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Prescribing strong opioids in patients with non-cancer pain: a description of their characteristics in an area of primary healthcare assistance

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ABSTRACT

Objective: Analyze all prescriptions of strong opioids in patients with non-cancer pain and review their frequency and characteristics.

Design: Transversal descriptive study.

Location: Primary healthcare area, attended by 24 family doctors, with 38,000 users.

Participants: All patients with non-cancer pain who were prescribed strong opioids on a certain date.

Method of data collection: Pharmacological data was collected from the Andalusian Health Service's prescriptions database. Clinical data from "Diraya" digital history.

Results: 138 patients were receiving this treatment on the date of study (3.6% of the population). Mean age: 78 years (± 11.6); 76.8% women. Duration of treatment: 555.4 days (± 667.7). Average opioid dose: 82 mg (± 54.9) morphine equivalent/day. Drug most used at treatment baseline (25%) and at the time of the audit (18.9 %): transdermal fentanyl 25 mcg. Appropriate starting dose: 76 %. Progressive modifications dose: 83 %. Most frequent reason for prescription: back pain (22 %). Analgesic measures were taken in 66 %. Side effects recorded in 11 %. 70 % were simultaneously taking benzodiazepines.

Conclusions: The prevalence of prescribing strong opioids in non-cancer patients is 3.6 ‰ of our population. At the time of the audit, treatment had been initiated a year and a half previously, the most commonly-used drug was transdermal fentanyl, also used for initiation of treatment and two out of three patients were simultaneously taking drugs from the benzodiazepine group.

Key words: Chronic pain, opioid analgesics, primary healthcare.

RESUMEN

Objetivo: Analizar todas las prescripciones de opioides mayores en pacientes con dolor no oncológico y revisar su frecuencia y características.

Diseño: Estudio descriptivo transversal.

Emplazamiento: Zona de salud de atención primaria, 24 médicos de familia, 38.000 usuarios.

Participantes: Todos los pacientes con dolor no oncológico que tenían prescritos opioides mayores en una fecha determinada.

Método de recogida de datos: Datos farmacológicos del programa informático de prescripciones del SAS, datos clínicos de la historia digital Diraya.

Resultados: 138 pacientes recibían este tratamiento en la fecha de estudio (3,6 ‰ de la población); media de edad: 78 años (± 11,6); 76,8 % mujeres. Duración media de los tratamientos: 555,4 días (± 667,7). Dosis media de opioide: 82 mg (± 54,9) equivalente morfina/día. Fármaco más utilizado al inicio del tratamiento (25 %) y en el momento del audit (18,9 %): fentanilo transdérmico 25 mcg. Dosis inicial apropiada: 76 %.

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Modificaciones progresivas de dosis: 83 %. Causa más frecuente de la prescripción: patología lumbar (22 %). En el 66,6 % se utilizaron escalones analgésicos previos. Constaban efectos secundarios en el 11 %. El 70 % tomaba simultáneamente benzodiacepinas.

Conclusiones: La frecuencia de prescripción de opioides mayores en pacientes no oncológicos es del 3,6 ‰ de nuestra población. En el momento del audit, el tratamiento está iniciado desde hace un año y medio, el fármaco más utilizado es el fentanilo transdérmico, que también lo es como inicio del tratamiento, y dos de cada tres pacientes están utilizando simultáneamente fármacos del grupo de las benzodiacepinas.

Palabras clave: Dolor crónico, analgésicos opioides, atención primaria.

INTRODUCTION

Strong opioid drugs represent one of the therapeutic alternatives available to family doctors for alleviating pain, which is one of the main reasons for clinical visits in primary healthcare (1,2). In Spain, according to data from the latest National Health Survey (3), approximately one out of every six adults interviewed reported chronic back or neck pain or report having osteoarthritis-related conditions, which are the main causes of chronic non-cancer pain (4-6).

Prescription of these types of drugs has increased over the last decade, both in Europe and in our country, although our consumption is lower than the European average (8th position, from greater to lesser consumption, among 12 countries compared) (7) and also lower in Europe with respect to consumption in Canada and the United States (8).

The use of strong opioids seems to be shown to relieve cancer pain and pain in terminal patients (9), but it is subject to certain controversies in alleviating chronic non-cancer pain, especially with respect to its long term efficacy (10, 11), as well as in functional results (12), in relieving lower back pain when compared with other analgesic drugs (13) or in fibromyalgia (14), where its lack of efficacy seems clear.

Furthermore, these drugs have no lack of adverse effects, which can give rise to their withdrawal in one out of every three patients (15), as well as the possibility of dependence in a small percentage of cases (16).

It is also worth bearing in mind, as regards opioid therapy in patients with chronic non-cancer pain, that there is no strong evidence to support recommendations on opioid dose and opioid type to use, as well as form of treatment initiation or duration (9).

For all the above, and considering the few studies in our country that review the use of these drugs in primary healthcare, we have set out to determine what percentage of the population in our health area is in treatment with these drugs, and to review these prescriptions' characteristics.

PATIENTS AND METHODS

Type of study

Descriptive transversal study.

Location

Urban health center which is the reference center for a population of 38,000 inhabitants and which is attended by 24 family doctors.

Subjects

All patients who were prescribed a drug from the strong opioid group, among which we include all those of the therapeutic group N02A of the ATC classification (17): oxycodone, hydromorphone, tapentadol, methadone, meperidine, buprenorphine, fentanyl and morphine, with the exception of tramadol, codeine and codeine derivatives, which are considered weak opioids (18). The selection comprised all patients who, on 31 May 2014, were in treatment with drugs of the strong opioid group. Patients were excluded when they had indications for cancer pain and when drugs were not prescribed by electronic prescription and which, therefore, left no record in the clinical history.

Data collection method

Drug data was obtained from the prescription database of the Andalusian Health Service and clinical data from the Diraya digital clinical history.

Statistics

Univariate statistics, with commonly-used measures of frequency and dispersion and bivariate Student t statistics, analysis of variance and analysis of correlation for quantitative variables and chi square for qualitative variables, with their corresponding confidence intervals.

Values of $p > 0.05$ were defined as insignificant. Results were analyzed with the SPSS statistical package version 15.0.

Variables

The main variables analyzed were: number of patients with this type of treatment and their percentage in relation our area's population, type and dose of opioid prescribed, treatment duration, previous use of analgesic stages (firstly non-opioids, secondly weak opioids and thirdly strong opioids), the use of some kind of pain assessment scale, reason for prescription, who makes the indication (family doctor, pain unit, emergency service, other), the existence of side-effects, the clinical history containing some kind of informed consent and simultaneous prescription of benzodiazepines.

We also assessed opioids prescribed at the initiation of treatment, their initial dose and whether this dose complied with the recommendations of the National Opioid Use Guideline Group (NOUGG) (19) (Table I). Furthermore, we analyzed whether or not the treatment was modified over time in prescriptions longer than one month. In cases where a modification was made to the dose, we assessed whether the quantity and the time interval for carrying this out complied with the recommendations of the guidelines mentioned above (19) (Table I). Finally, opioid doses were unified in morphine equivalent doses (MED) in mg/day, using the criteria of the NOUGG guidelines (19).

RESULTS

On the date of the study, we found 167 patients who were at that time in treatment with drugs of the strong opioid group; of these, the drug had been prescribed to 26 patients (15.6%) for cancer pain, and in 3 cases (1.8%) opioids had been prescribed according to the prescriptions database but there was no record in the clinical history so, as in the previous cases, they were excluded from the study. Finally, 138 patients were included in the study group, which represents an approximate spot frequency of strong opioid prescription for non-cancer pain of 3.6 per thousand in our area population.

Of these 138 patients, Tables II, III, IV and V show the results of the main variables analyzed.

This group's mean age was 78, and 77% were women. Mean duration of treatment was 555 days, and prescription indication was given by the patient's family doctor in 32% of cases. The maximum strong opioid dose prescribed, in morphine equivalent and mg/day, did not surpass 100 mg in 70% of cases and in 4% of cases a dose of 200 mg was surpassed in morphine equivalent. 70% of patients simultaneously took drugs of the benzodiazepine group. 11% of patients showed the existence of side-effects, with a prevalence of constipation. In 83% of cases, dosage modifications were progressive and in 67% analgesics were appropriately staged previously.

TABLE I
INITIAL OPIOID DOSE AND SCHEDULE OF DOSE MODIFICATION
[MODIFIED FROM NOUGG GUIDELINES (16,17)]

*Active ingredient**	*Initial dose*	*Increases*	*Interval for increasing dose*
Morphine	5-10 mg / 4-6 hours. Maximum 40 mg day	5-10 mg/day	7 days
Slow-release morphine	10-20 mg, once, twice or three times a day. Maximum 40 mg/day	5-10 mg/day	14 days
Oxicodone	5 mg every 4-6 hours Maximum 30 mg/day	5 mg/day	7 days
Slow-release oxicodone	10 mg, twice or three times a day. Maximum 30 mg/day	10 mg/day	14 days
Slow-release hydromorphone**	4 mg / twice a day. Maximum 8 mg/day	4 mg/day	14 days

* For buprenorphine and transdermal fentanyl, as well as for slow-release tapentadol, an appropriate initial dose is considered to be the lowest in commercial dosage form.
** Slow-release hydromorphone doses of 3 mg are not marketed in Spain, so dosage recommendations have conformed to the 4 mg dosage form.

TABLE II
RESULTS OF THE MAIN VARIABLES ANALYZED

Variable	*Number*	*%*
Sex:		
Women	106	76.8
Men	32	23.2
Origin of prescription		
Patient's family doctor	44	32
Pain Unit	19	13.8
Emergency Services	4	2.8
Other	24	17.4
Unknown	47	34
Initiation with appropriate dose	105	76
Unknown	5	
Progressive dose modifications in prescriptions longer than one month; n = 70	58	82.8
Peak dose reached in morphine equivalent in mg/day:		
– Less than 100 mg	96	69.6
– 100 to 200 mg	36	26.1
– More than 200 mg	5	3.6
– Unknown	1	0.7
Duration of treatment (months):		
– Less than one year	83	60.1
– More than/equal to 1 year and less than 2 years	18	13
– More than/equal to 2 years and less than 3 years	11	8
– More than/equal to 3 years and less than 4 years	10	7.2
– More than/equal to 4 years and less than 5 years	9	6.5
– More than/equal to 5 years	7	4.2
Dosage forms used at treatment initiation:		
– Transdermal	103	74.6
– Slow-release oral	30	21.7
– Non-slow-release oral	0	
– Unknown	5	3.6
Dosage forms used at the time of the audit:		
– Transdermal	104	74.8
– Slow-release oral	33	23.8
– Non-slow-release oral	1	0.7
– Parenteral	1	0.7
Informed consent	0	0
Use of analgesic assessment scales	1	0.7
Use of prior analgesic stages:		
First non-opioids, second weak opioids	92	66.6
Jump from non-opioids to strong opioids	27	19.6
Initiation with strong opioids without other prior analgesics	3	2.2
Cannot be determined	16	11.6
Patients with simultaneous prescription for benzodiazepines	96	70
Presence of side-effects	15	10.8
Side-effects		
Mental dullness/sleepiness/weakness	3	2.1
Constipation	7	5
Nausea, vomiting	2	1.4
Addiction	3	2.1

(Continues on next page)

TABLE II
RESULTS OF MAIN VARIABLES ANALYZED

Quantitative variables	*N*	*Mean*	*Minimum*	*Maximum*	*St. Dev.*
AGE in years	138	77.8	43.00	99.00	11.6
TIME in opioid use (days)	138	555.4	10.00	3,285.00	667.7
Peak opioid dose prescribed in morphine equivalent and mg/día	137*	82	10.00	300.00	54.9

*One loss for prescription transmucosal oral fentanyl 200 mcg/24 hours.

TABLE III
MAIN REASONS FOR PRESCRIBING OPIOIDS

Cause	*Number*	*%*
Back pain (lumbar canal stenosis, lumbar osteoarthritis, disk prolapse, sciatica, lumbar arthrodesis)	30	22
Generalized osteoarthritis	28	20
Osteoarthritis of the knee	14	10
Vertebral fracture	12	9
Spinal Osteoarthritis	8	6
Osteoarthritis of the hip	8	6
Polyarthralgia	6	4
Polyneuritis	3	2
Rheumatoid arthritis	3	2
Arthritis of the neck	3	2
Fibromyalgia	3	2
Other (Osteoarthritis of the shoulder, multiple sclerosis, chronic pancreatitis, rheumatic polymyalgia, hip fracture)	5	4
Unknown	15	11
Total	**138**	**100**

TABLE IV
STRONG OPIOIDS USED AT INITIATION OF TREATMENT

Drug and dose	*n*	*%*
Transdermal fentanyl 25 mcg	34	24.7
Transdermal fentanyl 12 mcg	28	20.3
Transdermal buprenorphine 35 mcg	18	13
Transdermal fentanyl 50 mcg	13	9.4
Slow-release oral tapentadol 25 mg	9	6,5
Transdermal buprenorphine 52.5 mcg	7	5
Slow-release oral tapentadol 50 mg	7	5
Slow-release oral oxicodone 5 mg	5	3.7
Slow-release oral oxicodone 10 mg	4	2.9
Transdermal fentanyl 75 mcg	3	2.1
Slow-release oxicodone 20 mg	2	1.6
Slow-release hydromorphone 4 mg	2	1.5
Slow-release oral morphine morphine 5 mg	1	0.7
Unknown	5	3.6
Total	**138**	**100.0**

The most-used active substance and dosage as initiation of the treatment was transdermal fentanyl of 25 mcg (25%). The opioid most used at the time of the audit was also transdermal fentanyl and a dose of 25 mcg/72 hours (53%). The most frequent cause for prescription was pain caused by lower back pain (22%), followed by generalized osteoarthritis.

In patients where medication was initiated according to NOUGG recommendations (19), mean opioid dose in morphine equivalent (MED) mg/day was significantly lower ($p < 0.01$, 95% confidence interval [CI-95] -10.3 at -54 mg/day MED) and peak dose reached was also lower ($p < 0.001$; CI-95: -29 at -72 mg/day MED).

Significantly, patients with side-effects had received a higher maximum opioid dose than those who did not show iatrogenesis ($p < 0.05$; IC-95: 2.4 at 65 mg/day MED).

We found no statistical association of sex, age or of the healthcare professional who gave the prescription with the rest of variables studied.

TABLE V
STRONG OPIOID IN USE AT THE TIME OF THE AUDIT

Drug and dose	*n*	*%*
Transdermal fentanyl 25 mcg / 72 hours	26	18.9
Traansdermal fentanyl 50 mcg / 72 hours	20	14.6
Transdermal buprenorphine 35 mcg / 72 hours	15	10.9
Transdermal fentanyl 75 mcg / 72 hours	11	8
Transdermal fentanyl 12 mcg / 72 hours	11	8
Slow-rel. tapentadol 50 mg / 12 hours	11	8
Transdermal buprenorphine 52.5 mcg / 72 hours	10	7.2
Slow-rel. tapentadol 25 mg / 12 hours	6	4.3
Slow-rel oxicodone 20 mg + naloxone/ 12 hours	5	3.6
Slow-rel. oxicodone 5 mg + naloxone/ 12 hours	4	2.9
Slow-rel. oxicodone 10 mg + naloxone/ 12 hours	3	2.2
Transdermal buprenorphine 70 mcg / 72 hours	3	2.2
Transdermal fentanyl 100 mcg / 72 hours	3	2.2
Fentanyl 100 mcg + traansdermal fentanyl 25 mcg /72 hours	2	1.4
Oral buprenorphine 200 mcg / 24 hours	2	1.4
Slow-rel. oxicodone 40 mg + naloxone / 12 hours	1	0.7
Oxicodone 10 mg / 8 hours	1	0.7
Slow-rel. tapentadol 100 mg/12 hours	1	0.7
Transmucosal oral fentanyl 200 mcg / 24 hours	1	0.7
Slow-rel. hydromorphone 4 mg / 12 hours	1	0.7
Slow-rel. hydromorphone 8 mg / 12 hours	1	0.7
Morphine vials 10 mg, sb, on demand*	1	
Total	139	100

*Rescue therapy together with transdermal fentanyl.

DISCUSSION

We know of no studies in our country that let us compare the prescription frequency found: 3.6 per thousand. In a recent population-based study carried out in Portugal (20) by phone survey, the frequency was 1.7 per thousand. In the United States, with relatively higher consumption figures than in Europe (21), it is estimated that between 4% and 5% of the population is in prolonged treatment with opioids (5), although we do not know whether these figures are comparable owing to possible differences in population type, healthcare system and the possible inclusion of weak opioids in these studies.

Mean treatment duration (555 days), surpasses the term reported in the work by Reid et al. (6) in a population aged from 65 upwards, which was 388 days. A recent population-based study carried out in Norway (21) reported that 24% of patients taking opioids continued treatment five years after initiation, and in a similar study carried out in Sweden (22), 27% continued with treatment three years after initiation. Although we cannot compare our figures with these studies' findings due to methodological differences, in our case, 4.2% of patients had been in treatment for five years. It is worth taking into account that the duration of the studies that analyzed opioids' efficacy with chronic non-cancer pain did not surpass 16 weeks (12) and, as repeatedly shown in the literature (5,11,13,23), there is no evidence of these drugs' efficacy over such extended periods of time.

Mean dose of opioids prescribed, in morphine equivalent in mg and day (82 mg), is lower in our study than the national average for 2012 (150 mg) (24). Also, only 4% of treatments surpasses 200 mg in morphine equivalent and day, a figure it is recommended not to exceed (9,19). Additionally, 70% of prescriptions were lower in dosage than 100 mg morphine equivalent daily dose; higher dosage seems related to a greater risk of overdose and death (25).

A third of drugs' initial indications were made by the family doctor, a proportion significantly lower than other works consulted (4,6), but difficult to compare because the studies were carried out in the United States, with a healthcare system and percentages and prescription types that differ from our environment. We have not been able to compare these figures with Spanish or European works, as we have found no similar studies.

No clinical history showed patients had been informed of the medication's possible side-effects or their consent for its use, as recommended by the guidelines consulted (9,19), and only one showed a scaled assessment of pain level. However, we should consider that one major limitation of the study is the high chance of faulty registration of data entered in the clinical history.

11% of cases showed possible side-effects attributed to opioids, a figure that differs greatly from the 94.6% in the recent study by Gálvez et al. (26). In all probability, the differences arise from the fact that this latter study was intended to seek prospective gastrointestinal symptoms in patients treated with

opioids and that cancer patients were included. Logically, larger opioid doses were associated with a greater presence of side-effects.

70% of patients were simultaneously taking benzodiazepines along with the opioids; a high proportion if we compare the work of Gálvez (26) (49%) and of Dobscha (4) (24%). It is interesting to bear this in mind, as benzodiazepines appear to be involved in 17% of deaths associated with opioid misuse (27).

The most-used opioid by far was fentanyl patches, both as initiation and throughout the whole treatment. The NOUGG guidelines (19) recommend morphine, oxicodone or hydromorphone as first choice for beginning treatment, and leaves fentanyl as a second alternative, after first using another opioid at doses from 60 to 100 mg morphine equivalent for two weeks.

Chronic back pain and osteoarthritis were the most frequent reasons for prescribing these drugs, findings that coincide with those of other works (4-6). It is worth recalling the Cochrane review (13), which mentions that opioids had not shown significant differences in alleviating back pain compared with analgesics.

As mentioned above, the main limitation of our study is the data source of some variables studied. In short, data collected exclusively from clinical histories run the ever-inherent risk of this type of data not being recorded. Conversely, the reliability of pharmacological data (type, dose and duration of the prescription) is high, as in Andalusia, for 8 years, the large majority of prescriptions have been carried out electronically.

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