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Risk factors for opioid addiction in chronic non-cancer pain

Teresa López-Arteaga [a], Carlos Moreno-Rubio [b], Alicia Mohedano-Moriano [c,d,*]

[a] Médico Psiquiatra. Directora Médica Área Integrada de Talavera. Hospital General Universitario Ntra. Sra. Del Prado. Talavera de la Reina, Spain
[b] Jefe de Servicio de Psiquiatría. Hospital General Universitario Ntra. Sra. Del Prado. Talavera de la Reina, Spain
[c] Titular de la Facultad de Ciencias de la Salud Talavera de la Reina. Universidad de Castilla-La Mancha, Spain
[d] Académica del Vicerrectorado de Ciencias de la Salud de la Universidad de Castilla-La Mancha, Spain

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ABSTRACT

Opioids are very effective pain medications, but they are not without complications. Its use in chronic cancer pain is clearly established, but not in chronic non-cancer pain. Opioid use has increased in recent years, but at the same time, it has been accompanied by an increase in side effects and related complications, including abuse, abuse and opioid addiction. If we look in the literature on the subject there is a global concern to make an adequate therapy with risk reduction, but the samples studied make it difficult to extrapolate results to the general population and even more so if we take into account factors such as psychiatric comorbidity. This leads us to consider the need to study our own population, its characteristics and see how it is being treated, to refine as much as possible on an appropriate prescription. The authors have carried out a cross-sectional study on patients with non-cancer chronic pain referred to psychiatry and the presence of opioid use disorder. We found risk factors related to the biopsychosocial characteristics of the patients and the characteristics of pain and its treatment. Knowing the risk factors, we can avoid yatrogeny, implement primary and secondary prevention and, ultimately, improve the quality of patient care.

1. Introduction

The role of opioid analgesics for the treatment of severe acute pain, postoperative pain, and cancer pain (CP) is well established. But its long-term effectiveness in Chronic Non-cancer Pain (CNCP) remains controversial. There is insufficient evidence to demonstrate the efficacy of long-term opioid treatment in CNCP (Kalso et al., 2004, [1,2]. Therefore, the main opioids should be reserved for the CNCP in those cases in which the first two steps of the World Health Organization (WHO) analgesic ladder have failed, and only if the expected benefits in relation to pain and function outweigh those risks. Regardless of the type of pain, the prescription of opioid analgesics must be adequate, prudent, safe and controlled [3]. Although no absolute contraindication has been established for the use of these drugs in the treatment of pain, there is evidence that in certain cases it is advisable to avoid their use. As a general rule, for the treatment of CNCP, it is recommended to follow the analgesic scale with a progressive approach, developing an individualized treatment plan that includes, from the beginning, pharmacological and non-pharmacological measures [4] until opioids.

In the last two decades, there has been a change in the perspective of opioid analgesia. In the United States, the turning point of this change must be located in the 1990s, when the American Pain Society began to consider pain as the fifth vital sign and established that the strategies to control pain had been used until then. An optimal profile (Manchikant et al., 2012). This new approach has led to an

* Corresponding author. Hospital General Universitario Ntra. Sra. Del Prado, Carretera de Madrid, Km. 114, Spain.
E-mail address: mteresala@sescam.jccm.es (A. Mohedano-Moriano).

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increase in the use of opioids in recent years, but at the same time, it has been accompanied by an increase in side effects and related complications, including opioid misuse, abuse and addiction. A 2011 report from the U.S Center for Disease Control (CDC) noted that sales of prescription opioid pain killers increased fourteen fold in the period from 1999 to 2010 in the US [5]. In 2011, 116 million Americans were treated with opioids, and prescription is on the rise. A meta-analysis published in 2015 estimated the prevalence of opioid analgesic addiction in the US population to be around 8–12% [6]. In the past decade in the US, opioid overdose death rates tripled, opioid-related emergencies increased by 153%, and treatment initiation for non-heroin opioid use increased by 236% [7]. Although the prescription of opioid analgesics and the complications derived from their abuse and abuse in Europe, have not reached the US figures, these two parameters have increased enough to be considered something of concern and a priority. In 2013, it was estimated that some 455,000 people in Europe had criteria for addiction to prescribed opioid analgesics [8]. European Monitoring Center for Drugs reported, the opioid problem in Europe remained a critical issue, with a worrying increase in opioid-related mortality. Up to eighteen European countries reported that more than 10% of patients who began treatment with opiates had problems related to their use, the problem not being heroin, but those prescribed such as methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone (European Monitoring Center for Drugs and Drug Addiction, 2017). The 2019 World Development Report (WDR) concludes that the increase in availability and over prescription, the trafficking of synthetic opioids and analogs of pharmaceutical and illegal production, have fostered a global epidemic increase in the prevalence of abuse, dependence and deaths associated with opioids, with the most critical situations in the US, Canada, Southeast Asia and Central Africa [9].

In 2019, the Spanish Ministry of Health Care published a report on medication use. The report analyzed opioid consumption based on prescribing data obtained by the Spanish National Health System from private and public health care sources, including hospitals. The results showed an increase in opioid consumption in Spain from 10.02 daily doses/1000 inhabitants/d in 2010 to 18.73 daily doses/1000 inhabitants/d in 2018 [10].

Some studies indicate abuse rates of between 20 and 24% of those who follow opioid treatment [11,12]. Other review studies, such as the one by Højsted and Sjøgren, found that up to 50% of patients taking opioids for CNCP become addicted [13]. One of the few prospective studies on the problem reported that 24% of patients taking opioids for chronic pain for an average of 36 months became addicted [14,15]. According to Just in 2019, more than a quarter of the patients in his sample were diagnosed with Opioid Use Disorder (OUD) and 9.3% of those studied showed compatible criteria for severity according to the current DSM-5 [16].

Factors that contribute to the formation of substance use disorders can range from biological variables to those that are social and environmental. Certain qualities of these factors constitute vulnerabilities that facilitate substance use and abuse. The impact of these vulnerabilities may be direct, such as ontogenetic effects that lead to an enhanced propensity to acquire nicotine and alcohol use during adolescence [17–19]. Other factors may be indirect, such as metabolic disorders that consist of variables like hypoinsulinemia, which can prime a neurobiological landscape that is favorable for substance abuse [20–23]. Likewise, pain serves as a significant contributing factor to substance use disorders (SUD), most notably opioid use disorder (OUD). Pain can be viewed as an indirect vulnerability that allows the convergence of biological, psychological, and social constructs that result in the facilitation of opioid abuse and the formation of OUD (Nazarian et al., 2022).

In short, we cannot homogenize the prevalence data of OUD in CNCP to date, due to the methodological variability of the studies, the samples studied and terminology (some studies talk only about addiction, others about dependency, others about misuse/abuse and others about OUD). We can say that in the last two decades there has been an increase in concern about consumption, mainly in CNCP, as there are no defined prescription indications for opioids in this group of patients and due to the imbalance that is created between the efficacy of treatment and adverse effects, mainly the addictive potential and ultimately, death by overdose. According to the review by Dennis et al., in 2015, it is observed that in the literature on the subject of opioid prescription there is a global concern to carry out an adequate therapy with reduced risks, however, not all studies have the same power or are carried out on the same type of population, so the results are not as trasnspose as we would like. In addition, in this review, it is observed that 50% of the study population had psychiatric comorbidity and were treated as the general population [24]. This leads us to consider the need to study our own population, its characteristics and see how it is being treated, to refine as much as possible on an appropriate prescription and with more ambition, to have specific clinical guidelines according to comorbidities. Therefore, the objective of this study is to determine the risk factors for addiction to opioids prescribed for pain in a sample with characteristics that are as homogeneous as possible to the population of the region, in order to carry out prevention before establishing opioid treatment at CNCP. Knowing the risk factors we can avoid iatrogenesis, implement primary and secondary prevention and, ultimately, improve the quality of patient care.

2. Methodology

2.1. Type of study

A cross-sectional study was carried out in a sample of 180 patients. The data was collected in the Psychiatry consultation from November 2015 to March 2018 through a clinical interview and through the electronic medical record. For the study of the variables, the data collected in the clinical history referring to the first consultation (cross-sectional study) were used. Clinical data throughout the evolution of the patients are not included.

2.2. Population and sample

Patients over 18 years of age, with CNCP referred to Psychiatry, in the Talavera Integrated Area (Spain), who had previously been followed up by the Pain Unit in our area and required a psychopathological assessment (Talavera de la Reina health area has a total

population of 146,117 patients, with a rate/1000 population over 65 years of 229/1000 inhabitants). All the patients had been previously evaluated by the Anesthesia and Resuscitation and/or Rheumatology services and met the following characteristics: having Fibromyalgic Syndrome (FS) with the presence of associated psychopathology, or CNCP with suspected OUD, or CNCP that did not respond adequately to their usual treatment and required contributory psychopharmacological treatment. Patients under 18 years of age, those with illicitly acquired opioid use disorder (not prescribed for pain), patients included in the Palliative Care Unit, and those with chronic cancer-type pain were excluded. Patients who were already undergoing check-ups in psychiatry were also excluded.

The calculation of the sample for our N = 180, was carried out with a confidence interval of 95% ($z = 1.96$) and p 0,05, resulting n = 124 patients.

2.3. Study variables

Each patient was given interview with a psychiatrist to collect demographic, social, and medical history information.

Sociodemographic factors: sex (men or women), age (groupings were made by age range for every ten years) and position within the siblings (It is usual in the psychiatric interview to know the place that the person occupies within their family); in the case of this variable, the patients were classified into three groups: younger, middle (not being the oldest or the youngest, regardless of birth position) and older.

Psychopathological factors: We studied whether or not they had a psychiatric history prior to the consultation and, if they had consulted, to find out what diagnosis they reported. In turn, the diagnoses given in the consultation based on the DSM-V criteria (in addition to the diagnosis of OUD) are collected. Special mention is made of personality disorders due to their association with Substances Use Disorder (SUD).

Pain related factors: We studied which specialties you consulted during the evolution of your pain (Anesthesia Pain Unit, Rheumatology, Traumatology and Rehabilitation), if there was a diagnosis of FS, the location of the pain (diffuse, in the spine (cervical, dorsal and/or lumbar and), or other locations). Finally, we evaluated the intensity of pain referred: patients were asked to rate their least, average, and worst pain during the past 2 weeks, as well as their current pain on a scale ranging from 0 to 10, with 0 indicating "No pain" and 10 indicating "Pain as intense as you could imagine" (Verbal Numerical Rating Scale, VNRS).

Factors related to opioid treatment: The prescribed opioid active principle and the dose that each patient was taking were collected. To homogenize the drug doses, the equivalence was made with milligrams of morphine (EMM = Equivalent daily dose in Milligrams of Morphine). The variable doses have been grouped in ranges of 50 EM M.

2.4. Data collection

The data was collected anonymously through a request for data explotation to the Information Technology Service of the Castilla-La Mancha Health System (SESCAM). Authorization by the ethics committee was not required because no clinical trials were carried out, and the actions carried out in the consultation were those corresponding to a standard psychiatric clinic, with implicit consent from the patients when accepting and go to the consultation.

2.5. Statistical study

Statistical analysis was carried out using the MEDCALC program (https://www.medcalc.org/calc/odds_ratio.php). We carry out a study of frequencies and Odds Ratio (OR) comparing "non-OUD patients" VS "OUD patients". Results with an OR greater than or equal to 1 were interpreted as risk factors, with results with p equal to or less than 0,05 being statistically significant.

To find the population mean, interval estimation was used. The confidence interval was 95% and the standard error of the mean and the principles of normal distribution were used to calculate its confidence limits. For dispersion measurements, the standard error was used. Qualitative variables were presented as percentages (CI 95%).

3. Results

Of the total sample (124 patients) 81 patients, (63,32%) were diagnosed with OUD. 79,03% of the patients were women and 20,96% were men (72,83% and 27,16% diagnosed with OUD respectively). Being a man turned out to be a risk factor for having OUD (OR = 3,63; CI [1,1632–11,3628]).

The most frequent age range both in the total population studied (33,87%), and in those who presented OUD (34,56%), was the age range between 51 and 60 years. The age interval of the sample was between 19 and 87 years and for OUD between 33 and 83 years. The age ranges from 51 to 60 years and 61–70 years presented OR greater than 1, (OR = 1,0943; CI [0,4990–2,3997] and OR = 1,8898; CI [0,6924–5,1581]). However, the result was not statistically significant.

If we look at the position among the siblings, within the sample, being the youngest and the middle have the same frequency (43,54%), not so in the case of OUD, 23,45% in the case of being the minor and 30,86% in the case of being the median. 12,9% of the sample were older siblings and 8,64% had OUD. Within this variable we did not find any risk factor for presenting OUD.

Regarding the pathobiography of the patients, it was observed that a high percentage (70,96%) reported having had some traumatic experience in their biography, this percentage being 64,19% for patients with OUD. But this variable did not turn out to be a risk factor for presenting OUD when taking opioids for CNCP. Previous consultation in Psychiatry was also analyzed, as well as the diagnoses that the patients reported having had throughout their evolution. 65,32% of the sample and 60,49% of the OUD group had

already consulted psychiatry at some time during their biography. The diagnoses we found in the OUD group were: 30,86% for Dysthymia (OR = 1,1533; [CI: 0,5098–2,6088]), 22,22% for adjustment disorders (OR less than 1), PD and SUD presented the same frequencies, 9,87%, with OR both greater than 1, but not significant (OR = 1,46; [CI: 0,3669–5,8181]) and (OR = 1006; [CI: 0,5666–178,65]) respectively) and, there was one case of psychosis in the group with OUD, but neither did it present a statistically significant result to be a risk factor (OR = 1,62; [0,0647–40,64]). 23,45% of the patients with OUD had no psychiatric history prior to the consultation. Both the diagnoses and the frequencies of presentation change a lot if we study the comorbid diagnoses that occurred after the consultation. Somatoform disorders: 49,38%, affective disorders type depressive episode: 23,45%, PD: 7,40%, dysthymia: 4,93%, SUD: 3,70%, psychosis: 1,23%, and both disorders adaptive, conversion and factitious disorder, the three diagnoses, presented the same frequencies: 2,46%. Being diagnosed with PD (OR = 3,36; [0,3912–28,8589]), conversion disorder (OR = 2735; [0,1284–58,28]), factitious disorder (OR = 2735; [0,1284–58,28]), SUD (OR = 3879; [0,1958–76,8521]) or psychosis (OR = 1,62; [0,0647–40,6486]) are risks for presenting OUD, but only having a diagnosis depressive episode (OR = 4,08; [1,1350–14,71]) is a risk factor with $p = 0,0313$.

When assessing the clinical history regarding pain, we studied how many specialties the patients had previously consulted. Having gone to 2 specialties due to pain occurred in 19,35% of the sample and in 19,75% of the group with OUD. OR for this group of patients was greater than 1 (OR = 1976; [0,4194–2,7651]), the same as the group that had gone to 3 specialties due to their pain (40.32% for the sample and 43,21% for the OUD group) (OR = 1,4203; [0,6603–3,0549]), but in neither of the two cases, having attended 2 or 3 specialties was not a risk factor for presenting OUD. Studying which specialties, the patients in the sample attended, we see that the majority had attended Rheumatology (66,13%), followed by the group that attended the Anesthesia Pain Unit (57,25%) and finally, those who they went to Traumatology (49,19%). The sum of these frequencies is not 1, because there are patients who had attended several specialties. When looking at these frequencies in the group with OUD, it can be seen that going to Anesthesia and Rheumatology occurs with the same frequency (59,26%) and going to Traumatology occurs with 41,67%. Going to the Anesthesia Pain Unit could have been a risk factor for OUD (OR = 1,26; [0,6002–2,6652]), but $p = 0,5367$.

Despite not being recommended for treatment, 59,67% of the sample had been diagnosed with Fibromyalgia and were taking opioids. Likewise, 51,85% of the patients presented OUD and Fibromyalgia. However, fibromyalgia was not a risk factor for OUD (OR = 0,3702; [0,1644–0,8338] $p = 0,0140$).

We classified pain according to the location reported by the patients. It is noteworthy that regarding an identification of diffuse, dispersed pain, without a specific location, opioids were prescribed to 41,93% of the patients, of which 37,03% were with OUD. localized pain in the spine presented a frequency of taking opioids of 40,32% and 39,50% for OUD. Finally, other locations of pain (related to neurological, urological, gynecological pathologies, etc.) presented a frequency of 12,09% for the sample and 9,87% for OUD. None of these studied variables presented data compatible with being risk factors for presenting OUD in CNCP. To assess the degree of referred pain, we used a Likert-type scale from 1 to 10 and grouped the results into ranges, considering less than 5 (4,83% of the sample and 2,46% of OUD), between 6 and 7 (15,32% of the sample and 9,87% of OUD), between 8 and 9 (29,83% of the sample and 20,98% of OUD) and finally, equal to 10 (15,32% of the sample and 13,58% OUD). For none of these variables we found an OR equal to or greater than 1, nor p equal to or less than 0.05, so we cannot say that the degree of pain is a risk factor or a protective factor for presenting OUD when taking opioids in CNCP.

It is interesting to observe the distribution of the type of active principle taken by the patients. Fentanyl is the most prescribed opioid both in the sample (38,71%) and in the OUD group (49,38%), it is also a risk factor for presenting OUD when taking opioids in CNCP (OR = 4,2683; [1,7651–10,3214] p = 0,0013). In decreasing order according to the frequency of prescription of each opioid according to the OUD group, we find: tapentadol (17,74% in the sample, 14,81% in OUD), tramadol (29,03% in the sample, 12,34% in OUD), naloxone/oxycodone (8,06% in the sample, 8,64% in OUD), morphine (4,03% in the sample, 4,93% in OUD), hydromorphone (1612% in the sample, 2,46% in OUD) and transdermal buprenorphine (0,8% in sample, 1,23% in OUD). Except tramadol and tapentadol (OR = 0,0921; [0,0374–0,2268]) and (OR = 0,5739; [0,2251–1,14,636]), naloxone/oxycodone, morphine, hydromorphone and transdermal buprenofine, present OR greater than 1, however none of them presented p less than 0,05, therefore not being risk factors for presenting OUD when taking it at CNCP.

Regarding the dose of opioids that each patient had prescribed, they were grouped based on the equivalence in milligrams of morphine and grouped in ranges of 25 mg. By grouping this, we avoid losing results that would be biased within a range that is too broad, but likewise, we found that there were dose ranges that no patient in the sample was taking. The average dose of the sample was 273,836 mg morphine equivalent and 343,72 mg morphine equivalent for the OUD group. The minimum and maximum value of the doses (8,3mg–8.000 mg) coincide in both groups (sample and OUD). We show the results in increasing order of frequency in the group with OUD: the most frequent prescribed dose was between 100 and 149 EM M (22,22%), in turn, this dose range presents (OR = 12; [1,5429–93,3278] p = 0,0176), being a risk factor for presenting OUD in CNCP. The next most frequently prescribed dose range is 50–99 EM M (20,98%), the next, 150–199 EM M with an OR greater than 1, but p = 0,2773. It also happens that the following most frequent range is not significant: 25–49 EM M (8,64%) (OR = 3,26; [0,8224–12,9758] p = 0,0925). The following dose ranges are: 200–249 EM M with 8,64%, 250–299 EM M with 4,93%, 300–349 EM M with 3,70%, 450–499 EM M with 2,46% and the ranges 1.050–1.099 EM M, 1.150–1.199 EM M, 1.350–1.399MME, 1.650–1.699MME, 1.800–1.849MME, 2.200–2.249MME, 3.700–3.749 MM E and 8.000–8.049MME, all with a frequency of 1,23%. Dose ranges not described in this section of results it is because there was no patient who had prescribed these doses of opioids.

(All the results are collected in Table 1).

Table 1
Frequencies of each variable on the sample, on the group of patients with OUD and Odds Ratio of each one.

VARIABLES	POOLED RESULTS	n = 124	*mean*	Opioid Use Disorder patients	Odds Ratio	CI 95%	*z*	*p*
Sex	Be woman	79,03	59	72,83%	0,2751	0,0880–0,8597	2,22	P = 0,0264
	Be man*	20,96	22	27,16%	3,6356	1,1632–11,3628	2,22	P = 0,0264
Age	21–30 years old	0,8	0	0,00%				
	31–40 years old	8,06	5	6,17%	0,5	0,1364–1,8334	1046	P = 0,2958
	41–50 years old	25,8	20	24,69%	0,847	0,3671–1,9544	0,389	p = 0,6971
	51–60 years old	33,87	28	34,56%	1,0943	0,4990–2,3997	0,225	p = 0,8220
	61–70 years old	19,35	19	23,45%	1,8898	0,6924–5,1581	1242	P = 0,2141
	71–80 years old	8,87	7	8,64%	0,9223	0,2543–3,3447	0,123	P = 0,9021
	80	3,22	2	2,46%	0,519	0,0705–3,8194	0,644	P = 0,5195
Position within the siblings	Minor	43,54	19	23,45%	0	0,0322–0,1928	6	P < 0,0001
	Medium	43,54	25	30,86%	0,2155	0,0975–0,4764	4	P = 0,0001
	Elderly	12,9	7	8,64%	0,3574	0,1228–1,0397	2	P = 0,0590
Stressful traumatic event		70,96	52	64,19%	0,3487	0,1378–0,8822	2225	P = 0,0261
Having consulted in Psichyatric		65,32	49	60,49%	0,5264	0,2325–1,1917	1539	P = 0,1237
Psychiatric history	Disthymia	29,83	25	30,86%	1,1533	0,5098–2,6088	0,342	P = 0,7320
	Adjustment disorders	25	18	22,22%	0,6593	0,2859–1,5203	0,977	P = 0,3285
	Personality disorder	8,87	8	9,87%	1,4612	0,3669–5,8186	0,538	p = 0,5906
	Substance Use Disorder (excluding opioids)	6,45	8	9,87%	1,00612	0,5666–178,6531	1573	P = 0,1157
	Psychosis	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	No psychiatric history	29	19	23,45%	0,4687	0,2109–1,0417	1,86	P = 0,0629
Comorbid psychiatric diagnosis	Somatoform	52,41	40	49,38%	1,3714	0,6139–3,0637	0,77	p = 0,4412
	Distymia	6,45	4	4,93%	0,5065	0,1202–2,1345	0,927	p = 0,3540
	Adjustment disorders	7,25	2	2,46%	0,1302	0,0258–0,6580	2466	P = 0,0137
	Personality disorder	5,64	6	7,40%	3,36	0,3912–28,8589	1105	p = 0,2693
	Conversion disorder	1,61	2	2,46%	2,7358	0,1284–58,2811	0,645	P = 0,5190
	Factitious disorder	1,61	2	2,46%	2,7358	0,1284–58,2811	0,645	P = 0,5190
	Substance Use Disorder (excluding opioids)	2,41	3	3,70%	3879	0,1958–76,8521	0,89	P = 0,3736
	Idiopathic insomnia	0,8	0	0,00%				
	Without diagnostic criteria for psychiatric disorder	3,22	0	0,00%				
	Psychosis	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	Depressive episode*	17,74	19	23,45%	4086	1.1350–14.7093	2154	P = 0,0313
Number of specialties consulted for pain	1 especialties	6,45	3	3,70%	0,2923	0,0663–1,2879	1626	P = 0,1040
	2 especialties	19,35	16	19,75%	1,0769	0,4194–2,7651	0,154	P = 0,8776

(*continued on next page*)

Table 1 (*continued*)

VARIABLES	POOLED RESULTS	n = 124	*mean*	Opioid Use Disorder patients	Odds Ratio	CI 95%	*z*	*p*
	3 especialties	40,32	35	43,21%	1,4203	0,6603–3,0549	0,898	P = 0,3692
	>3 especialties pooled	33,87	27	33,33%	0,9333	0,4283–2,0339	0,174	p = 0,8622
Having consulted in Anesthesia (Unit of Pain) for pain		57,25	48	59,26%	1,2648	0,6002–2,6652	0,618	P = 0,5367
Having consulted in Reumatologic		66,13	48	59,26%	0,385	0,1632–0,9081	2,18	p = 0,0292
Having consulted in Traumatologic		49,19	37	41,67%	23,89%	0,1012–0,5638	3268	P = 0,0011
Fibromyalgic syndrome		59,67	42	51,85%	0,3702	0,1644–0,8338	2399	p = 0,0164
Pain location	diffuse/widespread pain	41,93	30	37,03%	0,5615	0,2655–1,1874	1,51	P = 0,1309
	Cervical and/or lumbar spine	40,32	32	39,50%	0,907	0,4276–1,9241	0,254	p = 0,7992
	Others locations	12,09	8	9,87%	0,5636	0,1895–1,6765	1031	p = 0,3025
Degree of pain	<5	4,83	2	2,46%	0,2468	0,0433–1,4066	1576	p = 0,1151
	betwen 6-7	15,32	8	9,87%	0,3188	0,1172–0,8675	2238	P = 0,0252
	betwen 8-9	29,83	17	20,98%	0,3055	0,1368–0,6820	2894	P = 0,0038
	= 10	15,32	11	13,58%	1	0,2537–1,8633	0,737	P = 0,4614
What opioid were they taking	Tramadol	29,03	10	12,34%	0,0921	0,0374–0,2268	5188	P < 0,0001
	Tapentadol	17,74	12	14,81%	0,5739	0,2251–1,4636	1163	P = 0,2450
	Morphine	4,03	4	4,93%	2,1818	0,2362–20,1565	0,688	P = 0,4916
	Fentanyl*	38,71	40	49,38%	4,2683	1,7651–10,3214	3221	P = 0,0013
	Naloxone/oxycodone	8,06	7	8,64%	1,2613	0,3091–5,1463	0,324	P = 0,7463
	Hidormorphone	1612	2	2,46%	2,7358	0,1284–58,2811	0,645	P = 0,5190
	Transdermal Buprenorphine	0,8	1	1,23%	1,6012	0,0639–40,1462	0,286	P = 0,4242
EMM[a]	0-24 EM M	8,87	2	2,46%	0,0956	0,0196–0,4662	2904	P = 0,0037
	25-49 EM M	17,74	7	8,64%	3,2667	0,8224–12,9758	1682	p = 0,0925
	50-99 EM M	24,19	17	20,98%	0,613	0,2640–1,4232	1139	P = 0,2548
	100-149 EM M*	15,32	18	22,22%	12	1.5429–93.3278	2374	p = 0,0176
	150-199 EM M	11,3	11	13,58%	2,0952	0,5517–7,9573	1086	P = 0,2773
	200-249 EM M	8,87	7	8,64%	0,7189	0,2138–2,4169	0,533	p = 0,5937
	250-299 EM M	3,22	4	4,93%	5,0516	0,2656–96,0630	1078	P = 0,2811
	300-349 EM M	2,42	3	3,70%	3879	0,1958–76,8521	0,89	P = 0,3736
	400-449 EM M	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	450-499 EM M	1,61	2	2,46%	2,7358	0,1284–58,2811	0,645	P = 0,5190
	550-599 EM M	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	1.050–1.099 EM M	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	1.150–1.199 EM M	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688

(*continued on next page*)

Table 1 (*continued*)

VARIABLES	POOLED RESULTS	n = 124	*mean*	Opioid Use Disorder patients	Odds Ratio	CI 95%	*z*	*p*
	1.350–1.399 EM M	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	1.650–1.699 EM M	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	1.800–1.849 EM M	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	2.200–2.249 EM M	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	3.700–3.749 EM M	0,8	1	1,23%	1,6211	0,0647–40,6486	0,294	P = 0,7688
	pooled doses greater than 100	49,94	54	66,60%	5,1667	2,2965–11,6241	3970	P = 0,0001

(*) Variables with OR greater than 1 statistically significant to be a risk factor.
[a] EMM = Equivalent daily dose in Milligrams of Morphine.

4. Discussion

4.1. Sociodemographic factors

4.1.1. Sex. While the approach to chronic pain treatment is currently the same for women as it is for men, there are sex differences in terms of pain manifestation, coping, and aberrant behaviors. It is necessary to understand these sex differences in patients with chronic pain to help improve clinical evaluation, since they are variables to take into account for therapeutic management and minimize the risk of abuse [25]. Differences based on sex are found in the prevalence of certain pain conditions, as well as in the negative emotional sequelae of chronic pain. Women are at higher risk of developing multiple concurrent chronic pain conditions, as well as inflammation-related disorders. They also tend to tolerate greater severity of pain in an attempt to maintain their role in the functioning of the family. In women, depression is related to reporting higher levels of pain intensity, while in men, depression is more correlated with decreased activity levels. Such distinctions justify the need for more preclinical research on sex differences, differences that moderate nociceptive signaling. This is particularly important given the considerable differences in analgesic response between men and women [26]. Among patients with OUD, women report more depression and anxiety than men [27], as well as more medical problems throughout their course [28]. Women are more likely to use prescription opioids to cope with interpersonal stress and to use opioids upon waking in the morning [28]. While women are more likely to abuse opioid analgesics due to emotional distress, men tend to abuse opioids in an illicit setting [29]. In the study by Manubay, 2015, there were several sex differences in the impact of pain on daily functioning, as well as psychiatric features associated with the pain condition. Women associated more psychiatric comorbidity with higher baseline depression scores (measured by the Hamilton scale) compared to men and, in turn, presented higher levels of pain intensity (in the last week), and greater physical and social impairments. In relation to pain, while men presented more specific aberrant behaviors, such as increasing their dose without authorization [25]. Differences have also been observed in the pattern of use of opioid analgesics and illicit opioids. Women are twice as likely as men to receive prescriptions from 5 or more physicians in the past year. Among opioid abusers seeking treatment, women are more likely than men to receive opioids through a prescription [30]. Men, however, are significantly more likely to alter the route of administration when inhaling and injecting prescribed opioids, compared to women [28]. According to Sanger, 2018, being a woman has an OR: 1,385, CI 95% (1027–1866), (p = 0.033) to start treatment with opioids throughout a pain process [31], but it does not explain what risk there is that, once treatment is started, OUD will develop. On the contrary, in another study, it was found that, although the female gender does not play a role as a predictor of opioid misuse, there were mixed results for the effect of the male gender [32]. In our study, being a man turned out to be a risk factor for presenting OUD when taking opioids in CNCP. Based on these results, we believe that during a CNCP process, when focusing on the therapeutic plan, differences between men and women are necessary, since the sexual variables will determine different responses, both to the level of pain, the adaptation to it and the indicated pharmacological response.

4.1.2. Age. Youth, and mainly adolescence, are critical periods in neurodevelopment, so it seems clear that, at a younger age, the risk of addiction to substances, not just opioids, is greater, due to neuroplasticity and individual heritability (Chamber et al. al., 2003). However, painful pathology increases with age, so we have focused on studies in the adult population to analyze the age range most likely to have OUD in CNCP. According to data from the 2012 Dutch Health Monitor survey, risk factors associated with opioid prescription included being older than 65 years (odds ratio, 4.20 95% CI, 3.98–4.43), [33]. However, younger age has also been shown to be associated with postoperative OUD. Other cross-sectional studies [32,34] found that younger age seemed to increase the risk of opioid misuse, as concurred by Kuo in 2019, who found the risk to be higher for those under 65 years of age (Kuo et al., 2019). In our study, the age ranges between 51 and 60 years and 61 and 70 years, obtained an OR greater than 1, however the result was not statistically significant, so we cannot say that age is a risk factor. To present OUD when taking opioids in CNCP.

4.1.3. Position. Within the siblings of a family: Since the beginning of psychoanalysis, up to the constructivist and systemic models, the relationship between the siblings of a family has been studied, as well as the position they occupy within it, since belonging to this group and the dynamics created between members, influence the development of the individual and as such, on his personality,

interaction with the environment and the possible predisposition to suffer certain psychopathologies. In addition to being an older or younger sibling, male or female, each sibling is born at a specific time in the family's life cycle. Also factors such as death, prolonged absences, illness or migration of some of the members, can modify the functional position that an individual occupies in his family relational system. The order of birth in the family is important, not only from the point of view of the subject's self-image according to the place he occupies, but also because of the aspirations and expectations of the children that the parents formulate. Adler was the first to recognize how birth order was a significant factor in personality development. The relationship that exists between each birth order with the parental subsystem is different depending on the status of the sibling [35].

Throughout the clinical interviews carried out in consultation, it was observed that a group of patients mentioned their relationship with their family of origin, the problems that arose based on their relationship with their siblings, and the majority explained negative emotions regarding their family role, which they justified as a possible cause of their somatic discomfort. The discourse was similar in most cases, considering that an effort not valued by the family had resulted in a greater physical and psychological workload throughout the patient's life, which had led to chronic pain. It is due to these references that it was decided to include the position in the family as a study variable to verify whether or not there was indeed a real association between what was verbalized by the sample and the evolution of the pain process. The references on siblings are usually exposed from a psychodynamic approach and we have not found in the bibliography references to this variable as a study factor neither in the CNCP, nor in the development of OUD. According to the results of our study, if we categorize the patients as being the oldest, youngest or middle brother (considering this group any position within the siblings that is neither the oldest nor the youngest), we observe that there is no association significant with presenting OUD in the CNCP process. We believe that this variable should be taken into account in future research as a risk factor for addiction, not only to opioids, since the position within the siblings can condition the development of the individual's personality and therefore their ability to cope with negative stimuli.

4.2. Psychopathological factors

4.2.1. Stressful/traumatic events. Stress is the process by which any emotional or physiological event, or a series of events, results in maladaptive processes that prevent the recovery of homeostasis and/or basal stability (McEwen, 2006 and Sihna 2008). Examples of emotional stressors include interpersonal conflict, the loss of a significant relationship, unemployment, the death of a close family member, or the loss of a child. Physiological stressors include starvation or food deprivation, insomnia or sleep deprivation, severe illness, extreme hyperthermia or hypothermia, effects of psychoactive substances, and withdrawal symptoms. Stress-related adaptation involves the concept of allostasis, which is the ability to achieve physiological stability through change in the internal environment and maintain apparent stability at a new physiological set point (McEwen, 2006 and [36]. There are continuous adjustments to the internal environment, with fluctuations in physiology, mood, and activity as individuals respond and adapt to environmental demands [36]. Excessive stress for the organism, that is, the increase in allostatic load, produces a mismatch of adaptive regulatory systems, which leads to biological alterations that weaken adaptive processes and increase susceptibility to disease [36]. Therefore, high levels of uncontrollable stress and conditions of repeated and chronic stress promote an increase in dysregulated allostatic load, which leads to dysfunctional neuronal, metabolic, and biobehavioral states that contribute to maladaptive behaviors outside the homeostatic range. In our study, we have considered bereavement, having suffered an accident, suffering from an illness or having suffered from it in the past as stressful variables, as well as having undergone a major surgical process, work, family and personal relationships and gender violence (physical or psychological). In turn, we found that there were patients who, although they had not suffered stress in the first person, did verbalize traumatic suffering due to the experience of others, so the variable was subclassified according to the person who had experienced the precipitating stressor. Of the total sample, 70.96% reported having suffered a stressor, and 64.19% of the total number of patients with OUD verbalized it (30% denied it, and the remaining percentage did not answer the question). This tells us that it is necessary to measure the data in order not to fall into the subjective biases of the interviewer, since, on occasions, there are patients who manifest more emotional charge in the transmission of their experiences and can make us fall into the error of thinking that They are the most frequent within a population. In itself, reporting having suffered a stressful event had no significant association nor was it a risk factor for presenting OUD in our study.

4.2.2. Psychopathological comorbidity. Co-morbid psychiatric disorders were found in 40–80% opioid treatment seekers (Strain, 2002). Mainly depression has been seen to be related to OUD, but other psychiatric disorders, such as anxiety or poor impulse control and substance use, have been considered risk factors. Depression is found to be present in patients presenting with OUD at comparable increased rates of occurrence compared to the general population, regardless of the presence of pain [37,38]. Given the co-occurrence of psychiatric disorders with chronic pain or OUD, the role that chronic pain has as a separate risk factor for OUD is unclear [39]. In our study, the high percentage of patients who had already consulted psychiatry throughout their evolution is striking: 65.32% in the case of the sample and 60.49% in the case of the group with OUD. At the same time, the type of diagnosis reported by the patients and how this diagnosis changes at the time of the evaluation in which this study was carried out is striking. The frequency of dysthymia and adjustment disorders decreased. The similar frequency was maintained in the group diagnosed with PD and was exact in the case of psychosis. It is striking how new diagnoses appear in the sample: depressive episode, somatoform disorders, conversion disorders and factitious disorder. We have a hypothesis regarding these results, which is that we do not believe that the patients were misdiagnosed, but rather that the affective factor was the first to manifest within the painful pathology and was evaluated outside the clinical set of pain. It is very curious to see that within the group with OUD, 74.05% had another associated psychiatric diagnosis throughout their evolution and that almost 100% of the group with OUD (97.47%) had another associated diagnosis at the moment. Of the evaluation.

An increased risk of substance abuse in chronic pain has been found in patients with mood disorders, particularly unipolar depression. Chou et al. found that major depression, as well as the use of psychiatric prescription medications, were associated with an

increased risk of opioid misuse in patients with chronic pain [40] and Dennis et al. found that pain was significantly associated with co-occurring psychiatric disorder (OR: 2.1 95% CI: 1.6–2.9; I2 = 0.0%) [41]. Depression and previous opioid use disorder seem to be the psychopathological factors that best define the risk of OUD in CNCP [42]. A meta-analysis of 56 articles linking pain and depression found that 65% of people with depression have significant pain and 50% of those with pain have depression. Pain negatively affects the outcomes of depression. And vice versa. A community study found that patients with depression, anxiety, dysthymia or Post Traumatic Stress Disorder (PTSD) were significantly prescribed opioids during their evolution (Sullivan & Ballantyne, 2012) and according to Bedene, depressive symptoms are a risk factor for OUD with OR, 3.77 95% CI (3.41–4.18) [33]. In the context of our study, having a depressive episode-type affective disorder is a risk factor for presenting OUD with an OR = 4.086; [CI 95% (1.1350–14.7093)]. Similar to the Grattan study, patients who were not depressed had lower rates of opioid misuse [43].

Somatoform pain is one of the main symptoms of somatization spectrum disorders "a tendency to experience and communicate somatic distress in response to psychosocial stress". These disorders are highly prevalent, debilitating, challenging to treat, lead to at high levels of disability, excessive and ineffective use of medical care and is one of the factors that predicts poor response to opioid therapy in CNCP [44], however, it is not a risk factor for presenting OUD in our study. In our study we see that although the frequency of somatoform disorders is high, it is not a risk factor for presenting OUD when taking opioids.

SUD, including OUD, is associated with a number of psychopathological conditions, including personality [45]. In the case of personality disorders (PDs), it is currently possible to conclude that there is a clear epidemiological association between substance abuse and PD, without inferences about causality being possible. The result in our study is positive for presenting OUD with an OR of 3.36 CI 95% (0.3912–28.8589), but the result was not statistically significant. However, we believe that this may be due to the sample size. We believe that personality disorder is underdiagnosed and sometimes, as we know, masked by an affective disorder. But we cannot ensure that patients with OUD present more dysfunctional personality traits, but perhaps chronic pain generates maladaptive behaviors that influence personality traits.

Regarding substance use disorder, the literature shows that those with alcohol use (HR: 1.75 95% CI (1.60–1.92)) and non-opioid drug disorders (HR: 2.66 CI 95% (2.45–2.88)) are more likely to misuse opioids during CNCP [46]. Having used substances is traditionally a risk factor for OUD [47]. But our results show that there is no associated risk factor with a probability of 3.87% in the case of SUD as the main diagnosis and 9.87% in the case of personal history of SUD (Table 1). Probably a limitation in the study that could have influenced this data is that the sample size with a history of SUD prior to OUD was very small.

4.3. Pain-related factors

4.3.1. Specialties that have been consulted during the pain process. Of the total number of patients included in the sample, 66.13% had follow-up in Rheumatology for their type of pain. However, in the group of patients with OUD, the majority of referrals (59.26%) were made by the pain unit of Anesthesia and Rheumatology. This implies greater complexity in pain control, as well as a lower response to treatment, since going to the pain unit is one of the last therapeutic steps. If we analyze the care journey of the patients, that is, the specialties in which they had already been evaluated in relation to their pain, we observed an average of 3 specialties consulted prior to the evaluation by Psychiatry (not counting the follow-up by their own Physician of Primary Care). It is observed that having consulted in two specialties has an OR = 1.0769 [CI 95% (0.4194–2.7651)]) and in three specialties has an OR = 1.4203 [CI 95% (0.6603–3.0549)]), but none of these results was statistically significant. In addition, we might think that the trend would be increasing in the study of this variable, and that having consulted more specialties there would be a greater risk of presenting OUD, however this was not the case. The percentages of patients who attended more than 3 specialties were similar both in the sample and for the OUD group, but the OR was less than 1 and p = 0,8622 (OR = 0,93; [0,4283–2,0339]).

4.3.1. Present FS. Although half of the sample studied had a diagnosis of FS, this diagnosis is not in itself a risk factor for presenting OUD

The use of opioids for the treatment of pain in FS is of concern, since it is not indicated and we believe that this is directly related to medical prescription, influenced by excess demand. It would be necessary to investigate more deeply in our health area why we present these results, which are not consistent with the worldwide indications on the good analgesic treatment of FS. There is a moderate degree of evidence that tramadol, alone or associated with paracetamol, improves pain in FS. There is no evidence that major opioids are effective in the treatment of these patients. The Spanish Society of Rheumatology in its consensus document on FS only recommends the use of paracetamol and tramadol as analgesics in the treatment of these patients and does not consider the use of major opioids [48].

4.3.2. Location of pain

When designing this study, the three pain localization subcategories were considered artifices that did not correspond to the topographic reality of pain, but during clinical interviews patients tended to localize their pain in very different ways, so it was decided to use as subcategories those most frequently mentioned by the sample. None of these subcategories was a risk factor for presenting OUD, but it is noteworthy that opioids are prescribed for diffuse pain, not localized or osteoarticular (41.93% of the sample).

4.3.3. Graduation of pain intensity

Regarding the high intensity of pain, in turn, it has been associated with an increased risk of opioid abuse [43,49,50] and [51]. Regarding the pain intensity averages given by the patients, the total sample gave an average of 7.88/10 and in the group with OUD, the average was 8.29/10. This average is higher than that of the sample, which we believe is explicable, since when developing OUD, it is understood that they have had a process of pharmacological tolerance, as well as, quite possibly, opioid hyperalgesia. This should

make us think that opioid treatments are ineffective for the treatment of CNCP, or that, as we well know, hyperalgesia and tolerance develop, or that the reference to a certain degree of pain, being a subjective data, may be biased upwards by a possible secondary gain (sick role, obtaining analgesic treatment, etc.) or even, that there is a conceptual confusion between what is intensity of pain and its persistence, since on several occasions the patients understood that in the face of more constant pain throughout the day, the more score they had to give. However, in our study the degree/intensity of pain was not a risk factor for presenting OUD when taking opioids in CNCP.

4.4. Factors related to opioid treatment

4.4.1. Prescribed active principle. It coincides that, both in the total sample and in those with OUD, the most prescribed opioid is fentanyl for transdermal administration, with only 3 patients in the sample taking it via the oral route (2 patients) and the intranasally (1 patient). The indication for oral or intranasal administration only exists for breakthrough pain in maintenance treatment with opioids for chronic cancer pain. Therefore, it is not understood how patients with CNCP were prescribed these rescue formulations. Taking fentanyl did turn out to be a risk factor for presenting OUD with OR = 4.26; [CI95% (1.7651–10.3214)]. We believe that this issue is directly related to the prescribing physician. Fentanyl may be the best-known active principle in our environment and for this reason it is used in comparison with the frequency of use of the other opioids collected in the sample. In a study carried out in primary care, 3.6% of non-cancer patients were prescribed major opioids, with an increase in the consumption of transdermal fentanyl and tramadol, to the detriment of non-steroidal anti-inflammatory drugs [52]. We also believe that the decision to prescribe a type of opioid or not is given by the lack of knowledge when it comes to treating CNCP. Unlike most drugs associated with overdose deaths and other harms, opioids remain an important medical tool which, in certain cases, are even believed to be underprescribed [53].

4.4.2. Opioid dose (MME). Regarding the risk of OUD depending on the dose, in our study with daily doses between 100 and 149 MM E there is already a risk of future addiction, with OR = 12 [CI 95% (1.5429–93.3278)] p = 0.0176. According to Sehgal et al. patients treated long-term with opioids, in doses greater than 120 MM E/day, more frequently present symptoms of compulsion and dose escalation [54]. According to Chou et al. the risk would exist from doses greater than 100 MM E [40] and according to Campell, the risk increases with doses greater than 100 MM E and caution is advised with doses greater than 50 MM E [46]. Our results are close to the doses considered as risk factors in the literature, but we have not been able to see the trend of dose escalation. However, when calculating the grouped dose from 100 MME, we have found a statistically significant value that suggests more risk at more doses (OR = 5.1667; [CI95% (2.2965–11.6241)]). We believe that these results are due to the fact that the bulk of the patients are taking lower doses and that due to this, by grouping and increasing the sample of patients who take more than 100MME, it is observed that the dose increase would be a factor of risk.

5. Conclusions

The main conclusions of our study is that there are risk factors for presenting OUD when prescribing opioids in CNCP. These factors are gender, being a man, presenting a psychiatric comorbidity, especially a depressive episode, the type of opioid prescribed, transdermal fentanyl, and doses between 100 and 149 MM E.

6. Limitations

This study has fundamental limitations such as the sample size. We believe that this influences the fact that we found few risk factors in the study despite the perception at the time of data collection. Another limitation is the fact that we cannot establish a causal relationship as it is a cross-sectional study. We believe that in future studies we should establish the risk factors for having opioids prescribed in CNCP and, in turn, compare them with the risk factors for developing OUD in CNCP. We have not found studies similar to ours in Spanish populations, but we believe that it is a replicable study that could be extended to other health areas. Despite the fact that the results were not all that we expected, we are convinced of the importance of studying the use and prescription of opioids in CNCP, since we have observed irregularities in the doses, type of patient to whom they are prescribed, and medical variability in the use of drugs despite scientific evidence.

Author contribution statement

Teresa López Arteaga: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Carlos Moreno and Alicia Mohedano: Contributed reagents, materials, analysis tools or data.

Data availability statement

The data that has been used is confidential.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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