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RESEARCH ARTICLE

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Abuse and misuse of tramadol in patients with non-oncologic pain in a region of Southern Europe

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ABSTRACT

Background: Tramadol can cause dependence even within the recommended dose range. Its use has increased recently, especially in patients with chronic pain, and although a growing body of literature identifies a non-therapeutic use, patterns of misuse of tramadol is so far limited.

Methods: Two-year observational and cross-sectional study (January 2020 - December 2021) was conducted in 75 community pharmacies from Catalonia. To estimate the potential abuse and misuse of tramadol by patients visiting community pharmacy, and to establish the demographic characteristics of the tramadol users, a validated questionnaire based on the Finch criteria was designed. A total of 251 cases were registered.

Results: Data show that women were more involved (56.6%) and the highest proportion was found in the age interval of 46-65 years (42.6%). The combination of tramadol and paracetamol was reported in 54.6% of the cases and 73.7% corresponded to immediate-release tablets. In 93.6% of the cases, the request was preceded by previous use. Conversely, young men showed a higher non-prescription request for tramadol, reporting acute pain ($p < 0.05$). These results indicate that there is non-therapeutic use among patients who visit community pharmacies for information on two profiles.

Conclusion: This study shows that being an aged woman and suffering from chronic pain seems to involve a risk of generating dependence on tramadol. Likewise, a suspicion of recreational use of tramadol by young people has also been identified. There is a need to investigate how to manage chronic pain, given its complexity and take into account the risk of misuse that may come with tramadol. The involvement of characteristics such as gender as well as the pharmaceutical form in the development of tramadol misuse also

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needs to be analysed deeply. It is mandatory to evaluate the criteria for prescribing tramadol and initiatives to improve the knowledge of the health professionals and the population.

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KEYWORDS Tramadol; Prescription drug abuse; Misuse; Community pharmacy; Chronic pain

What is already known on this topic

- Tramadol is a weak opioid considered a preferred therapeutic option over other opioids due to its lower abuse potential.
- The greater worldwide availability and the growth of its use have led to increased abuse and diversion.
- The misuse of tramadol may be due to the need for self-medication because of the chronic pain.

What this study adds

- Data from the Observatory on Drug Abuse (MAO) showed misuse of tramadol in the Catalan population.
- Being an older woman, suffering from chronic pain and prior use of tramadol are factors that boost the development of misuse.
- The use of tramadol in immediate-release tablets and the request without a prescription are associated with younger men.

How this study might affect research, practice and/or policy

- Knowing that some behaviours and the previous use of tramadol may be associated with its misuse, it should be recommended to monitor the treatment.
- Community pharmacists should be active in identifying possible misuse and abuse of tramadol and report it to the doctor.

1. Background

Tramadol produces analgesia by affecting the nociceptive process and boosting the central modulation of pain. It also modulates pain by inhibiting serotonin and norepinephrine reuptake (Miotto et al., 2017; Subedi et al., 2019). It is prescribed to relieve moderate to severe pain management, including neuropathic pain (Bravo et al., 2017). Its effectiveness depends on the polymorphism in a particular cytochrome P450 (CUP) (Perry, 2021; Roussin et al., 2015).

The long-term efficacy and safety of weak opioids have not been established. The available studies have a maximum duration of 3 months. Despite this, tramadol use has increased in our environment in recent years (Government of Catalonia, 2020). Additionally, according to a study, tramadol use was associated with a higher risk of prolonged opioid use in patients with an acute episode of pain compared with other short-acting opioids (Thiels et al.,2019). At the same time, a growing body of literature identifies a non-therapeutic use and the United Nations Office on Drugs and Crime (UNODC) frames the discussion of tramadol very much in terms of the 'other opioid crisis' (UNODC, 2019).

Tramadol is often prescribed in combination with non-opioid analgesics like paracetamol. A fixed-dose combination of tramadol and paracetamol (37.5 and 325 mg, respectively) gives rapid onset and long duration of action, according to Subedi et al. (2019). In Spain, in 2024, the Spanish Agency for Medicines and Medical Devices (AEMPS, 2022) reported that the use of this combination has been increasing progressively in recent years, from a Defined Daily Dose (DDD) of 7.76 in 2017 to 11.73 in 2022. In relation to tramadol, its use has decreased during this period, from 2.9 DDD to 2.57. In Catalonia, data from 2022 outlined lower values, and the DDD of tramadol was 2.77 and tramadol plus paracetamol was 3.91 (Catalan Health Service, 2023).

Moreover, a study that characterized the trend of opioid use in Catalonia from 2007 to 2019 showed that the number of opioid users per 1,000 individuals and opioid dispensations per 1,000 individuals increased from 2013 to the end of the study period. It was mainly due to the use of tramadol (Xie et al., 2022). In addition, there was an age-dependent shift in opioid use: a slight decrease among younger adults, but a dramatic increase among older people, particularly in women (Xie et al., 2022; General Directorate of Addictions, 2020). In the United States and the United Kingdom, the number of prescription opioids and the abuse of these prescribed opioids have increased as well, according to Findikli and Altun (2016).

Tramadol dependence in the analgesic treatment is possible even within the recommended dose range. However, a descriptive, cross-sectional study (Roussin et al., 2015) performed over two months in 2008 in 61 pharmacies showed that misuse of tramadol was noted when doses above the maximum recommended dose (400 mg/d) were reported for more than 10 days. Furthermore, in 2022, Roussin et al. reported that the persistence in its use appears frequently linked to the fear of experiencing withdrawal symptoms or the desire to experience the psychoactive effects. Data from spontaneous reporting systems (Tjäderborn et al., 2009) and addiction to vigilance monitoring (Roussin et al., 2022) indicate an increased high risk for tramadol use and potential dependence. In addition, high-dosing regimens and long-time use of tramadol lead to neural adaptations (Harris et al., 2021;

Senay et al., 2003) and may cause physical dependency (Subedi et al., 2019). Thus, knowing how the medicine was obtained makes it possible to know whether the substance was used under medical supervision or not (Roussin et al., 2015; Tjäderborn et al., 2009).

Moreover, in 2020, Iwanicki et al. (2020), conducted a four-country study in Germany, Italy, Spain and the United Kingdom using data from a multi-indicator analysis in the period 2015–2018 to assess the extent of the misuse among the general population of tramadol. It concluded that tramadol misuse and abuse were infrequent both in absolute number of cases and in comparison to conventional prescription opioids, which is in agreement with the United Nations Office on Drugs and Crime (UNODC, 2022).

The greater worldwide availability of tramadol (Mortier et al., 2020) has led to higher abuse and diversion. However, in accordance with the UNODC, the non-medical use of tramadol remains low in Europe (Layne et al., 2021), despite it accounted for 54% of reported quantities of pharmaceutical opioids seized in the period 2016–2020 (UNODC, 2022).

Overall, epidemiological data suggested that tramadol would be less likely associated with diversion. Despite this, different studies have also concluded that tramadol produces desirable euphoric, stimulant, and relaxing effects that increase its abuse potential (Miotto et al., 2017). For example, the non-medical use of prescription drug (NMURx) national survey showed that besides heroin, in Spain, there was a concomitant abuse of prescription opioids and they were the highest for methadone, tramadol and codeine (Fonseca et al., 2014).

Even so, Middle Eastern and African countries are displaying a growing number of tramadol abusers and a serious public health concern (Miotto et al., 2017; Zabihi et al., 2011). Because of this evidence, in 2017, at the 39th World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) meeting, tramadol was recommended to be the subject of a critical review in a future meeting (WHO, 2018). Currently, it is under national control in several countries, according to Jalali et al. (2017) and on 18 August 2014, the Drug Enforcement Administration (DEA) officially placed tramadol into Schedule IV of the Controlled Substances Act (DEA, 2014).

In Spain, tramadol is a prescription-only medicine, although it is not on the list of controlled substances. For all of this, developing tools that allow the surveillance of non-therapeutic use of tramadol is essential to ensure good pain management and proper medication use.

Additionally, in Spain, community pharmacists: provide basic services to the population such as information on pharmacological treatments for patients, collaborate in the monitoring of the individualized use of medicines

to detect adverse drug reactions (ADRs), or participate in programmes promoted by the Health Administration on quality assurance in pharmaceutical care. One of the advantages of the pharmacy network is that the number of inhabitants per pharmacy is around 2,200 and allows medicines to reach citizens in urban areas and in the most remote villages (General Pharmaceutical Council of Spain, 2025).

In the last times, pharmacy in Spain has evolved towards a patient-focused approach and healthcare activities have been set. One of them is the epidemiological surveillance system – Medicine Abuse Observatory, MAO – set up in Catalonia as part of the sentinel pharmacies scattered through the territory.

The MAO was created in 2017, as a project supported by the Catalonia Pharmacists Council and the Ministry of Health of the Government of Catalonia. It allows us to analyse trends in the abuse and misuse of medicines by the population of Catalonia through community pharmacies (Perelló et al., 2021, 2023).

The collection of data regarding medicine abuse and misuse was performed by a questionnaire-based screening tool which was developed considering the signs and elements that identify a drug-seeking behaviour and that would arise at the community pharmacy. This information became a key source for identifying some initial behavioural patterns regarding the misuse of tramadol in treating non-oncologic pain.

The present study aims to identify trends of tramadol abuse and misuse through the MAO by patients visiting the pharmacy and to know the indicators associated with the phenomenon, such as demographic characteristics of the tramadol users. Additional objectives were to provide knowledge to be able to develop prevention strategies and to validate the usefulness of the OMA for monitoring specific medicines.

2. Methods

2.1. Data source

A two-year observational and cross-sectional study (January 2020 – December 2021) was conducted in community pharmacies to detect suspected cases of non-therapeutic use of tramadol. The approach was performed by the MAO, the epidemiological surveillance system set up in Catalonia in 2017 (Perelló et al., 2021, 2023). To collect data, it was designed a questionnaire-based screening tool which was developed considering the signs and elements that would arise in the community pharmacy. This information became a key source for identifying some behavioural patterns regarding the misuse of tramadol in treating non-oncologic pain.

To make easier the reporting, the Abuse Drug Questionnaire (ADQ) was encompassed through a web-based survey. Data collection software Typeform (Typeform SL, Barcelona, Spain) was embedded into the Barcelona College of Pharmacists' website, the principal online work tool for pharmacists in this area of Spain. This software transformed the ADQ electronic data into an Excel spreadsheet to operate it.

Data were obtained from 75 community pharmacies, which constitute a proportional stratification of the population in Catalonia based on Spain's sentinel model and criteria of representativeness (Jambrina et al., 2022). Training sessions aimed at pharmacists were carried out multiple times and focused on three parts: the theoretical framework (concepts, trends and world data); the basis of the method (criteria to identify behaviours related to drug-seeking) and operational procedures (dispensing service, patient interview, identifying signs and online form comprehension).

2.2. Questionnaire development

A multi-choice questionnaire was designed to evaluate the demographic characteristics of tramadol users and their health problems. It was based on Finch's criteria (Finch, 1993) which allows the identification of signs and behaviours that clearly indicate that drug abuse exists. These elements are: (1) a pattern of calling for refills after hours and/or repeatedly needing early refills, (2) prescriptions from multiple doctors, (3) frequent visits to A&E, (4) strong preference and knowledge for a particular medicinal product, and (5) incongruence between severity of the complaint and the physical presentation. Based on this theoretical framework, the patients who requested tramadol and showed at least two of these signs were asked about their previous use, the need to increase the dose, and whether they had felt discomfort when they tried to stop the treatment. Finally, the case was registered.

The questionnaire consisted of an anonymous multiple-choice test containing 18 closed and 1 open-ended question categorised into four parts (Table 1). Questions 1 and 2 required pharmacist identification; in questions 3–8, the health problem and prescription involved were included. Patient demographic information was enquired in questions 9–12, and questions 13–18 were intended to further characterise the previous use of tramadol. In this sense, it was requested information such as the need to increase the dose or frequency of use without consulting the doctor, the need to go to the doctor more often to get the prescription, or the use of the medicinal product as a treatment for symptoms other than pain. Finally, an open-ended question was included (Table 1).

Patient information was obtained anonymously during the interview; neither verbal nor written consent was needed.

Table 1. Multiple-choice questionnaire to evaluate the potential tramadol abuse and misuse.

Questionnaire to evaluate the potential tramadol abuse and misuse	Question Number	Question text	Answer
Pharmacist identification	1	Pharmacy ID	Number
	2	Pharmacist	Name
Health problem and prescription form/ involved	3	Prescription?	Yes/No
	4	Right prescription?	Yes/No
	5	Health problem	Chronic pain/Acute pain/Other
	6	Medicine requested	Tramadol/Tramadol + paracetamol/Tramadol + dexketoprophen
	7	Dosage regimen	Tramadol: 50 , 100 mg/6 h, 50 , 100 mg/8 h, on-demand, N/A Tramadol + paracetamol: 37,5/ 325 mg/24 h, 75/650 mg/24 h, 300/2600 mg/24 h, on-demand, N/A Tramadol + dexketoprophen: 75/25 mg/24 h, 225/75 mg/24 h, on-demand, N/A
	8	Pharmaceutical form	Immediate release tablet/Slow release tablet/Oral drops/ Injectable
Demographic information	9	Who takes the drug	Me/Family/Patient
	10	Patient age	<25/25-35/36-45/46-65/>65
	11	Patient origin	Native/Not native
	12	Patient sex	Male/Female
Previous use and patient management	13	Previous use	Yes/No
	14	Need to increase the dose or frequency of use without consulting the doctor	Yes/No
	15	Need to go to the doctor more often to get the prescription	Yes/No
	16	Use for symptoms other than pain	Yes/No
	17	Discomfort when stop the treatment	Yes/No
	18	Symptoms	Anxiety/Muscle pain/Fever/ Sweating/Insomnia
Observations	19	Observations	

2.3. Statistical analysis

The categorical variables were analysed as percentages. The X^2 test was used with the aim to compare the obtained proportions, and a *p*-value <0.05 was considered statistically significant (SPSS software, version 18, SPSS Inc., Chicago, IL, USA).

In order to find similarities in the individual profiles simultaneously a multiple correspondence analysis (MCA) was performed by R version 4.1.2 (R Foundation, Austria) (https://www.R-project.org/) using the packages FactoMineR (https://

cran.r-project.org/web/packages/FactoMineR/index.html) for the analysis and factoextra for the visualisation (https://cran.r-project.org/web/packages/factoextra/index.html). When two categories present high coordinates and are close in space it can be considered directly associated between them. A variable well represented by two dimensions is that with a cos2 value for one variable category close to one. This MCA analysis allows us to find similarities between participants in the basis of their characteristics and behaviour and establish the degree of association between different variables.

3. Results

3.1. Medicine and patient profile

3.1.1. Tramadol user demographic characteristics

During the study period, 251 possible cases of abuse and misuse of tramadol were identified and reported. The patient distribution profile was not equally distributed (Figure 1). Regarding sex, they were mostly women (56.6%, Figure 1(A)). Another important variable was whether the cases belonged to native (residents or a person known by the pharmacist) or non-native patients in the pharmacy. Overall, an approximately 75/25 proportion was found for native/non-native patients (Figure 1(B)). When the age of the patient was considered, the highest proportion was found in the age interval of 46–65 years (42.6%), followed by >65 years (37.5%), 36–45 years (14.3%) and 25–35 years (4.8%), being the lowest proportion the youngest interval of age considered (<25 years, 0.8%, Figure 1(C)). The most involved health problem was chronic pain (64.5%) followed by acute pain (29.1%). In 6.4% of the cases, pharmacists did not report it (Figure 1(D)).

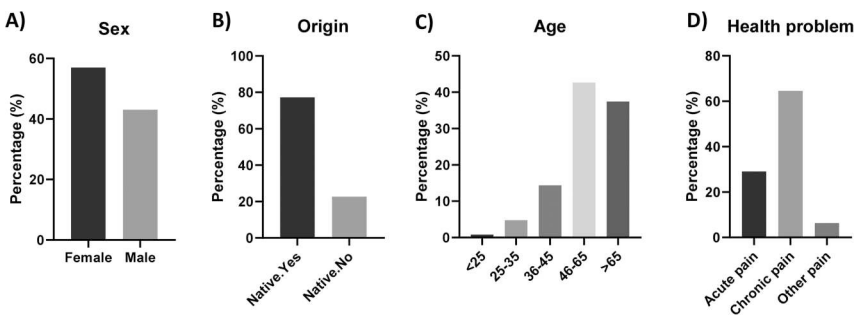

Figure 1. Profile of the tramadol consumer. Distribution of participants by (A) sex, (B) origin, (C) age and (D) health problem. Values are expressed as percentages for each condition in a total of 251 participants.

3.1.2. Pharmaceutical form and dosage regimen

The pharmaceutical form and characteristics of use were also analysed (Figure 2). Regarding the substance, the combination of tramadol and paracetamol was reported in 54.6% of the cases, tramadol alone in 40.6%, and only in 4.8% of cases it involved paracetamol plus dexketoprofen (Figure 2(A)). Referring to the pharmaceutical form, 73.7% of the registers corresponded to immediate-release tablets or capsules, and 22.7% to slow-release tablets or capsules (Figure 2(B)). Concerning the dosage regimen, in 76.5% of the cases it was in agreement with those recommended in the summary of the product characteristics (SmPC). On the other hand, in 13.1% of the cases, the dose was on demand; in the rest, the consumer did not know or corresponded to a different dosage regimen (Figure 2(C)).

3.1.3. Medicine request

Considering all the cases, the people asking for the medicine were the consumers themselves, and only in a low percentage of cases (approximately 25%) it was done by others (Figure 2(D)). In addition, the request was

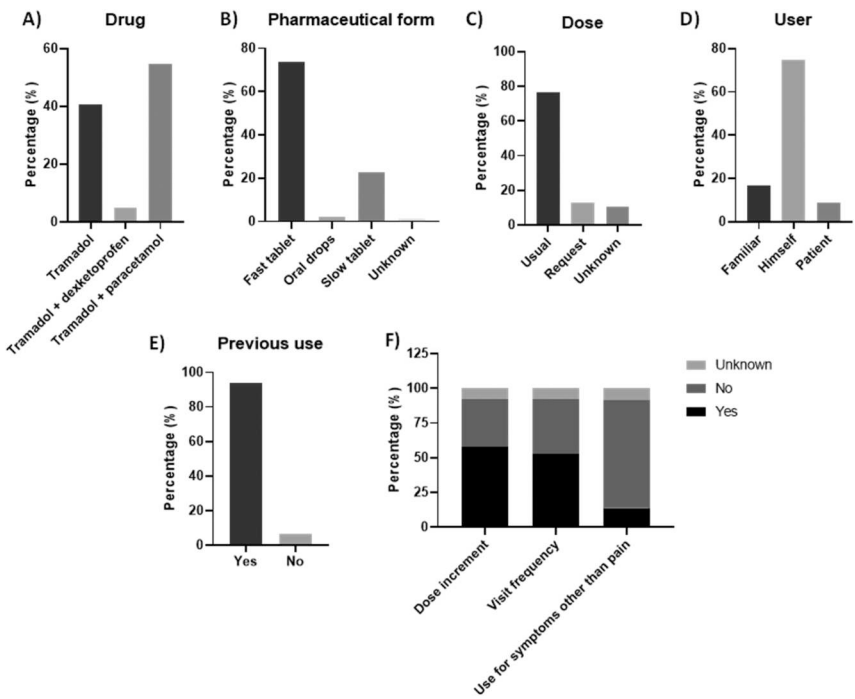

Figure 2. Pharmaceutical aspects of tramadol requests. Distribution of participants by (A) type of medicinal product, (B) pharmaceutical form, (C) dosage regimen, (D) type of user, (E) history of previous use, and (F) other aspects related to consumption. Values are expressed as percentages for each condition in a total of 251 participants.

performed mainly (93.6%) following a previous use (Figure 2(E)). Other aspects also analysed were the need to increase the dose without seeing the doctor, in 57.8% of the cases, and the need to go to the doctor more often to get the medicine, in 52.6% of cases. Moreover, only 13.5% of consumers claimed to have used tramadol to treat symptoms other than pain (Figure 2(F)).

3.1.4. Adverse reactions

Tramadol consumption could be associated with discomfort or adverse reactions when stopping the treatment (Figure 3). Specifically, 45.8% of patients reported discomfort experiences when they stopped the treatment (Figure 3(A)). In most cases, the symptoms declared were muscle pain (67.8%) and anxiety (53.9%) (Figure 3(B)).

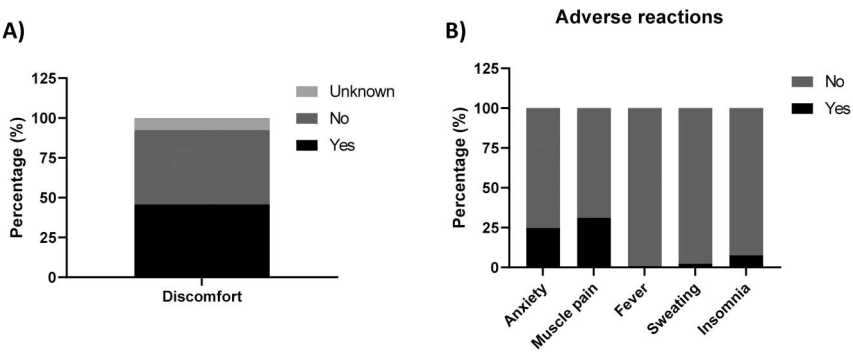

Figure 3. Discomfort and adverse reactions derived from tramadol consumption. Proportion of patients describing discomfort (A) and with specific adverse reactions (B). Values are expressed as percentages for each condition in a total of 251 participants.

3.2. Multiple correspondence analysis (MCA)

All validated registers of the present study allowed us to obtain information about the patient profile, the behaviour, the characteristics of the medicine and pharmacovigilance-related aspects. First, the participant's features were multi-parametrically approached to analyse similar profiles between the individuals and evaluate associations between variable categories by multiple correspondence analysis (MCA) (Figure 4). The model provided a variance of 11.1% for Dim-1 and 9.3% for Dim-2 (Figure 4(A)).

The contribution of each variable in Dim1 and Dim2 was analysed (Supplemental Material Fig. S1), allowing us to observe that 'Prescription' was the most correlated with Dim-1 and 'Discomfort when stopping the treatment' was with Dim-2 (Figure 4(B)). This finding was in line with the visualisation of the results in Figure 4C, in which it can be observed that some

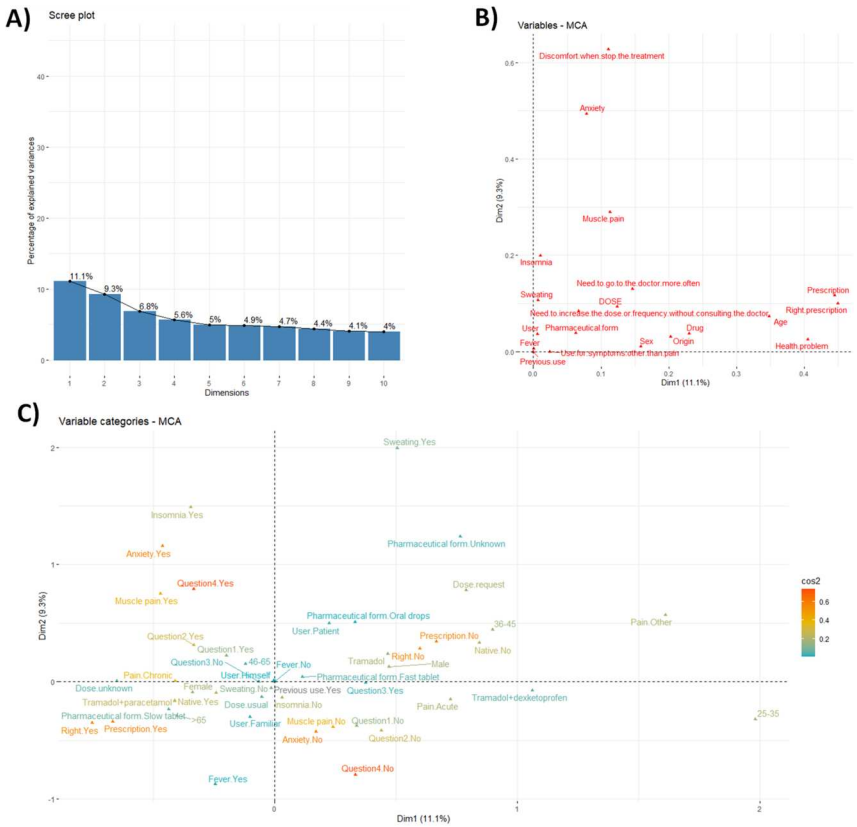

Figure 4. Multiparametric analysis of all variables analysed regarding tramadol notifications. Percentage of explained variances for each dimension in the model (A). Distribution of the variables in the first two dimensions (B) and correlation plot of them (C). Values are derived from the dataset of a total of 251 participants.

REQUEST categories had the highest COS2 value, such as 'Prescription No'. Moreover, it can also be seen that 'Anxiety' and 'Discomfort when stopping the treatment' were very close and appeared on the negative y-axis (Dim-2) in the MCA. Thus, the population characteristics based on these three main aspects were studied in depth: type of prescription (Table 2), health problem (Supplemental Material Table S1), and discomfort when stopping the treatment (Supplemental Material Table S2).

3.3. Medicine request and type of prescription used

The patient profiles were analysed based on whether the medicine was requested with a prescription or not (Table 2). The patient distribution profile was not equally distributed among sexes and ages. Regarding the sex, they were mostly men when the medicine was requested without a

Table 2. Analysis of the patient and medicinal product profiles based on whether or not the medicinal product was requested with a prescription. Values are expressed as percentages for each condition in a total of 251 participants.

Variable	Item	No prescription, $N = 132$	Prescription, $N = 119$
Sex	Female	64 (48.5%)*	78 (65.5%)
	Male	68 (51.5%)*	41 (34.5%)
Origin	Yes	91 (69%)*	103 (86.6%)
	No	41 (31%)*	16 (13.4%)
Age	<25	2 (1.5%)	—
	25–35	10 (7.6%)*	2 (1.7%)
	36–45	26 (19.7%)*	10 (8.4%)
	46–65	55 (41.7%)	52 (43.7%)
	>65	39 (29.5%)*	55 (46.2%)
Health problem	Chronic pain	66 (50%)*	96 (80.7%)
	Acute pain	52 (39.4%)*	21 (17.6%)
	Other	14 (10.6%)*	2 (1.7%)
Medicine requested	Tramadol	64 (48.5%)*	38 (31.9%)
	Tramadol + paracetamol	59 (44.7%)*	78 (65.5%)
	Tramadol + dexketoprophen	9 (6.8%)	3 (2.5%)
Dosage regimen	Usual	102 (77.3%)*	107 (89.9%)
	On demand	23 (17.4%)*	10 (8.4%)
	N/A	7 (5.3%)*	2 (1.7%)
Pharmaceutical form	Immediate release tablet	107 (81.1%)*	77 (64.7%)
	Slow release tablet	19 (14.4%)*	38 (31.9%)
	Oral drops	4 (3%)	2 (1.7%)
	N/A	2 (1,5%)	2 (1.7%)
Who takes the drug	Me	95 (72%)	91 (76.5%)
	Family	22 (16.7%)	20 (16.8%)
	Patient	14 (10.6%)	8 (6.7%)
Previous use	Yes	119 (90.2%)*	116 (97.5%)
	No	13 (9.8%)*	3 (2.5%)
Need to increase the dose or frequency of use without consulting the doctor	Yes	73 (55.3%)	72 (60.5%)
	No	43 (32.6%)	44 (37%)
	N/A	16 (12.1%)	3 (2.5%)
Need to go to the doctor more often to get the prescription	Yes	63 (47.7%)	69 (58%)
	No	53 (40.2%)	47 (39.5%)
	N/A	16 (12.1%)	3 (2.5%)
Use for symptoms other than pain	Yes	16 (12.1%)	18 (15.1%)
	No	99 (75%)	97 (81.5%)
	N/A	17 (12.9%)	4 (3.4%)
Discomfort when stop the treatment	Yes	58 (43.9%)	57 (47.9%)
	No	59 (44.7%)	58 (48.7%)
	NS	15 (11.4%)	4 (3.4%)
Symptoms	Anxiety	34 (58.6%)	28 (49.1%)
	Muscle pain	38 (65.5%)	40 (70.2%)
	Insomnia	9 (15.5%)	10 (17.5%)
	Sweating	3 (5.2%)	3 (5.3%)

*$p < 0.05$.

prescription, and women when the request was with a prescription ($p < 0.05$). When the age was considered, the highest proportion was found in the age interval of 46–65 years (43.7% and 41.7%), followed by > 65 years (46.2% and 29.5%, $p < 0.05$), 36–45 years (8.4% and 19.7%, $p < 0.05$) and 25–35 years

(1.7% and 7.6%, $p < 0.05$). The lowest proportion was found in the youngest interval of age considered (< 25 years).

Another important variable was whether the cases belonged to native or non-native patients. The proportion of registers from non-natives is the highest in those who request the medicine without a prescription (31% *vs* 13.4%, $p < 0.05$). Regarding the health problem, in both cases, chronic pain was mostly involved, with the highest proportion in medicine requests with prescription (80.7% *vs* 50%, $p < 0.05$). The most requested medicine was tramadol for requests without a prescription, and tramadol with paracetamol for prescription requests (48.5% *vs* 31.9% and 44.7% *vs* 65.5%, $p < 0.05$).

Concerning the pharmaceutical form, those of immediate-release were most reported in requests without a prescription (81.1% *vs* 64.7%, $p < 0.05$), and no difference was observed regarding dosage regimen, although on-demand was also more frequent (17.4% *vs* 8.4%). In most cases (approximately 75% in both situations), the patients themselves were who made the request and a very high percentage of them claimed that they had previously consumed the medicine (90.2% in requests without a prescription versus 97% in prescription requests, $p < 0.05$). In fact, in 55-60% of cases, they had to increase the dose and frequency of taking the medicine without a doctor's advice. About 50% of users often went to the doctor to get more prescriptions, especially those who requested the medicine with a prescription, although no significant difference was observed. Regarding the use of tramadol for symptoms other than pain, in most cases (75-80%), they expressed that they did ask for tramadol for other purposes. However, approximately 50% said that they suffered discomfort when they stopped treatment. The most reported symptoms were muscle pain and anxiety.

3.4. Health problems and discomfort

The patient and medicine profile analysis was also performed based on whether the health problem was chronic or acute pain (Supplemental Material Table S1). Patient distribution profile was similar regarding sex and origin, but different related to age. A higher proportion of older people reported chronic pain (> 65 years, 43.8% *vs* 30.1%, $p < 0.05$). A significant difference was observed concerning the prescription, with 59.3% of patients with chronic pain instead of 28.8% of those who reported acute pain ($p < 0.05$). Besides, the most requested medicine in patients with chronic pain was tramadol plus paracetamol (65.4% *vs* 35.6%, $p < 0.05$), but there was no difference in the dosage regimen. Other variables were considered, such as whether the patient referred a previous use, a need to increase the dose/frequency of use without consulting the doctor, and the need to go to the doctor more often to get the prescription. The highest proportion of cases corresponded to those subgroups with chronic pain ($p < 0.05$). Regarding the discomfort when stopping the treatment, the

patients with chronic pain showed a high proportion of symptoms such as anxiety, muscle pain, insomnia or sweating ($p < 0.05$).

On the other hand, the discomfort described when the treatment was stopped led to the distribution of tramadol users in those with or without displaying this symptom (Supplemental Material Table S2). Considering this classification, there was no difference between the patient distribution profile regarding sex and the origin. However, a higher proportion was found in the age interval of 46–65 years to have symptoms.

With respect to the other variables, a differential pattern was observed for those patients who had stated that they needed to increase the dose/frequency of use without consulting the doctor, and/or need to go to the doctor more often to get the prescription ($p < 0.05$).

4. Discussion

The present study highlights that there are two profiles of users associated with the non-therapeutic use of tramadol. On the one hand, there is a pattern that corresponds to young men who request immediate-release tablets of tramadol without a prescription and who report acute pain. This situation could indicate recreational purposes, as the doses were higher, without a medical dosage regimen and more attractive for psychoactive effects, in line with other studies (Roussin et al., 2022). In fact, recent evidence suggests that the abuse liability of tramadol may have been previously underestimated concerning oral administration, especially in some Middle East and African countries, where diversion is a predominant source of the medicine (WHO, 2018).

On the other hand, this study especially shows that tramadol requests with a prescription supported its use for the treatment of chronic pain in approximately 80% and are associated with women of older ages in 65.5% of cases. This result could strengthen data from some published evidence that describes a direct association between tramadol dependence with older women (Roussin et al., 2022; Tjäderborn et al., 2009). Additionally, in 2016, Findikli and Altun, reported that many adults over 65 suffer from at least one painful condition commonly associated with increasing age. In Catalonia, the results of the survey on the state of health of the population in 2021 showed that emotional distress increases with age, which occurs in 34.7% of people aged 75 and over, especially in women (Schiaffino & Medina, 2022). Also, the study shows that previous use of tramadol may be related to the self-reward or feeling of well-being that it produces. These data are in line with some published results (Findikli & Altun, 2016; Roussin et al., 2022). Indeed, the WHO review on tramadol, post-marketing epidemiologic abuse-related data and that from the adverse events reporting system (AERS) demonstrate an addiction liability of tramadol (drug craving, dosage escalation, consumption despite adverse effects, and visiting multiple doctors) (WHO, 2018).

Moreover, the present data shows that anxiety and muscle pain were the most reported symptoms claimed when patients stopped treatment. These side effects, as well as others like tremors, sleep disorders or impaired well-being, may occur without apparent dependence, according to Roussin et al. (2022) and Tjäderborn et al. (2009). Information from the Pharmacovigilance Center of Catalonia (Directorate-General for Healthcare Planning and Regulation, Ministry of Health, Government of Catalonia, 2023) reported that 54.8% of the reports involving tramadol described neurological and psychiatric adverse reactions. The most frequently found were dizziness, headache, anxiety, tremors, and withdrawal syndrome. In addition, the Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS), described on 31 December 2022 that 38.5% of notifications corresponded to suspected cases of drug dependence, 18.5% to overdose and 7.4% to drug abuse.

It is essential to consider the influence of bio-psychosocial factors on the experience and perception of chronic pain since it can explain why long-term treatment with opioids for chronic pain does not offer the expected results (Findikli & Altun, 2016). The high prescription rates of immediate-release presentations containing tramadol and paracetamol by the National Health System are linked to the high percentage of patients who requested the medicine with a prescription meeting the criterion for suspected misuse. In line with this, according to Salazar et al. (2023), there is a correlation between tramadol prescription and tramadol-related mortality.

Also, immediate-release (IR) opioids that relieve pain for a shorter duration are preferred over extended-release (ER) ones, which relieve pain for a longer time, although ER opioids are safer and offer much more consistent results (Nalamachu & Shah, 2022; Nicholson, 2009). In that sense, it should be developed awareness initiatives like the one taken in the United States called the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) (FDA, 2018). This last one, includes measures such as a safety labelling change and a new boxed warning about the risks of misuse and abuse. It also helps better communication of the serious risks of opioid pain medications to patients and health care professionals (FDA, 2023).

Starting treatment with an opioid medicine in patients with non-oncologic chronic pain (NOCP) should be done after determining the cause and type of pain, as well as the intensity and functional limitations they cause in the patient (Subedi et al., 2019). Tramadol is established as a second-level option on the WHO analgesic scale and it should be considered when paracetamol or non-steroid anti-inflammatory drugs (NSAIDs) are contraindicated due to patient characteristics (Agency for Health Quality and Assessment of Catalonia, 2018). Likewise, it should be considered that patients who receive a tramadol prescription for the first time could develop an increase in opioid use in the following years (Birke et al., 2019). This, suggests that the first opioid prescription

may be the first step towards long-term opioid use, which is associated between each refill and week of opioid use with large increases (Harris et al., 2021). Thus, it would be necessary to identify the potential risk of abuse or dependence on strong opioids in the patient (Miotto et al., 2017).

For all that, the increasing use of tramadol is worrying given concerns regarding the increase in problematic opioid use and considering that the evidence supporting the use of weak opioids in DCNO is scarce (Agency for Health Quality and Assessment of Catalonia, 2018).

The limitations of this study are related to the lack of a clear correlation between the rate of prescription and the percentage of patients who misuse or abuse tramadol. However, the statistical analysis of the cases provides knowledge about the trends of this phenomenon and points to the type of patient who may be involved since it allows defined profiles. Also, the subjectivity of the pharmacist can be a limitation, but this is solved by carrying out different training sessions throughout the study period to settle questions and possible decline of skills.

5. Conclusion

Although epidemiological data do not show a significant problem with tramadol diversion, different studies demonstrate the existence of misuse or abuse of the drug due to its euphoric, stimulating, and relaxing effects. In this approach, it was found that being an aged woman and suffering from chronic pain seems to involve a risk of generating dependence on tramadol. So, higher levels of pain and poor control may be associated with abuse or misuse of tramadol. On the other hand, situations such as the need to go to the doctor often to demand more prescriptions or the increase in the dose without consulting him enable a suspicion that there is probably a problem with the use of tramadol by the patient. So, there is a need to evaluate the criteria for prescribing and monitoring tramadol treatment as well as initiatives to improve population knowledge about the risks of misuse of tramadol. Pharmacists must be aware of this phenomenon and take precautions when dispensing it. Additionally, the suspicion of recreational use of tramadol by young people, who try to get it without a prescription arguing acute pain, makes it mandatory to follow up with this population to avoid health risks such as those produced by polysubstance use.

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Data availability statement

The datasets that support the findings of this study are available from the first author (M.P.) upon reasonable written request.

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