ORIGINAL RESEARCH

Tapentadol and Oxycodone/Naloxone Prescribing Patterns in Primary Health Care in Catalonia, Spain: A Cross-Sectional Study

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Objective: To characterize the use of tapentadol and the combination oxycodone/naloxone in primary health care. Data on their use and possible misuse will allow the identification of risk factors and to design protocols to reduce and prevent avoidable harm to patients being treated for pain.

Design: A descriptive, cross-sectional and multicenter study was performed.

Setting: Fifty-three primary health care teams, which provides healthcare for 1,300,000 inhabitants.

Patients: A total of 1840 patients had active prescriptions of tapentadol and 985 of oxycodone/naloxone.

Methods: Demographic (age, sex) and clinical (glomerular filtration rate; active liver disease; dosing and duration of treatment), prescribed daily dose (according to age, sex, length of treatment), concomitant analgesic treatment and diagnosis. Patient information was obtained from medical records.

Results: Most of the patients were women (>74.0% in both cases), and the average age was 69.3 years (women: 70.1±13.2; men: 66.7±13.9 years) in the case of tapentadol and 70.6 years (women: 64.0±13.6; men: 72.6±14.3 years) in the case of oxycodone/naloxone. Only 12.2% of patients taking tapentadol and 12.1% taking oxycodone/naloxone had a normal renal function. In both cases, 4.1% of patients had active liver disease. The average length of treatment was 246.4 days in oxycodone/naloxone and 199.0 days in tapentadol. It was recorded that 85.1% of patients in the case of tapentadol and 89.0% in the oxycodone/naloxone had at least another drug prescribed for pain. About 42.2% of patients treated with tapentadol and 34.4% of patients treated with oxycodone/naloxone had associated neuralgia as a diagnosis.

Conclusion: The pattern of use and profile of patients with tapentadol and oxycodone/naloxone had more similarities than differences, and suggested that prescribing practice, and monitoring should be assessed regularly to ensure patient safety and effective management of pain.

Keywords: clinical practice pattern, chronic pain, opioids, oxycodone/naloxone, primary health care, culture, tapentadol

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Introduction

Although there is no uniformity in terms of its definition, chronic pain is generally understood as the one that persists beyond 3 or 6 months from its appearance or beyond the expected healing period for a given lesion.[1] Chronic pain is one of the most frequent causes why general population looks for medical treatment, and is

often poorly managed.[2,3] Approximately 20% of United States adults have chronic pain[4] and it also affects 20% of European citizens.[5] Spain shows a prevalence of chronic pain in the adult population (≥18 years) of 16.6%.[6]

Chronic opioid therapy has limited data supporting its long-term effectiveness more than three months for the management of chronic non-malignant pain[7] and the use in the long term remains controversial, also because of the adverse events.[8] Besides, it must be taken into account that chronic pain is often accompanied by mood and sleep disorders, and other chronic conditions that can result in complex medication regimens and an increased risk of drug interactions and side effects.[7]

Regarding opioids' side effects, the most habitual encompass dry mouth, vomiting, nausea, fatigue, increased sweating, itching, drowsiness and constipation, with a remarkable negative impact on patient quality of life.[8,9] Tapentadol demonstrated to have fewer side effects at the central nervous system (CNS), which could reduce dependence[10,11] and fewer gastrointestinal side effects than morphine and oxycodone.[12] In this regard, the combination of naloxone with oxycodone improves opioid-induced bowel dysfunction, characterized by constipation, incomplete evacuation, bloating, and increased gastric reflux, which helps increase the acceptability of opioid treatment for pain.[13,14]

In Spain, tapentadol is still covered by patent law and dosage forms are only marketed as trademarks, both the extended-release tablets (dosages of 25, 50, 100, 150, 200 and 250 mg) and the immediate-release tablets (dosages of 50, 75 and 100 mg).[15] Oxycodone/naloxone combination is marketed as trademarks and generics of extended-release tablets in different dosages (5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg).[16] An increase in the consumption of tapentadol and oxycodone/naloxone expressed in defined daily doses per 1000 inhabitants per day (DHD) over the years 2014 to 2017 (1.3% DHD tapentadol and 1.4% DHD oxycodone/naloxone to 2.3% DHD and 1.9% DHD, respectively) was found in our study area of primary health care. Despite the increasing influence of general practitioners on the opioid analgesics' prescription for the chronic pain treatment, to our knowledge, there were no findings in the literature of descriptive studies and comparative analysis of the use of these drugs in primary care practice.[8] Thus, the aim of the present study was to characterize the use of tapentadol and the combination oxycodone/naloxone in primary health care. Data on their use and possible misuse will allow the identification of risk factors and to design protocols to reduce and prevent avoidable harm to patients being treated for pain.

Materials and Methods
Design and Setting of the Study
A descriptive and cross-sectional multicenter study was carried out. It covered fifty-three primary health care teams in the Primary Care Directorate (DAP) Costa de Ponent of the Catalan Institute of Health (ICS), which provides healthcare for 1.3 million inhabitants.[17,18]

Data Source, Collection, and Variables
The target population were patients with an active prescription of tapentadol or the oxycodone/naloxone combination on August 13, 2018. The Summary of Product Characteristics (SmPC) of all (brand-named and generic) marketed prescription medicines containing these drugs were reviewed to evaluate their authorized therapeutic use. The information of the patients was obtained and extracted anonymously.

The variables studied about patient data were age, sex, glomerular filtration rate (GFR: >90 mL/min, 60–89 mL/min, 45–59 mL/min, 30–44 mL/min, 15–29 mL/min and data not registered) and active liver disease. As for the prescription data: duration of treatment (>30 days, 31–90 days, 91–180 days, 181–366 days, 1–2 years, and more than 2 years), prescribed daily dose according to age (in case of oxycodone/naloxone doses are only referred to as oxycodone since the dose of naloxone is always half of oxycodone), sex and length of treatment, concomitant analgesic treatment and diagnosis. Patient data was obtained from clinical records (e-CAP computer program), whereas diagnoses were defined according to the International Classification of Diseases (ICD-10). The computer program used (e-CAP) contains patients' demographic data, clinical history, diseases, drugs, treatment plans, vaccinations, allergies, radiology images, analytical and test results, therapeutic procedures, hospital discharge dates, and visits to hospital emergency.[17]

Regarding the ICS, it is the main provider of public health services in Catalonia, Spain. It is a leading provider in its three basic areas of activity: healthcare (its main area), research and teaching. The ICS provides health services to 83% of all Catalan citizens (over 5.5 million people).[18] It is comprised of 8 hospitals and 287 primary care teams, located throughout the entire Catalan territory. The primary care teams are made up of a varying

number of professionals (general practitioners, pediatricians, nurses, auxiliary nurses, dental surgeons, social workers, and administrative staff) and are responsible for providing free primary healthcare to the population that lives within their catchment area. The management structures or DAPs are directly responsible for all the health centers, services, and institutions within their corresponding area. Concretely, DAP Costa de Ponent directly manages primary health care services in the southern Barcelona Metropolitan Area (Catalonia, Spain).[18]

Ethical Review Board Approval

Given that the extraction of information was carried out anonymously and the relationship was not available to recover which real cases the information corresponds to, it was not necessary to ask for the informed consent of the patients studied or institutional review board approval, in accordance with Spanish regulations prior to January 2, 2021 (Order SAS/3470/2009, of December 16, which publishes the guidelines on post-authorization studies of an observational type for medicines for human use and Chapter VI of Royal Decree 577/2013, of July 26, which regulates pharmacovigilance of medicinal products for human use).

Data Analysis

Discrete variables were expressed in proportions or frequencies, and continuous variables as means and standard deviations, and it was assumed that the data were normally distributed. Frequencies were compared in a bivariate analysis using χ square and means using Student's t test or analysis of variance. As a post hoc test was used Bonferroni. Pearson's correlation was used in the relationship of two quantitative variables. A p-value ≤ 0.05 was considered statistically significant. The data were analyzed using SPSS software, version 17.0.

Results
Description of the Population

At the time of the study (13 August 2018), 1840 patients had active prescription of tapentadol and 985 patients of the combination oxycodone/naloxone. In the case of tapentadol, all patients were prescribed extended-release tablets and 0.3% (N = 6) of them had also oxycodone/naloxone at the same time. As for oxycodone/naloxone, 0.6% (N = 6) of patients had also tapentadol at the same time.

The 74.8% (N = 1377) of patients with active prescription of tapentadol extended release and 74.1% (N = 729) of patients in the case of oxycodone/naloxone were women. No statistical differences were found in terms of sex between patients taking tapentadol and those taking oxycodone/naloxone. Regarding patients' age, the average was 69.3 years (women: 70.1±13.2 years, male: 66.7±13.9 years) in the case of tapentadol and 70.6 years (women: 64.0±13.6 years; male: 72.6±14.3 years) in oxycodone/naloxone. The age of women who took tapentadol was slightly higher but statistically significant than those who took oxycodone. The distribution of patients by age is shown in Figure 1A.

Renal and Hepatic Function

As for the renal function, in the case of tapentadol, 12.2% of patients (N = 225) had a normal renal function (GFR> 90 mL/min) and in the case of oxycodone/naloxone, 12.1% (N = 119). Figure 1B shows the distribution of patients depending on the GFR value registered to determine the stage of kidney disease. In addition, it was found that around 5% of patients (5.6%, N = 104 in case of tapentadol and 4.8%, N= 47 in case of oxycodone/naloxone) had no data recorded for their renal function.

Regarding liver function, 4.1% of patients with tapentadol (N=75) had active liver disease. Liver disease includes hepatitis C virus, hepatitis B virus, alcoholic and non-alcoholic fatty liver disease, autoimmune hepatitis, cholestasis/diseases of the biliary tract, hepatotoxicity for medicines or herbal supplements, and hepatotoxicity leading to cirrhosis. In the case of oxycodone/naloxone, 4.1% of patients (N = 40) had active liver disease.

There was no found co-prescription of the two drugs in patients with impaired renal or hepatic function.

Treatment Duration

The duration of treatment with extended release tapentadol and oxycodone/naloxone is ranged from less than one month to more than 2 years (Figure 1C). Oxycodone/naloxone treatments had a longer duration than tapentadol treatments (246.4±283.8 days vs.199.0±219.7 days, respectively) and this difference was statistically significant (p < 0.005).

Prescribed Daily Dose

The average daily dose prescribed to patients treated with extended-release tablets of tapentadol and patients treated with oxycodone/naloxone was, respectively, 112.3±87 mg (range: 6.1 mg - 1000 mg) and 23.5±20.6 mg of
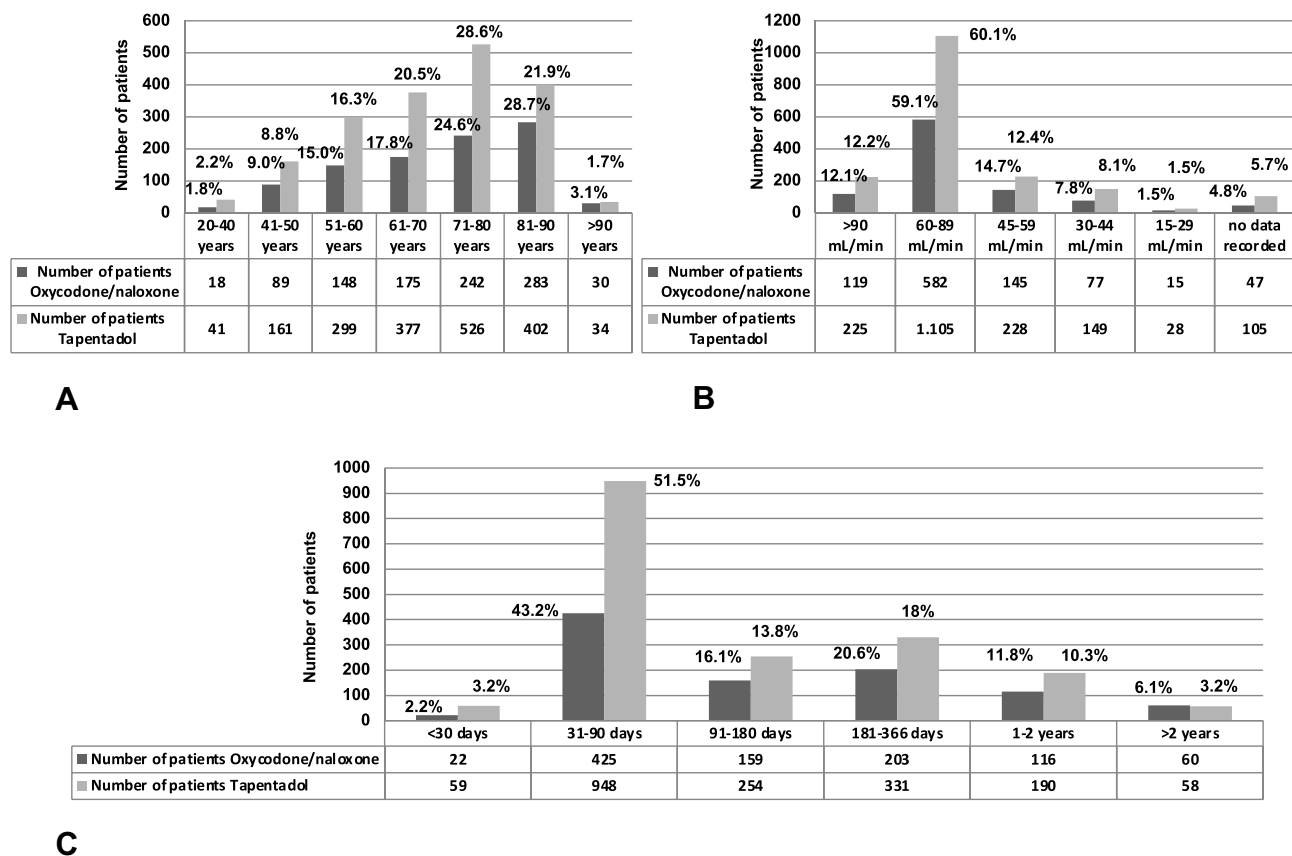
Figure 1 Distribution of patients by age (**A**), by Glomerular Filtration Rate (**B**), and by duration of treatment (**C**) with tapentadol vs oxycodone/naloxone.

oxycodone (range: 1.2 mg −160 mg). We found, in the case of tapentadol, 146 patients (7.4%) with doses below 50 mg/day (underdosed) and above 500 mg/day (overdosed). In oxycodone/naloxone, we found 179 patients (18.2%) with doses lower than the recommended 10/5 every 12 h. The daily dose was calculated according to frequency and dosage, finding frequencies of 1 every 99 h. Figure 2A shows the average daily dose established according to age groups. In the case of tapentadol, the highest daily dose was in the age group of 41–50 years (average 123.2±109.3 mg), although there were no significant differences in the daily dose in any of the age ranges established (p = 0.065). In general, younger patients (range: 20–40 years) were taking lower doses of tapentadol, however, three of those patients were taking more than the authorized dose (500 mg according to the SmPC).

With respect to the oxycodone/naloxone, the highest daily dose was in the age group between 20 and 40 years (average of 36.2±35.2 mg of oxycodone). The oldest patients (range: 81 - >91 years) were taking the lowest doses and no patient were taking more than the authorized dose (160 mg of oxycodone/80 mg of naloxone according

to the SmPC). There were statistically significant age-related differences in the average daily dose of oxycodone (p < 0.005).

Furthermore, there appeared to be a negative significant correlation between age and average daily dose in patients taking oxycodone/naloxone (r = −0.173; p < 0.005).

On the other hand, the average daily dose used was lower in women than men in both medicines (Figure 2B). In the case of oxycodone, the dose in men (26.8±25.7 mg) was statistically significant higher (p = 0.012) than that of women (22.4±18.3 mg).

When analyzing both the average daily dose data of the drugs and the duration of treatment (Figure 2C), patients treated with the lowest daily dose of tapentadol had the shortest duration of treatment. In addition, there appeared to be a significant positive correlation between the two variables (r = 0.097; p < 0.005). In the case of oxycodone/naloxone, patients with treatment length between one and two years were the ones with the highest average daily dose. In this sense, a significant correlation between the two variables was found (r = 0.073; p = 0.022).
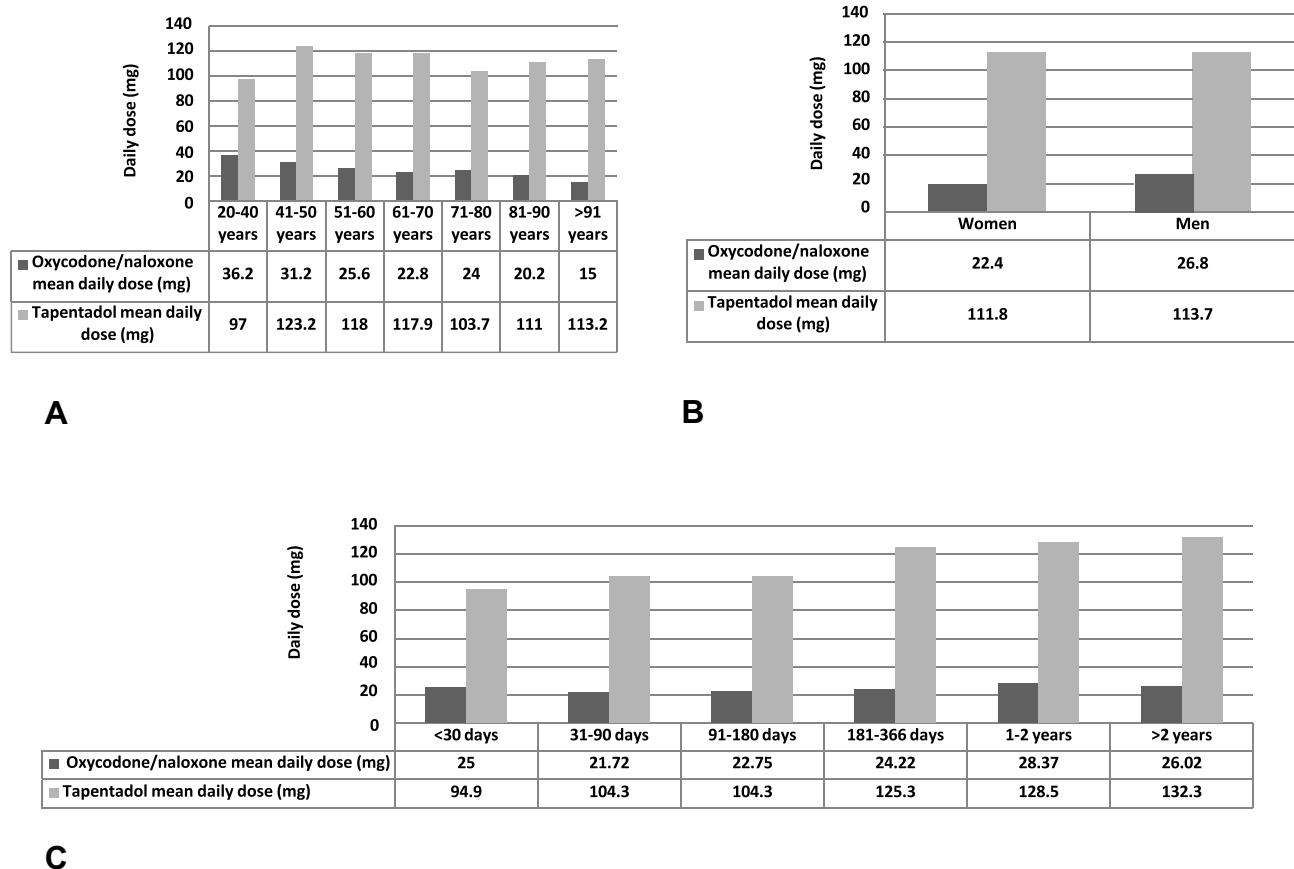
A

	20-40 years	41-50 years	51-60 years	61-70 years	71-80 years	81-90 years	>91 years
■ Oxycodone/naloxone mean daily dose (mg)	36.2	31.2	25.6	22.8	24	20.2	15
■ Tapentadol mean daily dose (mg)	97	123.2	118	117.9	103.7	111	113.2

B

	Women	Men
■ Oxycodone/naloxone mean daily dose (mg)	22.4	26.8
■ Tapentadol mean daily dose (mg)	111.8	113.7

C

	<30 days	31-90 days	91-180 days	181-366 days	1-2 years	>2 years
■ Oxycodone/naloxone mean daily dose (mg)	25	21.72	22.75	24.22	28.37	26.02
■ Tapentadol mean daily dose (mg)	94.9	104.3	104.3	125.3	128.5	132.3

Figure 2 Average daily dose according to age groups (**A**), to sex (**B**), and to duration of treatment (**C**).

Drug Treatment Combination with Tapentadol and Oxycodone/Naloxone

These drugs were also prescribed along with additional pain drugs, such as, NSAIDs, antiepilectics such as pregabalin, other non-opioid analgesics such as metamizole, anxiolytics and hypnotics, selective inhibitors of serotonin reuptake inhibitors (SSRIs), antiepileptics such us gabapentin, sedatives, tricyclic antidepressants (TCAs) and other opioid analgesics. Besides, patients could be taking simultaneously more than one medication (Figure 3). Therefore, in the case of tapentadol, it was recorded that 85.1% (N = 1566) of patients had at least another drug prescribed for pain. Mainly, 56.0% (N = 1030) of patients had a concomitant acetaminophen, 21.4% (N = 393) pregabalin, 21.1% (N = 388) metamizole, 11.6% (N = 214) diazepam, 7.1% (N = 196) duloxetine and 10.5% (N = 193) gabapentin. As for oxycodone/naloxone, 89.0% of patients (N = 877) had at least another drug prescribed for pain. Predominantly, 60.1% (N = 592) of patients had concomitant acetaminophen, 23.7% (N = 233) pregabalin,

21.8% (N = 215) metamizole, 13.0% (N = 128) diazepam, 11.3% (N = 111) gabapentin and 11.2% (N = 110) duloxetine. Patients with oxycodone/naloxone treatment took more adjuvant drugs (1.9±1.2 drugs) than patients with tapentadol treatment (1.7±1.2 drugs) and this difference was statistically significant (p = 0.005).

Diagnoses

The study found that 42.2% of patients treated with tapentadol (N = 776) had neuralgia as a diagnosis, 14.4% of patients (N = 265) osteoarthritis, 7.8% (N = 144) had more than one diagnosis of pain, 5.3% (N = 97) neoplasic processes, 5.3% (N = 94) fracture and osteoporosis, 4.7% (N = 86) fibromyalgia, and 4.3% (N = 76) did not have a diagnosis (Table 1). There were 0.43% of patients (N = 8) with an incorrect indication including depressive disorder (N = 4) and diabetes mellitus (N = 4).

In the case of treatment with oxycodone/naloxone, 34.0% of patients (N = 335) had neuralgia as a diagnosis, lumbago with sciatica, sciatica, and spondylosis, 15.8% (N = 156) intervertebral disc disorders, 13.6%
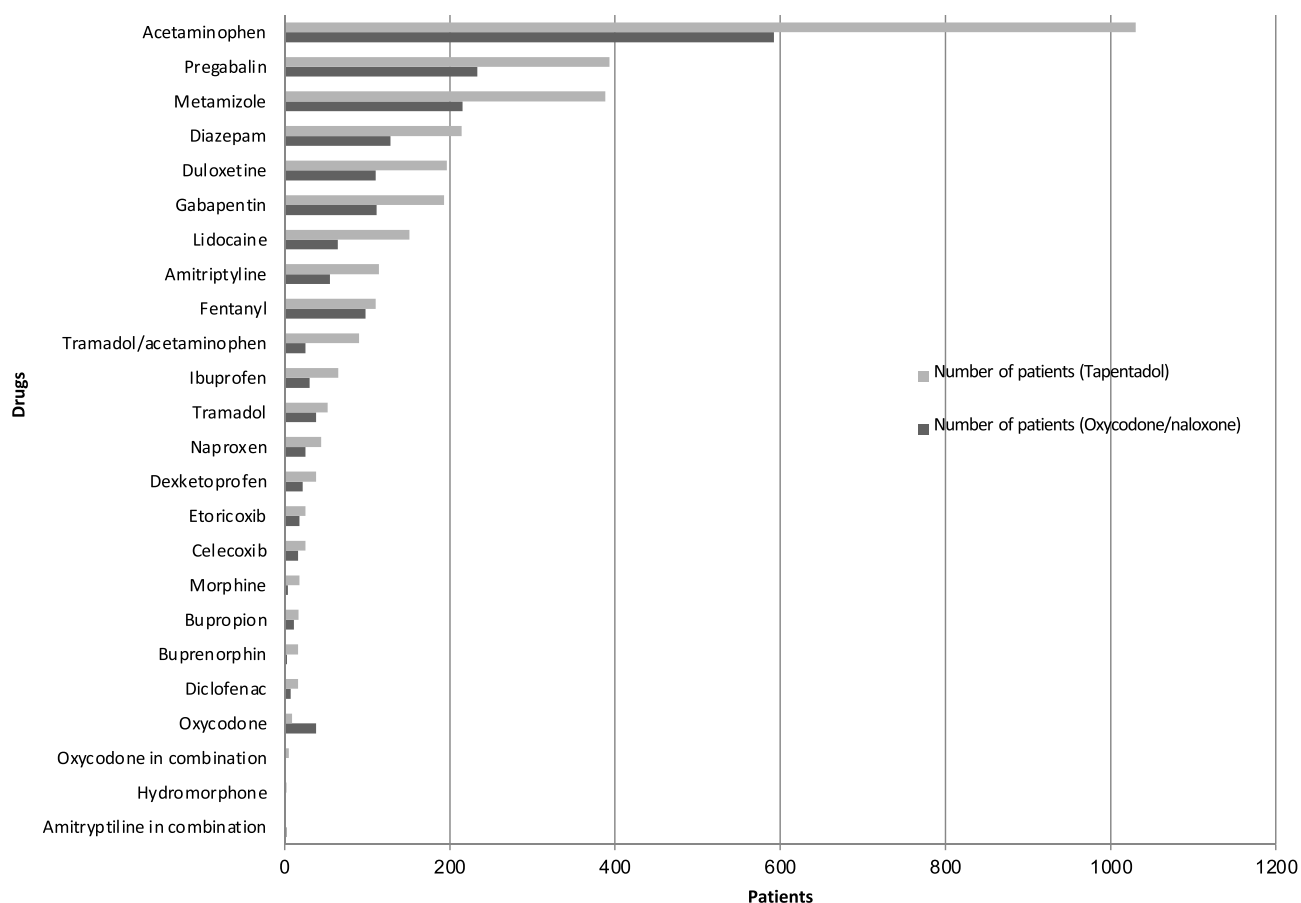
Figure 3 Distribution of drug treatment combination and number of patients.

(N = 134) osteoarthritis, 12.4% (N = 122) had more than one diagnosis of pain, 7.9% (N = 78) fracture and osteoporosis, 5.1% (N = 50) neoplasic processes and (N = 50) chronic pain, 4.9% (N = 48) fibromyalgia and 4% (N = 39) did not have a diagnosis (Table 1).

On the other hand, 5.1% (N = 93) and 6.5% (N = 64) of patients had other diagnoses, respectively (Tables 1–3).

Diagnoses vs Daily Dose

In the case of tapentadol, the highest daily dose was in the incorrect indications of depressive disorder and diabetes mellitus (175.0±155.4 mg and 137.5±75 mg, respectively) followed by unspecified rheumatism (135.3 ±170.6 mg) and the lowest was for unspecified osteoarthritis (62.5 ±28.8). There were no statistically significant differences in the daily dose in tapentadol according to diagnosis (p = 0.094).

In oxycodone/naloxone the highest daily dose was for unspecified rheumatism (33.3 ±26.6 mg) and the lowest for unspecified osteoarthritis (17.5±12.8 mg). Nevertheless, there were statistically significant differences in the daily dose of oxycodone with respect to the diagnoses (p = 0.049). The significant differences (p = 0.032) were found between the daily dose of osteoarthritis (21.0±16.4 mg) and neoplasic processes (33.2±29.3 mg), after applying Bonferroni test.

Diagnoses vs Treatment Duration

In the case of tapentadol, the highest treatment duration was in the incorrect indication of depressive disorder (365.5±301.7 days) followed by osseous stenosis (242.8 ±223.1 days) and unspecified rheumatism (242.2±316.5 days) and the shortest was for non-associated diagnoses (94.8±66.8 days). There were statistically significant differences in the duration of tapentadol treatment concerning the diagnoses (p < 0.005). Concretely, the significant differences were found concerning neoplasic processes (122.3±102.2 days) and neuralgia (208.3±225.7 days), and neoplasic processes and other diagnosis (239.2 ±279.7 days), neuralgia (208.3±225.7 days) and not associated diagnosis (94.8±66.8 days), osteoarthritis (198.4 ±199.5 days) and not associated diagnosis (94.8±66.8 days), fibromyalgia (229±278.1 days) and not associated

Table 1 Distribution of Patients Taking Tapentadol and Oxycodone/Naloxone and Their Diagnoses

Diagnosis	ICD-10	Tapentadol		Oxycodone/Naloxone	
		N	%	N	%
Neuralgia*	**	776	42.2	335	34
Osteoarthritis	M15, M16, M17, M19, M48	265	14.4	134	13.6
Neoplasic processes	***	97	5.3	50	5.1
Fracture and osteoporosis	****	94	5.1	78	7.9
Fibromyalgia	M79.7	86	4.7	48	4.9
Joint pain	M25.5	53	2.8	26	2.6
Chronic pain	R52.2	48	2.6	50	5.1
Osseous stenosis	M99.3	36	2	13	1.3
Unspecified rheumatism	M79.0	34	1.9	6	0.6
Unspecified Osteoarthritis	M19.9	18	1	16	1.6
Algoneurodystrophy	M89.0	8	0.4	4	0.4
Paraplegia	G82	4	0.2	-	-
Depressive disorder	F33.2	4	0.2	-	-
Diabetes mellitus	E10	4	0.2	-	-
More than 1 diagnosis associated		144	7.8	122	12.4
Other diagnosis		93	5.1	64	6.5
Not associated diagnosis		76	4.1	39	4

Notes: *Neuralgia, lumbago with sciatica, sciatica, spondylosis, dorsalgia, lumbalgia, intervertebral disc disorder. **D86.9, G35, G50.0, G53.0, G56.2, G56.4, G62.0, G62.9, G63.0, G63.2, M17.9 M34, M35.3, M41, M43.1, M45, M46.9, M47, M47.2, M47.8, M47.9, M48.0, M50.2, M50.9, M51.0, M51.1, M51.2, M51.9, M53.1, M54, M54.1, M54.2, M54.3, M54.4, M54.5, M54.8, M65.8, M70.6, M75, M75.0, M75.1, M75.8, M75.9, M76.6, M79.1, M79.2, M99.3, M99.5, T14.0. *** C50.9, C79.5, C50, C34.9, C61, C64, C18.9, C79.8, C16.9, C67.9, C71.9, C72, C78.0, C80, C96.9, C01, C06.9, C18.7, C25.9, C47.8, C53.9, C78.6, C81, C90.0, C22. **** T08, M80.9, M81, S32.0, M80, M81.9, S22.0, S32.8, M48.4, M80.4, S12.9, S22.3, S32, S42.2, S42.3, S62.6, S82.2, S82.4.

diagnosis (94.8±66.8 days), more than one diagnosis associated (216.5±236.2 days) and not associated diagnosis (94.8±66.8 days), other diagnosis (239.2±279.7 days) and not associated diagnosis (94.8±66.8 days), after applying Bonferroni test (p=0.035, p=0.031, p=0.002, p=0.036, p=0.013, p=0.012, p=0.031, respectively).

The highest duration of treatment with oxycodone/naloxone was in patients with more than one diagnosis (315.5 ±371.8 days) and the shortest for algoneurodystrophy (90.0 ±0 days). There were statistically significant differences in the duration of oxycodone/naloxone treatment about the diagnoses (p < 0.005). In this case, the significant differences were found about neoplasic processes (135.9±76 days) and more than one diagnosis associated (315.5±371.8 days), not associated diagnosis (92.1±61.1 days) and more than one diagnosis associated (315.5±371.8 days), fibromyalgia (311.4±379.5 days) and more than one diagnosis associated (315.5±371.8 days), after applying Bonferroni test (p=0.013, p=0.001, p=0.027, respectively).

Discussion

This is a drug utilization study focus on a population with active prescription of tapentadol or the combination oxycodone-naloxone in a specific region of a country, and its results do not necessarily be directly applicable to others. However, it provides information about prescription patterns such as dose prescribed and the extent of use by higher-risk populations and their results could be representative of other countries.

Description of the Population

Tapentadol was used approximately 2 times more than oxycodone/naloxone at the cutoff date. This could be explained by the fact that tapentadol extended release is related with substantially lesser incidences of gastrointestinal side effects than oxycodone/naloxone combination.[12,19–21]

In addition, all patients used prolonged-release tablets also in tapentadol (the only one that has immediate-release tablets), which are indicated to control severe chronic pain and not acute pain.[15,16,22] This also indicates that the six patients who were taking the two medications simultaneously were a duplication that would have to be intervened by de-prescribing one of the two opioids, since they did not intend to treat breakthrough pain in which immediate-release analgesics are used as a "rescue" medication.[15,16]

Table 2 Other Diagnoses Associated with Tapentadol Prescription

Other Diagnoses Tapentadol	ICD-10	N	%
Other disorders of the peripheral nervous system	G64	4	0.22
Peripheral vascular disease, unspecified	I73.9	4	0.22
Injury of unspecific body region	T14	4	0.22
Lateral epicondylitis	M77.1	3	0.16
Enthesopathy, unspecified	M77.9	3	0.16
Herpes zoster without complication	B02.9	2	0.11
Hypothyroidism, unspecified	E03.9	2	0.11
Post viral fatigue syndrome	G93.3	2	0.11
Stroke, not specified as hemorrhage or infarction	I64	2	0.11
Systemic lupus erythematosus, unspecified	M32.9	2	0.11
Cervicobrachial syndrome	M53.1	2	0.11
Rotator cuff syndrome	M75.1	2	0.11
Another osteonecrosis	M87.8	2	0.11
Endometriosis, not specified	N80.9	2	0.11
Pelvic and perineal pain	R10.2	2	0.11
Abdominalgia	R10.4	2	0.11
Paresthesia of skin	R20.2	2	0.11
Other and unspecified abnormalities of gait and mobility	R26.8	2	0.11
Tear of meniscus, current injury	S83.2	2	0.11
Problems related to living in residential institutions	Z59.3	2	0.11
Hemorrhagic thrombocythemia (essential)	D47.3	1	0.05
Iron deficiency anemia, unspecified	D50.9	1	0.05
Sarcoidosis, unspecified	D86.9	1	0.05
Parkinson's disease	G20	1	0.05
Other chorea	G25.5	1	0.05
Other specified extrapyramidal and movement disorders	G25.8	1	0.05
Lesion of ulnar nerve, unspecified side	G56.2	1	0.05
Causalgia	G56.4	1	0.05
Other diseases of spinal cord	G95	1	0.05
Other peripheral vertigo	H81.3	1	0.05
Essential hypertension (primary)	I10	1	0.05
Atrial fibrillation and atrial flutter, unspecified	I48	1	0.05
Phlebitis and thrombophlebitis of unspecified site	I80.9	1	0.05
Unspecified acute lower respiratory infection	J22	1	0.05
Anal fistula	K60.3	1	0.05
Cholangitis	K83.0	1	0.05
Other chronic pancreatitis	K86.1	1	0.05
Gastrointestinal hemorrhage, unspecified	K92.2	1	0.05
Decubitus ulcer and pressure area	L89	1	0.05
Lupus erythematosus	L93	1	0.05
Psoriatic and enteropathy arthropathies	M07	1	0.05
Gout, unspecified	M10.9	1	0.05
Sicca syndrome (Sjogren)	M35.0	1	0.05
Spinal instabilities	M53.2	1	0.05
Contracture of muscle	M62.4	1	0.05
Other synovitis and tenosynovitis	M65.8	1	0.05
Trochanteric bursitis	M70.6	1	0.05
Palmar fascial fibromatosis (Dupuytren)	M72.0	1	0.05
Plantar fascial fibromatosis	M72.2	1	0.05
Achilles tendinitis	M76.6	1	0.05
Other specified osteochondropathies	M93.8	1	0.05

(Continued)

Table 2 (Continued).

Other Diagnoses Tapentadol	ICD-10	N	%
Interstitial cystitis (chronic)	N30.1	I	0.05
Urinary tract infection	N39.0	I	0.05
Other specific disorders of the male genital organs	N50.8	I	0.05
Congenital hiatus hernia	Q40.1	I	0.05
Neurofibromatosis (nonmalignant)	Q85.0	I	0.05
Another chest pain	R07.3	I	0.05
Difficulty in walking, not elsewhere classified	R26.2	I	0.05
Ataxia, unspecified	R27.0	I	0.05
Unspecified urinary incontinence	R32	I	0.05
Multiple superficial injuries, unspecified	T00.9	I	0.05
Injury of muscles and tendons of unspecified body region	T14.6	I	0.05
Crushing injury and traumatic amputation of unspecified body region	T14.7	I	0.05
Complication of procedure, unspecified	T81.9	I	0.05
Follow-up care involving plastic surgery of lower extremity	Z42.4	I	0.05

Table 3 Other Diagnoses Associated with Oxycodone/Naloxone Prescription

Other Diagnoses Oxycodone/Naloxone	ICD-10	N	%
Peripheral vascular disease, unspecified	I73.9	4	0.41
Trochanteric bursitis	M70.6	3	0.30
Sacroiliitis, not elsewhere classified	M46.1	3	0.30
Other disorders of the peripheral nervous system	G64	2	0.20
Arthropathic psoriasis	L40.5	2	0.20
Chondromalacia patellae	M22.4	2	0.20
Zoster without complications	B02.9	2	0.20
Chronic kidney disease, unspecified	N18.9	2	0.20
Parkinson disease	G20	2	0.20
Diabetic polyneuropathy (e10-e14 + with common fourth character)	G63.2	2	0.20
Systemic involvement of connective tissue	M35.9	I	0.10
Other chondrocalcinosis	M11.2	I	0.10
Other congenital deformities of hip	Q65.8	I	0.10
Other specified urinary incontinence	N39.4	I	0.10
Osteonecrosis, unspecified	M87.8	I	0.10
Unstable angina	I20.0	I	0.10
Medical care, unspecified	Z51.9	I	0.10
Palliative care	Z51.5	I	0.10
Calculus of kidney	N20.0	I	0.10
Headache	R51	I	0.10
Impacted cerumen	H61.2	I	0.10
Nerve root and plexus compressions in other dorsopathies	G55.3	I	0.10
Diabetes mellitus type 2 without complications	E11.9	I	0.10
Discitis, unspecified	M46.4	I	0.10
Dyspnea	R06.0	I	0.10
Severe depressive episode without psychotic symptoms	F32.2	I	0.10
Hemiplegia, unspecified	G81.9	I	0.10
Ankylosing hyperostosis	M48.1	I	0.10
Lesion of ulnar nerve	G56.2	I	0.10

(*Continued*)

Table 3 (Continued).

Other Diagnoses Oxycodone/Naloxone	ICD-10	N	%
Superficial injury of unspecified body region	T14.0	1	0.10
Systemic lupus erythematosus	M32	1	0.10
Hypertensive heart disease without heart failure	I11.9	1	0.10
Unspecified human immunodeficiency virus (HIV) disease	B24	1	0.10
Pulmonary heart disease, unspecified	I27.9	1	0.10
Neurofibromatosis (nonmalignant)	Q85.0	1	0.10
Persons encountering health services in other specified circumstances	Z76.8	1	0.10
Polyneuropathy, unspecified	G62.9	1	0.10
Unspecified problem related to medical facilities and other health care	Z75.9	1	0.10
Problems related to living in residential institution	Z59.3	1	0.10
Rectal prolapse	K62.3	1	0.10
Sequelae of poliomyelitis	B91	1	0.10
Impingement syndrome of shoulder	M75.4	1	0.10
Phantom limb syndrome with pain	G54.6	1	0.10
Carpal tunnel syndrome	G56.0	1	0.10
Nephrotic syndrome, unspecify	N04.9	1	0.10
Calcific tendinitis of shoulder	M75.3	1	0.10
Sacrococcygeal disorders, not elsewhere classified	M53.3	1	0.10
Crushing injury and traumatic amputation of unspecified body region	T14.7	1	0.10
In growing nail	L60.0	1	0.10
Varicose veins of lower extremities with ulcer	I83.0	1	0.10

Although the use of tapentadol or oxycodone/naloxone between sex was diverse, there was a higher percentage of women than men with active prescriptions of these drugs. This difference could be explained because the pain threshold in women and men is different.[23–25]

Renal and Hepatic Function

In the study, 1.5% of patients treated with tapentadol (N = 28) and 1.5% of patients treated with oxycodone/naloxone (N = 15) had severe (GFR: 15–29 mL/min) chronic kidney disease (CKD). According to the SmPC, tapentadol has not been studied in controlled efficacy trials in patients with severe CKD; therefore, its use is not recommended in this population.[15] Also, patients with CKD have shown higher plasma concentrations of oxycodone and naloxone. Thus, caution should be taken when using oxycodone/naloxone medications in patients with mild CKD (GFR: 60–89 mL/min) and in the case of patients with severe CKD, strict medical surveillance is needed.[16]

As for liver function, around 4% of patients from each group (28 patients treated with tapentadol and 15 with oxycodone/naloxone) suffered from impaired liver function. The impairment of opioid metabolism increases in line with increased liver dysfunction, hence major changes in opioid metabolism have been detected mainly in patients suffering from severe liver diseases, ie, cirrhotic patients. Therefore, among opioids that could require a prolonged dose interval, or a dose reduction are tapentadol and oxycodone.[26] According to the SmPC, tapentadol should be used with caution in patients with moderate hepatic impairment. In the case of severe hepatic impairment, no clinical studies have been found with tapentadol; therefore, its use is not recommended in this population.[15] As for oxycodone/naloxone, clinical trials have shown that plasma concentrations of both oxycodone and naloxone are higher in patients with impaired liver function. This means that medicines containing oxycodone and naloxone as active ingredients are contraindicated in patients with moderate or severe liver failure.[16]

Finally, although in general no dose adjustment was necessary in elderly patients in any of the treatments, considering the age profile of the population of the present study and that elderly patients are more likely to have kidney and liver dysfunction, caution must be exercised when choosing the dose, as recommended.

Treatment Duration

Almost half of the patients, both in tapentadol (51.5%) and oxycodone/naloxone (43.2%), had durations of treatment between one and three months. However, almost the other half (45.3 and 48.6% in tapentadol and oxycodone/naloxone, respectively) had treatment durations ranging from more than 90 days to more than 2 years, despite the very limited evidence on the efficacy and safety of long-term opioid treatment.[27,28]

Often, the liability for chronic pain management and decision in starting an opioid therapy lies on the general practitioners and other non-specialist opioid prescribers, as emergency doctors.[26] Insufficient training and information about opioid management protocols, time pressure to assess patients properly are some of the reasons that could explain the off-label prescription of opioids.[26] A pain specialist or access to specialized and integrative care to re-evaluate the treatment might be needed in patients who had no improvement for the first three months.[7,9]

Prescribed Daily Dose

In this study variable differences were found between the two drugs. Thus, in the case of tapentadol, no statistically significant differences were found in the prescribed daily dose as a function of age. However, an increase in daily doses is observed in older patients (age groups 81–90 and >90 years). Quite the opposite happened in the oxycodone/naloxone combination, where there was a trend of decreasing daily dose values with increasing age that was statistically significative.

The general warning on the safety of patients based on the daily dose used, considering the majority age group found in the present study and the renal and liver functions of these patients, could be especially relevant in the case of tapentadol. Furthermore, only in the case of tapentadol, 3 patients were found who, although young, exceeded the authorized dose according to the SmPC.[16] On the other hand, underdosed patients were found in both tapentadol and oxycodone/naloxone (7.2% and 18.2%, respectively).

Therefore, some patients included in this study had improper dosages, so prescribed daily doses for these patients should be reviewed in the prescription program to prevent both overdosing and underdosing. According to European Pain Federation, the correct dose of an opioid is the lowest possible dose that achieves the desired outcome.[9,26] The decision to modify opioid dosage must be made considering pain reassessment since increased risk of serious harms appears to be dose-dependent,[27,28] patient adherence on treatment, and frequency of monitoring, among others.

Besides, additional evidence confirms an association between opioids and increased risk of serious harms that appears to be dose-dependent,[27,28] they should only be introduced when strictly necessary and with due respect to a continuous risk-benefit analysis.

If we analyze the daily dose according to sex in both treatments, men took more doses than women. Although these differences were significant only in the case of oxycodone/naloxone, this is consistent with published data suggesting that elderly patients and females may suffer from bias in pain assessments or dosing[23] this could be, as it was commented before because women had less intensity of pain than men.[23–25] Results of a genome wide association study suggested that differences experienced by men and women in chronic pain are likely to have a genetic basis.[29]

By studying the daily dose depending on the duration of treatment, in both cases an increasing length of treatment increased the daily dose used, being significant, both positive correlations. The literature shows a strong relationship between initial exposure to opioids and the likelihood of long-term use and, therefore, an increase in tolerance.[30] Thus, the progression of long-term opioid use, should be prevented, in cases where it is not necessary, or it is clinically inadequate.[9,26,31]

Drug Treatment Combination with Tapentadol and Oxycodone/Naloxone

Tapentadol and oxycodone/naloxone followed a similar pattern related to concomitant medications. It is remarkable that more than 85% of patients were taking simultaneously so many pain medications, being some of the most used analgesics, antiepileptics, antidepressants, anxiolytics, selective serotonin reuptake inhibitor and sedatives. As it was mentioned before, polymedication is considered an important risk factor, because involves a major therapeutic complexity and a lower adherence to treatment, which negatively influences the achievement of expected clinical improvement. In addition, the increase in potential drug interactions and side effects, especially in the elderly due to the decrease in hepatic, renal and cardiac functions, should be noted.[16]

Diagnoses

The diagnoses for which tapentadol and oxycodone/naloxone are prescribed followed a similar pattern. Around 42% of tapentadol and around 34% of oxycodone/naloxone prescriptions were for neuralgia, spondylosis, lumbago with sciatica or intervertebral disc disorders. The second common diagnoses in both drugs were related to osteoarthritis, which is the most usual form of joint disease and the main cause of pain and physical disability in the elderly.[26] The third were related to fractures and osteoporosis.

Only around 5% of diagnoses were neoplasms for the two drugs studied. Around 4% of patients had not associated diagnosis, in those cases, the dose was lower than in the others, and length of treatment was 94 days.

At this point, it is important to highlight, that opioids should only be introduced when strictly necessary. Many patients may tolerate and respond to this treatment, and it should not be denied to them when deemed medically necessary by a responsible physician.[9,26,31]

Throughout the discussion, several interventions that would be necessary to improve the use of these drugs have already been indicated. Thanks to this study, inappropriate posology of tapentadol and oxycodone/naloxone has been detected and in September 2019 the recommended posology of both drugs has been added to the electronic primary care clinical station (ECAP). The ECAP prescription module proposes now the approved dosage regimen for each drug and the physician should review and modify the prescription if necessary. Furthermore, other interventions would be, for example, better practices in promotion of medicines and subsequent training to prescribers and other health professionals to raise awareness about opioids risk.[26] Wong et[32] al pointed out the implementation of interventions for emergency department utilizing patients with chronic noncancer pain could decrease the frequency of visits, care-associated costs, amount of opioid administration and prescription.

Conclusions

We found that the use of tapentadol and the combination oxycodone/naloxone in primary health care was characterized by female patients between 71 and 90 years of age and with mild or moderate decrease in renal function. Typical use was of one of these opioids at lower doses than men for an average of 31 to 90 days. Daily doses were higher in longer treatments, mainly of between one and two years of duration.

To conclude, the pattern of use and profile of patients with tapentadol and oxycodone/naloxone had more similarities than differences. The study suggested that prescribing practices and patient monitoring should be assessed regularly to ensure patient safety and effective management of pain.

Patient and Public Involvement

Patients and the public were not involved in the design or execution of this study.

Data Sharing Statement

Data used in this study are available from the corresponding author upon reasonable request.

Ethics Approval

Ethical approval was not required as it was made a secondary analysis of suitably anonymized data sets. It was not an experimental study and patients were not recruited.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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