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ORIGINAL ARTICLE

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Health benefits of an adverse events reporting system for chronic pain patients using long-term opioids

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Background: Safety data from long-term opioid therapy in the real world has been poorly studied in chronic non-cancer pain (CNCP). The aim was to design a pharmacovigilance data recording system and assess whether participation in this recording system improves pain management, enhancing patient's health status.

Methods: A pharmacovigilance data recording system was conducted during 24 months. Data were self-reported by patients (pain, adverse events [AEs] and healthcare resources use) and physicians (morphine equivalent daily dose [MEDD] prescribed and suspected adverse drug reaction [ADRs]). Outcomes from patients with (case) or without (controls) suspected ADRs and cases follow-up were also compared with Spanish Pharmacovigilance System data.

Results: A total of 753 patients were recruited in 897 visits. Fentanyl and tramadol were the most prescribed opioids, 89% with concomitant drugs, pregabalin being the one with the most potential drug interactions. Cases presented significantly higher pain intensity (VAS 67 ± 26 vs 59 ± 30 mm, $P < 0.05$), number of AEs (8 ± 6 vs 5 ± 3 AEs/patient, $P < 0.01$), polypharmacy related to pain (65% vs 34%, $P < 0.01$) and MEDD (139 ± 130 vs 106 ± 99 mg/d, $P < 0.01$) than controls. Furthermore, cases presented significant higher changes in pharmacological pain therapy due to pain, unplanned emergency visits and hospital admission than controls. Physicians notified 168 suspected ADRs mostly related to neurological or psychiatric events and 8% of them were previously unknown.

Conclusions: This data recording system provided important information to achieve a better control of CNCP pharmacological pain therapy, improving patient's health status and reducing costs to the Health System.

KEYWORDS

chronic non-cancer pain, opioids, patient's reports of adverse events, pharmacovigilance data recording system, suspected adverse drug reaction

1 | INTRODUCTION

The safety of prescribed drugs represents a major public health concern. Estimates suggest that approximately 0.5% of all emergency department visits and primary care visits result from a suspected adverse drug reaction (ADR), defined as any harmful and unintentional response to a medication; however, only 1% of them are reported.[1] Information is available to prescribers through summary product characteristics (SPC) and literature based on clinical trials, which are acknowledged as only identifying a proportion of them without reflecting everyday practice.[2,3] Also, data about side effects of long-term use of opioids continue being scarce.[4-6] Even

more, pharmacological pain management typically requires multiple drugs that could present synergistic or adjunctive effects and, usually, are prescribed at high doses.[7] This overall drug profile is often overlooked and oversimplified in clinical trials.[8]

Safety data of long-term opioid therapy have been poorly studied in chronic non-cancer pain (CNCP)[9-11] and common ADRs include gastrointestinal symptoms as nausea, vomiting and constipation;[12] dependency and dosage tolerance;[13] endocrine disorders;[14] or opioid-induced hyperalgesia.[15] Thus, spontaneous reporting systems to collect suspected ADRs have become the most important component for pharmacovigilance monitoring to improve patient's health status and reduce health system resources utilisation.[16] However, sub-reporting remains a barrier to ascertain the real incidence.[17,18] In this context, patients could play a part by better reporting adverse events (AEs), defined as any undesirable event experienced by a patient, regardless of whether is suspected or not to the drug administered, to physicians that might improve pharmacovigilance activities.[19-21]

We designed a pharmacovigilance data recording system where patients actively participated reporting AEs, as a tool to help physician perception of the problems attributable to pharmacological pain therapy. The primary aim of this study was to assess whether the participation of patients improves patient management in terms of a better pharmacological pain therapy control, enhancing their health status. In addition, we wanted to assess if this data recording system could reduce costs to the Health Care System.

Editorial Comment

Long-term opioid treatment in chronic non-cancer pain is still a contentious issue, highlighted by the recent opioid epidemics in many countries. Diversified outcome data are sorely needed, mainly as a guide to clinical treatment. This study used pharmacovigilance reporting in chronic pain patients focusing, on adverse events and possible adverse drug reactions, enabling intervention that led to reductions in adverse events and drug prescriptions.

2 | METHODS

2.1 | Study design

A retrospective non-interventional study was conducted over a period of 24 months from September 2012 to August 2014 at the Pain Unit of the Department of Health of Alicante-General Hospital, Spain. Patients filled the forms/questionnaires prospectively (between 2012-2014) at their regular visits and clinical data were analysed at the end of the study (between 2015-2016). This manuscript represents the first part of a cost-effectiveness study approved by the accredited Ethics Committee of the General Hospital of Alicante.

2.2 | Protocol

A data recording system of patient's report of AEs and suspected ADRs reported by physicians, associated to long-term opioid therapy for CNCP management, was developed based in national and international guidelines for submitting AE reports for publication.[22] In the recording system, patients, before their visits, self-reported their assessment of pain using scales of effectiveness and a questionnaire of safety supported by a nurse trained in pain management. Data were incorporated in their medical records by the physician who also collected clinical and pharmacological history of patient's pain. In addition, physicians evaluated the possibility to notify any suspected ADRs to the Spanish Pharmacovigilance System, and adjust pharmacological pain therapy. Prescription was performed by four anesthesiologists, but ADRs were revised by a clinical pharmacologist and re-evaluated by two members of the research team. Opioid rotation or switch from one opioid to another was performed in case needed to improve the response to analgesic therapy or reduce adverse effects.

2.3 | Control, case and case follow-up patients

Outpatients of the Pain Unit were recruited along 24 months. Inclusion criteria were: (a) adult (≥18 years old), (b) under long-term opioid therapy (for 6 months or longer), (c) diagnosis of CNCP and (d) with adequate mental status for properly filling in the scales and questionnaire. Patients were divided into "case" and "control" groups depending on the presence of suspected ADR noted in a clinical visit. At least one follow-up visit was performed in case patients ("case follow up").

2.4 | Patients self-reported data

2.4.1 | Effectiveness data

Pain intensity was determined using the validated 100-mm Visual Analogue Scale (VAS, 0 "no pain" to 100 "worst possible pain")[23] and a Likert-based scale[24] (descriptors: none, mild, moderate, severe and extreme pain). Pain relief was determined using a 100-mm VAS (0 "no relief" to 100 "maximum relief") and Likert-based scale (none, mild, moderate, severe and extreme pain relief). Quality of life related to health measures was assessed by the EQ-VAS[25] (0 "worst" to 100 "best health status").

2.4.2 | Safety data

To collect AEs reported by patients, a questionnaire with a list of most frequent ADRs (indicated in opioids SPC as "very common" and "common"[26]) and a blank field to add any other AE developed. In addition, questions about if patients had changed any prescribed drugs, had had any emergency department visit or hospital admission, due to pain or other causes, since their last clinical visit were included.

2.5 | Suspected ADRs noted

According to the Spanish Pharmacovigilance System, a suspected ADR is any undesirable event happening to the patient while using a drug and suspected to be caused by the medication. Physicians must report a suspected ADR to the Spanish Pharmacovigilance System when it meets any of the following criteria: new (unknown in literature or SPC), severe (causes death, threatens the life of the patient, causes hospitalisation or prolongation, causes incapacity for work or induces birth defects), any ADR with clinical relevance of a new approved drug, or from drugs under additional pharmacovigilance monitoring by European Medicine Agency.[27]

The Naranjo algorithm is a questionnaire designed to determine the probability of whether an ADR is due to the drug rather than to other factors. When physicians notified a suspected ADR, causality assessment of the ADR was done using the Naranjo algorithm[28,29] (≥9 points, definite; 5-8 points, probable; 1-4 points, possible; ≤0 points, doubtful) for the three suspected drugs included in the notification card. In our study, only the drugs and suspected ADRs with the highest causality score in Naranjo algorithm were selected. So, for the analysis, each observation had one suspected ADR and one suspected drug.

A request was made to the Spanish Pharmacovigilance System about the suspected ADRs associated to opioids reported from all over Spain at the same period of time to compare their data with ours.

The following variables were collected from the assessment of each suspected ADR: type of reaction (type A: intrinsic or predictable, dose-related toxicities and type B: idiosyncratic or drug reactions that occur rarely and unpredictably amongst the population);[30] potential appearance (new drug added to the prescription; dependent of a dose increase; other drugs not related to pain added to the prescription or clinical concomitant effects as potential drug-drug interaction [DDI] including all drugs involved in the suspected ADR notification card; information not available); severity (severe or non-severe); action taken to resolve it (no change, dose reduction, drug withdrawal, increase dose and substituted generic to brand drug); and final outcome (recovering, fully recovered, recovered with aftermath, fatal, unknown due to not documented after the initial report, worsening).

Suspected ADRs notified were classified using the terminology of the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0): Preferred Term (PT) and System Organ Class (SOC).[31,32] Furthermore, suspected ADRs were analysed taking into account their frequency at the SPC of the Online Information Center of Medicines of Spanish Agency of Medicines and Health Products (AEMPS-CIMA)[26] (very common [VC, ≥1/10], common [C, ≥1/100 < 1/10], uncommon [UC, ≥1/1000 < 1/100], rare [R, ≥1/10 000 < 1/1000], very rare [VR, <1/10 000] and unknown frequency [UF]).

2.6 | Pharmacological pain therapy

Physicians collected: patients' prescribed pain therapy (opioids and concomitant drugs [antiepileptic, antipsychotic, anxiolytic, antidepressant or muscle relaxant]), drug doses, polypharmacy on pain therapy (defined as ≥5 drugs prescribed in relation to pain) and type of pain. Total daily dose of opioids was converted to morphine equivalent daily dose (MEDD), estimated using equianalgesic dose.[33] Using the Hospital electronic Health Information System, the percentages of drug prescriptions at the Pain Unit along the study period were recorded.

Drugs with the highest causality assessment in Naranjo algorithm for each suspected ADR notified, were categorised according to the Anatomical, Therapeutic, Chemical classification of the World Health Organization (ATC/DDD Index 2016 WHO).[34] Although each suspected ADR was associated to the drug with the highest causality assessment score, and potential DDI was evaluated for all drugs included in the notification card using SPC (AEMPS-CIMA)[26] and Stockley's drug interactions.[35]

2.7 | Statistical analysis

Shapiro-Wilk normality test was chosen to perform parametric or non-parametric tests for comparisons. All continuous variables fitted to normal distribution, thus parametric tests were used. Continuous variables are presented by mean ± standard deviation (SD) and categorical variables are expressed by absolute counts and/or percentages. *T*-Test for independent samples and the Pearson X^2-test were used to assess variations in the study parameters between groups. All statistical analyses were performed with the software R 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria) and Graph Pad Prism 5.01 (GraphPad Software, La Jolla, CA, USA). *P*-values of <0.05 were considered to indicate statistical significance.

3 | RESULTS

Between September 2012 and August 2014, a total of 753 patients with long-term use of opioids for CNCP (603 controls, 150 cases and 126 cases follow-up patients) were included (Figure 1). Demographic and pain clinical-therapeutics data related to pain are shown in Table 1. Regarding the aetiology of pain, 24% of patients presented nociceptive pain, 61% mixed-type pain and 15% neuropathic pain. Most frequent clinical diagnosis was low back pain (80%) and comorbidities anxiety (62%) and depression (38%). No significant differences in pain type, diagnosis and comorbidities were found between case and control patients.

3.1 | Effectiveness data

Pain intensity was significantly higher in case than control patients (VAS 67 ± 26 vs 59 ± 30 mm, $P = 0.028$). Female frequency (77% vs 63%, $P = 0.016$), polypharmacy on pain therapy (65% vs 34%, $P < 0.001$) and MEDD mean (139 ± 130 vs 106 ± 99 mg/d, $P < 0.005$) were also significantly higher in case patients than in controls, with more drug rotations (52% vs 21%, $P < 0.001$), emergency department visits (50% vs 18%, $P < 0.001$) and hospital admissions (24% vs 6%, $P < 0.001$) due to pain. Furthermore, cases

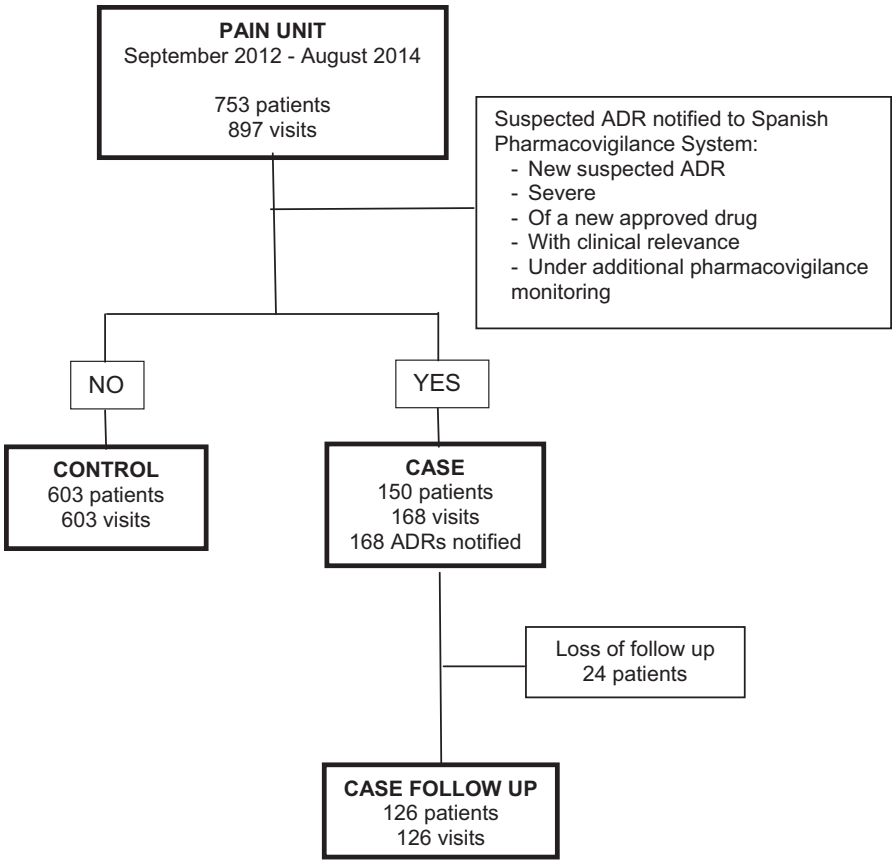

FIGURE 1 Flow chart of patient selection: controls, cases and follow-up of cases

presented significantly higher drug rotations (52% vs 36%, $P < 0.005$) and emergency visits (50% vs 37%, $P < 0.05$) due to pain than case follow-up patients.

3.2 | Safety data

Patients reported a total of 4289 AEs, the number of AEs per patient being higher in case vs control patients (8 ± 6 vs 5 ± 4 AEs/patient, $P < 0.001$). In case follow-up patients, AEs were significantly reduced (6 ± 3 AEs/patient, $P = 0.005$). No significant differences in AEs distribution by SOC and PT were observed between case and control groups. In both groups, the most frequently reported AEs belonged to nervous system (23%) and psychiatric disorders (22%). Interestingly, analysing by PT, the most common AEs were dry mouth (59%), constipation (47%) and nervousness (45%).

3.3 | Assessment of suspected ADRs

During the 2 years of the study the Spanish Pharmacovigilance System registered a total of 2364 suspected ADRs associated to opioids from 1500 patients. These data were compared with the 168 suspected ADRs collected in this study (4% of AEs reported by patients) (Table 2).

Naranjo causality assessment of suspected ADRs notified in the study resulted in 64% of them as possible and 36% as probable. Unclassified suspected ADRs (20%) were due to lack of information regarding to the causality assessment. Most of them were type A (93%) and severe (41%), requiring in 90% of the cases drug withdrawal following our established protocol. Ninety-three per cent of the patients fully recovered, with no fatal suspected ADRs. Clinical data suggested that suspected ADRs were related to: 48% new drug addition to the prescription, 15% drug dose increase, 20% other drugs not related to pain added to the prescription or clinical concomitant effects and in 17% information was not available.

The most frequent suspected ADRs reported, classified by SOC, were: 26% nervous system and 16% psychiatric disorders. Comparing with data of Spanish Pharmacovigilance System, distribution of suspected ADRs by SOC was similar, with the exception of gastrointestinal disorders which were two times more frequent in national data, and reproductive system disorders which happened eight times more in our study. Furthermore, our study found 9% of new suspected ADRs not previously reported in the SPC, 85% related to females (Table 2).

3.4 | Pharmacological pain therapy

3.4.1 | Drug-drug potential interactions

Characteristics of potential DDI from all the drugs included in the suspected ADRs notification cards are shown in Table 3. Each drug was registered for each DDI. Data show a total of 295 potential DDI, mostly due to pregabalin (n = 96), tramadol (n = 87) and

TABLE 1 Demographic and pain clinical-therapeutics data related to pain of the patients included in the study (grouped in control, case and case follow-up patients)

Variables related to pain	Control patients (n = 603)	Case patients (n = 150)	Case follow-up patients (n = 126)
Self-reported by patients			
Sex (% Female)	63	77**	78
Age (mean ± SD)	64 ± 11	66 ± 14	64 ± 13
Pain intensity (VAS, mm, mean ± SD)	59 ± 30	67 ± 26*	63 ± 27
Pain relief (VAS, mm, mean ± SD)	33 ± 31	32 ± 29	29 ± 29
Likert pain intensity (%)			
None	8	3	3
Mild	6	2	8
Moderate	25	31	28
Severe	32	34	28
Extreme severe	29	30	31
Likert pain relief (%)			
None	30	20	19
Mild	12	22	22
Moderate	38	39	47
Severe	11	15	10
Extreme severe	9	4	2
EQ-VAS (mm, mean ± SD)	41 ± 25	42 ± 22	40 ± 25
Adverse Events (mean ± SD/patient)	5 ± 4	8 ± 6**,††	6 ± 3
Due to pain			
Emergency visit (%)	18	50**,†	37
Hospital admission (%)	6	24**	16
Change in drug (%)	21	52**,††	36
Due to other causes			
Emergency visit (%)	14	13	12
Hospital admission (%)	7	8	6
Change in drug (%)	9	14	13
Collected by physician			
Suspected ADRs notified (total)	0	169**,††	0
Polypharmacy on pain therapy (%)	34	65**	58
Morphine equivalent daily dose (MEDD) (mg, mean ± SD)	106 ± 99	139 ± 130**	118 ± 90

*Case vs control patients $P < 0.05$; **$P < 0.01$
†Case vs case follow-up patients $P < 0.05$; ††$P < 0.01$.

oxycodone (n = 73). Tapentadol reached a total of 68 potential DDI followed by gabapentin (n = 57).

3.4.2 | Drug associated to suspected ADRs

From the 168 suspected ADRs found in this study, 149 were related to pharmacological pain therapy and 19 to other drugs not related to pain that were excluded from the analysis shown in Table 4.

Opioid prescription at the Pain Unit was: 25% fentanyl, 16% oxycodone/naloxone, 13% oxycodone, 7% tapentadol, 7% morphine, 6% buprenorphine and 2% hydromorphone. Most of the patients took more than one opioid (41% took two opioids and 31% three). Eighty-nine per cent of the case patients received concomitant prescriptions together with opioids: 30% simple analgesics, 26% tramadol, 63% antiepileptics (26% two antiepileptics), 37% anxiolytics (21% two anxiolytics) and 36% antidepressants.

Analysing suspected ADRs by frequency in the SPC of the suspected drug, 18% were very common (≥1/10), 36% common (≥1/100 to <1/10), 21% uncommon (≥1/1.000 to <1/100), 4% rare (≥1/10.000 to <1/1.000), 12% of unknown frequency and 9% did not appear at the SPC of the suspected drug (Table 4). The frequency of suspected uncommon, rare and of unknown frequency ADRs in our study was higher than frequency estimated in the SPC of the drugs.

TABLE 2 Characteristics of suspected ADRs notified compared with Spanish Pharmacovigilance System data

	Spain[a]	Pain unit of general hospital of Alicante								
			Appearance[b] (%)		Naranjo causality[c] (%)		Severity (%)	AT[c] (%)	OC[c] (%)	
System organ class	Suspected ADRs (%)		New	DDE	Possible	Probable	Yes	DW	FR	Suspected ADRs No in SPC of suspected drugs
Nervous system	24	26	25	35	14	13	34	23	24	1 Jacobsen movement, pregabalin
Psychiatric	11	16	16	27	13	4	45	15	18	1 Nightmares, morphine
Gastrointestinal	28	12	17	4	10	5	30	15	14	1 Caries, fentanyl
General	10	12	9	15	8	4	60	11	11	1 Hyponatremia, pregabalin
Skin	11	11	15	8	10	2	26	10	11	1 Alopecia, oxycodone
Reproductive system	<1	8	2	4	2	1	23	3	3	1 Erectile dysfunction, tramadol 1 Anorgasmia, oxycodone 1 Menorragia, Tapentadol
Respiratory, thoracic	3	3	5	0	2	1	80	4	4	1 Laryngeal stridor, tapentadol
Cardiac	1	2	1	8	0	2	100	2	2	1 Syncope, lacosamide
Musculoskeletal	2	2	1	0	1	0	75	1	1	1 Muscular cramp, tramadol
Hepatobiliary	<1	2	2	0	1	1	100	1	1	2 Bilirrubin increase, tapentadol
Vascular	2	2	2	0	0	1	100	1	1	-
Immune system	<1	1	1	0	0	1	100	1	0	-
Renal and urinary	1	1	1	0	1	0	50	1	1	-
Haematologic	<1	1	0	0	1	0	100	1	0	-
Ocular	1	1	1	0	0	1	100	1	1	-
Total			48	15	64	36	41	90	93	13

[a]National data from Spanish Pharmacovigilance System.
[b]Cause appearance: new drug added to prescription [New] and dose dependent effect [DDE].
[c]Naranjo causality, action taken drug withdrawal (AT/DW) and outcome fully recovered (OC/FR), data of n = 135 patients due to lack of information regarding the causality assessment.

TABLE 3 Number of combinations of opioids and concomitant drugs in patients with suspected ADRs notified

	Opioids							
	Tramadol	Tapentadol	Oxycodone	Fentanyl	Morphine	Buprenorphine	Hydromorphone	Total
Concomitant drugs								
Pregabalin	26	17	29	14	2	3	5	96
Duloxetine	12	10	15	8	4	3	1	53
Lacosamide	4	6	9	6	-	1	-	26
Gabapentin	18	17	10	4	3	2	3	57
Levetiracetam	1	-	-	-	-	-	-	1
Oxcarbazepine	-	-	-	-	1	-	-	1
Sulpiride	1	1	-	-	-	-	-	2
Diazepam	8	10	6	2	-	-	-	26
Zolpidem	4	3	1	1	-	-	-	9
Baclofen	13	4	3	3	1	-	-	24
Total	87	68	73	38	11	9	9	295

Suspected ADRs associated to analgesics, including opioids, represented the most frequent (71%). The drug most frequently associated with suspected ADRs was tapentadol (20%). A total of 20% of suspected ADRs were attributed to antiepileptics. Suspected ADRs with "probable" score at Naranjo algorithm (36%, n = 49) are marked in bold at Table 4.

TABLE 4 Prescribed analgesics and concomitant drugs implicated in suspected ADRs

Group (ATC code)	Suspected drug (% Prescription)	MEDD[a] (mg/d)	Suspected ADRs (%)		Adverse drug reactions[c,d,e] (frequency at SPC of drug; SOC of MedDRA)	DDI[f]
			Alicante	Spain[b]		
Analgesics						
Analgesic Opioid STEP II N02A-X	Tramadol (9%)	79	6	4	C: 1 Sweating[D], 2 Edema[G], 1 **dizziness**[N1], 1 somnolence[N] UC: 1 Pruritus[D] R: 1 Jaw tension[N], 1 **anxiety**[P1] NO SPC: 1 Muscular cramp[M]	
	Tramadol/ Acetaminophen (17%)	89	5	23	VC: 3 Dizziness[N] C: 1 Dry mouth[GT] UC: 2 Asthenia[G] R: 1 Systolic hypertension[V] NO SPC: 1 Erectile dysfunction[R]	
Analgesic Opioid STEP III N02A	Tapentadol (7%)	127	20	7	VC: 3 **Headache**[N2], 3 **somnolence**[N2] C: 5 **Nightmares**[P2], 1 anxiety[P], 1 insomnia[P], 2 dyspepsia[GT], 1 diarrhoea[GT], 1 suffocation[D], 2 pruritus[D], 2 hallucinations[P] UC: 1 **abdominal pain**[GT1], 1 Alteration of perception[N], 1 chest pain[R] UF: 1 myalgia[M], 1 **Memory alteration**[N1] NO SPC: 2 **Elevated bilirubin**[H1],1 menorrhagia[R], 1 laryngeal stridor[RE]	
	Oxycodone/ Naloxone (16%)	115	11	10	C: 2 **Diarrhoea**[GT1], 1 **vomiting**[GT1], 1 **sickness**[GT1], 1 somnolence[N], 1 **dizziness**[N1], 1 asthenia[G], 1 hyperhidrosis[D] UC: 1 Disorientation[P], 1 edema[G], 1 dyspnoea[RE] UF: 2 **Oral ulceration**[GT2], 2 **erectile dysfunction**[R1] NO SPC: 1 Anorgasmia[R], 1 alopecia[D]	+ Tramadol: Dizziness Disorientation
	Fentanyl (25%)	170	11	5	C: 1 Headache[N], 1 mucosa dryness[GT], 1 erythematosus aeruginosus reaction[D], 1 dizziness[N] UC: 1 **Euphoria**[P1], 1 oral ulcerations[GT], 1 **skin rashes**[D1], 2 erectile dysfunction[R], 1 **pruritus**[D1], 1 **hypotension**[V1] UF: 2 Hallucinations[P], 2 **edema**[G1] NO SPC: 1 Dental caries[GT]	
	Buprenorphine (6%)	155	7	8	VC: 1 Dizziness[N], 4 pruritus[D] UC: 1 **Somnolence**[N1], 3 disorientation[P], 1 **stir**[P1] UF: 1 erythematosus aeruginosus reaction[D]	+ Escitalopram: Somnolence
	Morphine (7%)	46	4	2	C: 2 Somnolence[N], 1 dizziness[N] UF: 1 Alteration of dream[P], 1 disorientation[P] NO SPC: 1 nightmares[P]	
	Hydromorphone (2%)	292	4	1	VC: 1 **Sickness**[GT1] C: 2 **Dyspnoea**[RE1], 1 edema[G] UC: 2 **Erectile dysfunction**[R1]	
	Oxycodone (13%)	103	2	1	VC: 1 Sickness[GT] UC: 2 Syncope[N]	
	Fentanyl rapid release	150	1	1	VC: 1 **Headache**[N1]	

(Continues)

The most frequent DDI was observed for antiepileptics with fentanyl, oxycodone, tapentadol and buprenorphine, and were related to cognitive effects.

Suspected ADRs data from this study were similar to notification data in Spain. Differences were found in ADRs attributed to tramadol, which were four times higher in national data. In contrast, suspected ADRs attributed to pregabalin and tapentadol were slightly higher in our study.

4 | DISCUSSION

The AEs recording system analysed in this study could contribute to a better characterisation of pharmacological pain therapy effects, making it possible to perform the appropriate adjustments to improve patient's management and Health System resources use after being implemented. The results indicated that patients' perceptions of AEs and their active participation were relevant to improve

TABLE 4 (Continued)

Group (ATC code)	Suspected drug (% Prescription)	MEDD[a] (mg/d)	Suspected ADRs (%)		Adverse drug reactions[c,d,e] (frequency at SPC of drug; SOC of MedDRA)	DDI[f]
			Alicante	Spain[b]		
Concomitant drugs						
Antiepileptic N03A	Pregabalin	134	12	2	VC: 2 **Somnolence**^{N1}, 4 **dizziness**^{N1}, 1 headache^{N} C: 2 **Disorientation**^{P1}, 1 insomnia^{P}, 1 fall (broken pelvis)^{G} UC: 2 Pruritus^{D}, 1 **asthenia**^{G1} R: 1 Urinary retention^{RN} UF: 1 **bradypsychia**^{N1} NO SPC: 1 **Jacobsen movements**^{N1}, 1 **hyponatremia**^{G1}	+ Oxycodone: Somnolence, disorientation, bradypsychia + Fentanyl: Dizziness
	Lacosamide	353	3	1	VC: 1 Dizziness^{N}, 1 headache^{N} C: 1 Vomiting^{GT}, 1 pruritus^{D} NO SPC: 1 **Syncope**^{C1}	
	Gabapentin	124	3	1	VC: 1 Somnolence^{N}, 1 **dizziness**^{N1} C: 1 Dyspepsia^{GT}, 1 **bilateral blurred vision**^{O1} UF: 1 **Myoclonias**^{N1}	+ Tapentadol: Somnolence + Buprenorphine: Dizziness
	Levetiracetam		1	<1	UF: 1 Leukopenia^{HE}	
	Oxcarbazepine	80	1	0	UF: 1 **Fever**^{G1}	
Psycholeptic Antipsychotic N05A	Sulpiride	103	1	0	UC: 1 **Orofacial tremor**^{N1}	
Psycholeptic Anxiolytic N05B/C	Diazepam	166	1	<1	UF: 1 Downfall^{G}	
	Zolpidem	191	1	<1	C: 2 Somnolence^{N}	+ Fentanyl: Somnolence
Psychoanaleptic Antidepressant N06A	Duloxetine	104	5	<1	C: 2 Stir^{P}, 1 dyspepsia^{GT} UC: 1 Urinary retention^{RN}, 1 **tachycardia**^{C1}, 1 **arterial hypertension**^{V1} R: 1 Phychosis^{P}	+ Fentanyl: Stir
Muscle relaxant (Central action) M03BX	Baclofen		1	0	C: 1 Sickness^{GT}	

[a]Morphine equivalent daily dose (MEDD, mg/d, mean).
[b]National data from Spanish Pharmacovigilance System.
[c]Frequency at summary product characteristics (SPC) of the drug: very common (VC, ≥1/10), common (C, ≥1/100 and <1/10), uncommon (UC, ≥1/1000 and <1/100), rare (R, ≥1/10 000 and <1/1000) and unknown frequency (UF, cannot be estimated from the data obtained).
[d]Superscript of ADRs indicates the System Organ Class to which it belongs: C=Cardiac, D=Dermatological, G=General, GT=Gastrointestinal, HE=Haematologic, H=Hepatobiliary, M=Musculoskeletal, N=Nervous, O=Ocular, P=Psychiatric, RN=Renal, R=Reproductive, RE=Respiratory, V=Vascular.
[e]Suspected ADRs with "probable" causality assessment score at Naranjo algorithm are marked in bold and a superscript indicates the number of ADRs that are "probable".
[f]Drug-drug interactions (DDI). Drug added to the suspected drug and ADRs implicated in DDI.

their therapy and clinical management, and should be an integral part of a pain management strategy. The active participation of patients in reporting AEs allowed increasing the sensitivity to detect ADRs from 1 every 123 AEs, to 1 every 25 in our study. In addition, the recording system was able to define a subgroup of patients (cases) that represented a population with worst pain and therapeutic control, more drug side effects and increased healthcare resources utilisation. The follow-up of these patients showed improved their pain control decreasing pain intensity (VAS 63 ± 27 mm vs67 ± 26 mm), MEDD (118 ± 90 mg/d vs 139 ± 130 mg/d), polypharmacy (58% vs 65%), healthcare resources utilisation pain (emergency visits [37% vs 50%], hospital admissions [16% vs 24%] and drug changes [36% vs 52%]) and AEs per patient (6 ± 3 AEs/Patient vs 8 ± 6 AEs/Patient).

Relief of pain has gained more attention in recent years and efforts are made to consistently evaluate and treat pain.[36] In 2013, chronic pain management in Spain was inadequate, with a large variability in pharmacological combinations used.[37] Like in our study, most patients were elderly women with combined pharmacological therapy for moderate pain.[38] Weak opioids, as tramadol or codeine, are recommended for mild to moderate pain that has not responded to first-line treatments. In our study, a total of 26% used tramadol mainly as rescue medication if pain remained uncontrolled or as concomitant drug to help major opioids titration. In contrast, major

opioids as morphine can be tried in patients who have not responded to weaker opioids. A low initial dose and slow upward titration is recommended, with closely monitor patients for AEs or aberrant behaviour, and revise the treatment plan accordingly. In 2014, the use of opioid analgesics in Spain increased up to 24%, fentanyl being the most prescribed opioid. In our study, fentanyl, and oxycodone were the most prescribed opioids in accordance with Spanish prescription data related to CNCP.[39,40]

Special considerations need to be done in opioid treatment of CNCP due to the scarce evidence in long-term outcomes and possible side effects. It is well known that chronic opioid therapy can lead to a number of adverse consequences related to gastrointestinal, nervous system, endocrine or psychiatric disorders that might outweigh any potential benefit.[41-45] In our study, 41% of the suspected ADRs were severe, mostly related to the nervous system, and they fully recovered in 93% of the cases after drug withdrawal. This indicates that the recording system developed could help to restore patients' health status quicker and without the use of other pharmacological or non-pharmacological interventions when our protocol was applied.

Furthermore, this system detected that patients assume most of the AEs related to their pain therapy. Surprisingly, this study found a 9% (85% females) of new suspected ADRs not included in SPC, opening two new research lines about reproductive adverse events as libido reduction and erectile dysfunction (eight times more in our study) in collaboration to Reproductive and Sexual Health Services.

To identify one ADR, physicians usually dealt with more than 123 AEs.[46] In our system, this ratio was higher, with one suspected ADR for each 25 AEs. In consequence, the frequency of suspected ADRs uncommon, rare and very rare was higher than frequency estimated at the SPC. This recording system combined with the Naranjo algorithm use could improve the physician ability to detect the uncommon, rare, of unknown frequency and new suspected ADRs.

New analgesic agents, tapentadol and oxycodone/naloxone, prescribed in 7% and 16% of the patients, were implicated in up to 20% and 11% of suspected ADRs, respectively. Both new drugs have been commercialised claiming a potential benefit to constipation, a fact that was not confirmed in our study, where constipation had the same prevalence, around 60%, than with the rest of opioids. This difference in constipation frequency for tapentadol and/or oxycodone/naloxone found in our study might be explained because our study was performed in real world patients that were polymedicated with several opioids co-prescribed presenting a high potential DDI[47]. Present data showed that polypharmacy was common,[48] being more frequent in the case group. It is important to note that when discussing "co-prescribing" this does not necessarily mean that the prescriptions are coming from the same physician. Thus, this monitoring system could provide a new tool for physicians to improve patient management through the detection of ADRs and subsequently amelioration of drug prescription through patient follow-up. This system could be a valuable way to collect safety information of drugs after their approval than clinical trials or pharmacoepidemiological studies.[49] This information might be useful for identifying and minimising preventable ADRs, generally enhancing the ability of prescribers to manage opioids in CNCP.[50] Therefore, logically they should form an integral part in determining a pain management strategy.

Our data indicated that patients with ADRs showed significantly higher pain intensity, unplanned acute care visits at the emergency department, hospital admissions and changes in pharmacological pain therapy than patients without ADRs. It is important to ask patients about AEs that they might suffer, also to register in the clinical history and note the ADR that the physician considers associated with the patient's treatment. Then, a follow-up of both, AE and ADRs, should be done by the physician to analyse if a modification in the therapeutic treatment is needed (deprescribing or prescribing a new treatment) and if the AE/ADR is resolved. Usually, physicians focus on achieve therapeutic efficacy, but the same interest should be apply to evaluate and prevent AEs/ADRs, especially the more common and bothering, as we did in our study. With our reporting system, by increasing the detection of AEs, physicians were more aware of possible ADRs associated with pharmacological treatment and follow-up of these patients resulted in a better health status management in these patients. In conclusion, this recording system provided important information to achieve a better control of the pharmacological pain therapy of CNCP patients. Management and follow-up of cases reduced AEs and drug prescriptions, thus, enhancing their health status and reducing costs to healthcare system after being implemented. The results indicated that patient perceptions of AEs are relevant and should be an integral part of a pain management strategy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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