proportions are calculated as row proportions. Differences in proportions were calculated as the difference between the proportions (n/N) of the opioid users and nonusers for each subscale (95% CI). Statistical analysis was conducted using the χ^2 test.

Moreover, the available evidence has relied on observational studies or randomized controlled trials with significant limitations because of the variability of study designs, clinical heterogeneity, small sample sizes, and short follow-up periods (3–6 months). Therefore, there is insufficient qualitative and quantitative data to allow further conclusions regarding the long-term effectiveness of opioids.[17,23,39,43,44,48,50,65] To address some of these limitations and to assess real-world clinical practice concerning opioid effectiveness, we performed an observational, prospective cohort study in CNCP patients with 2 years of follow-up.

In our study, the opioid users were older, less educated, and most of them were retired. These sociodemographic characteristics are consistent with previous research on the CNCP population.[11] In fact, being female, increased age, and lower education are predictors of a higher prevalence and intensity of pain and its associated disability.[21,30]

The opioid prescription rate found in the present study was considerably high, taking into account other accounts of prescription rates described for CNCP patients.[1,18,38] This may be explained by the fact that our sample was selected from an MCPC and not from the general population or primary care. In the participating MCPCs, pain management includes a wide variety of treatment options, such as pharmacological therapy, psychological assessment, invasive procedures, and rehabilitation medicine, depending on pain etiology and the clinical response to each treatment. Opioid prescription, in accordance with the available guidelines,[16,22,26,65] was considered when nonopioid and adjuvant therapies failed or when they were not clinically appropriate. However, it should be noted that beginning opioid treatment or dose titration relies exclusively on the clinical evaluation of these patients by the attending physician.

It is also important to note that, during all follow-up periods, opioid prescription rate had increased, particularly driven by an increase in strong opioid prescriptions. In spite of this, there were no improvements regarding functional outcomes and quality of life in these patients, as substantiated by no improvement in all S-TOPS domains and in the BPI interference and severity scores. Moreover, opioid nonusers reported significant improvements in pain symptoms, physical function, and BPI severity scores at 1 year of follow-up. At 2 years, opioid nonusers still reported significant improvement in pain symptoms. Therefore, our results raise concerns regarding the limited effectiveness of opioids in CNCP, despite their widespread use.[39,48,50]

Few studies have assessed functional outcomes and quality of life in CNCP patients.[24,36,47] A Cochrane systematic review regarding long-term effectiveness of opioids[49] reported inconsistent results regarding patient quality of life improvement up to 12 to 13 months of follow-up. To address this issue, we assessed opioid effectiveness regarding the core outcomes recommended by IMMPACT: pain symptoms, physical function, family/social function, emotional disability, and satisfaction with outcomes and healthcare.[24] In our study, there was no improvement in functional outcomes and quality of life in CNCP patients prescribed opioids over 2 years of follow-up.[13,38,58]

Despite these results, at 12 months of follow-up, the opioid users reported significant improvement in satisfaction with outcomes and care, and at 24 months, opioid users still reported higher satisfaction with outcomes. Patient satisfaction has been extensively studied in several medical areas,[12] but there are few reports regarding patient satisfaction in chronic pain treatment.[46] Satisfaction is defined as a subjective and individual evaluation of care, and it is considered a significant outcome in CNCP treatment assessment. It is important to distinguish satisfaction with care (quality of care) and satisfaction with outcomes (quality of treatment results). This difference may explain our paradoxical higher satisfaction rates, despite the reported limited improvement in functional and quality of life outcomes. Indeed, the improvement in satisfaction with care may be explained by some aspects of the patient-provider relationship in the opioid users, such as higher confidence, regular clinical supervision, and a clear definition of therapeutic goals. Furthermore, in accord with some authors, these contributions to patients' satisfaction may exceed that of pain relief.[12,20,31]

The positive effect on patients' satisfaction with outcome may highlight the importance of perceived pain control in these patients' lives despite limited pain relief. Indeed, there are studies that report the positive relation of perceived control over pain and patient satisfaction reports.[23,46,52]

Strengths and Limitations

One of the strengths of this study is its observational and prospective design over a sufficiently long period of follow-up (2 years), adequately reflecting the real-world scenario of the patients and the actual effectiveness of long-term opioid therapy.[33,39] Indeed, most of the available studies on opioid effectiveness in CNCP are limited to short follow-up periods (up to 6 months). For instance, Chou et al[17] found no studies in their systematic review that evaluated long-term opioid effectiveness (>1 year) on outcomes concerning pain, function, and quality of life. Moreover, to minimize the influence of confounding factors, we used a propensity score-matching analysis. This is a robust statistical analysis method that allowed us to adjust our sample for a number of confounding variables that could affect opioid effectiveness assessment in CNCP patients.[57] To the best of our knowledge, our study is the first to specifically use this statistical analysis to assess opioid effectiveness over the long term.

There are still few reports in the literature concerning important core outcome domains in CNCP, such as physical functioning, participant ratings of improvement and satisfaction with treatment, sleep and fatigue, emotional functioning, and interpersonal functioning. Most of the available studies only report effects on pain symptoms and adverse effects.[47] Therefore, in accordance with the IMMPACT recommendations, we have

included core outcome measures for CNCP (pain symptoms, physical function, emotional disability, family/social disability, and patient satisfaction [outcome/care]).[24,47] Moreover, we also used 2 different tools (S-TOPS and BPI questionnaires) to evaluate the clinical importance of improvement in chronic pain outcomes, as recommended by IMMPACT.[25,32]

A potential limitation of this study was its reliance on patient self-report data, namely, telephonic interviews. However, all clinical information had been verified through hospital records consultation.

The fact that our sample was composed of highly selected and more complex pain patients may have contributed to an overestimation of the opioid prescription rate, but it reflects the reality of the most affected patients. Therefore, care must be taken when considering these results' generalizability. Indeed, the unique population-based study available in Portugal has estimated an opioid use rate in CP patients of only 4.37%.[6]

Another limitation of the study was its observational nature, which included the risk of loss of patients to follow-up and the presence of confounding variables. To minimize the first, we developed patient retention strategies, namely, through frequent telephonic contacts with the recruited patients. To overcome the second, our study compared CNCP patients treated with opioids and their propensity score-matched controls, reducing the potential bias that may interfere with outcome assessments.[10,35,70] We have chosen a caliper width of .2 to ensure that more subjects could be successfully matched, but at the expense of a better balance. The available recommendations about this issue indicate that the decision about the caliper should take into account the need to maximize comparability between study groups and the need to maximize the effective number of subject matches (effective sample size); different caliper levels should be tested. Therefore, as many authors have recommended, a caliper of .2 was chosen as the width for our sample as the best balance between group comparability and effective sample size.

Conclusions

This study adds important knowledge to the current literature by providing a real-world clinical assessment of opioid effectiveness in CNCP patients over 2 years of follow-up. Moreover, it highlights the absence of improvement in the function and quality of life of CNCP patients on opioid therapy. It is relevant to emphasize that although opioids still have a role in CNCP, they should only be continued if there is proven clinical benefit. Therefore, the adequate selection of patients and clinicians' education are crucial to maximize opioid effectiveness and promote safer use.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2018.12.007.

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