

## Risk Indicators in Fentanyl Use: Opportunities to Improve Outcomes with a Personal Pharmaceutical Care Approach in Community Pharmacies

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### Abstract

Fentanyl is a commonly prescribed opioid analgesic dispensed in community pharmacies for the treatment of severe chronic pain or pain of oncological etiology. The effectiveness and safety of its use depend to a large extent on the knowledge about this molecule and its conditions of use. Fentanyl is capable of generating withdrawal symptoms and dependence that can lead, in situations of abuse and consumption of combined use, with other legal and/or illegal psychoactive substances. Fentanyl's defined daily dose (DDD, the average maintenance dose assumed per day for a drug used for its main indication in adults), is 0.6 mg for sublingual tablets, 0.6 mg for nasal and 1.2 mg for transdermal route (WHO Collaborating Center for Drug Statistics Methodology).

This 2-year retrospective observational study (2018 - 2019) aims to assess the risk indicators of fentanyl use so that those indicators can be used as part of a personalized pharmaceutical care program in a community pharmacy, in order to improve outcomes and to promote its safe use based on the profile of each patient.

Forty-seven patients (62% women, 33% men) received fentanyl dispensation, 45% were older than 70 and 24% were between 61 - 70 years old. 63% of total dispensations were administered in the form of "patches", 31% by sublingual tablets, and 6% by nasal spray. Some patients exceeded the DDD when fentanyl was prescribed combining more than one dosage form. Prescribed daily doses (PDD) of 1.8 mg and 2.4 mg were found in 6% and 2% of patients, respectively. Regarding interactions with other drugs, the concomitant use of fentanyl with benzodiazepines (BZP) and selective serotonin reuptake inhibitors (SSRIs) stands out, with significant differences by gender being observed. While 29% and 20% of female Fentanyl users use BZP and SSRIs, only 7% and 5% of male fentanyl users use BZP and SSRIs. Both sexes visited the community pharmacy far less often than recommended (once per month during the course of treatment), with 82% of male users going just 1 - 5 times in a period of 24 months, and only 5% of female users complying with the recommended number of visits (considered to be 20 times or more in a 24-month period). The community pharmacy has the opportunity to contribute to the effective and safe use of fentanyl with personalized Pharmaceutical Care. Prescriptions with dosages of more than 1.2 mg/day and/or with a combination of more than one pharmaceutical form of fentanyl, the simultaneous use of BZP and SSRIs and a low number of visits to the pharmacy (less than 1 visit/month) will be considered indicators of an opportunity to provide pharmacotherapeutic follow-up.

**Keywords:** Fentanyl; Community Pharmacy; Dispensing; Pharmaceutical Care; Drug Related Problems (DRP); Risk

## Introduction

Opioid drugs are characterized by having a selective affinity for central and peripheral opioid receptors ( $\kappa$ ,  $\mu$ , delta receptors), inhibiting the transmission of nociceptive entry and the perception of pain. In addition to their analgesic action, they generate different withdrawal and dependence symptoms that can lead to abuse and combined consumption of other legal and/or illegal psychoactive substances. Chronic use of opioids in non-oncological indications is associated with a significantly higher risk of mortality, including that of overdose, so the evaluation of the risk vs. benefit of their prescription and use must be well calibrated [1].

According to the ECOM database (Specialties for the Consumption of Medicines of the Spanish Ministry of Health and Consumption) [2,3], the consumption of opioids in Spain has increased considerably, rising from 0.03 to 4.4 DDD/1000 population per day since 1992. In Australia, fentanyl prescriptions also increased significantly between 2000 - 2011 [4]. In the United Kingdom [5] the main indication for major opioids is the treatment of neuropathic pain and, as in other countries, there is a generalized diversion to abuse, misuse and mortality related to the use of major opioids. In the treatment of musculoskeletal pain, it is suspected that 25% of patients excessively use opioid analgesics with respect to the national guidelines established by the UK [6]. In Israel, where the consumption of major opioids increased by around 68% between 2009 and 2016 [7].

Tapentadol, fentanyl, oxycodone, oxycodone - naloxone and morphine stand out among the opioid drugs due to their high consumption. Although oral morphine remains the first choice among the major opioids, it is worth noting the increase in the consumption of fentanyl. In those patients who do not achieve sufficient analgesia with morphine, the use of alternative opioids, such as fentanyl, is opted for due to its high potency and its administration in transdermal forms [8]. Thus, transdermal fentanyl is the opioid of first choice in Germany [9]. However, there is concern about its special affinity of fentanyl for receptors in essential brain structures for the control of emotions, pain and, especially, reward, causing stereotypical effects of euphoria and relaxation highly associated with drug addiction [10].

The extension of the use of fentanyl from cancer pain to the treatment of chronic pain of different etiology has led to the intensification of the control of opioid prescriptions and dispensations by the different drug observatories [11]. In Canada, the province of Alberta, due to its high consumption rates, ranks as one of the world regions with the most cases of fentanyl overdose and a worryingly high mortality, which has led to the activation of strict control systems in prescription and dispensing. The Canadian government itself has recognized the existence of "The Fentanyl Epidemic" due to the notable diversion of users to the illegal consumption of this molecule [12]. The incorrect prescription of fentanyl in the context of the treatment of unstable pain can increase the risk of toxicity and the insecurity of its use, especially depending on the pharmaceutical form [13]. The incorrect use of fentanyl patches carries a risk of mortality due to misuse [14]. Thus, deaths have been described due to the simultaneous application of more than 7 patches of 25  $\mu\text{g}/\text{h}$  with other drugs with potentially dangerous interactions. These risks associated with the pharmaceutical forms of patches are not only described for the adult population, but also in the pediatric population [15].

Likewise, the use of substances such as fentanyl in elderly people has been associated with cognitive disorders, circulatory problems, respiratory involvement, diabetes, hepatitis and liver cirrhosis [16]. In Australia, the prescriptions of fentanyl in patients over 80 years of age have been associated with an increase in mortality [4]. In Canada [17] 63% of opioid users are older than 65, which highlights the risk of DRPs (drug related problems) or situations that cause or may cause the appearance of negative medicine outcomes (NMOs) or patient health results not suited to the objectives of pharmacotherapy and associated or potentially associated with drug use. DRPs are elements of the process that entail an increased user risk of suffering an NMO [18].

There are reliable reviews [19] on the misuse of fentanyl that conclude that this drug may be contributing greatly to the increase in deaths related to major opioids. The misuse of substances such as fentanyl undoubtedly has a social impact since they lead to the overuse

of health resources, such as hospital emergency services. Associated health spending is growing, spending that is beginning to be comparable to that of chronic diseases such as diabetes [20].

Therefore, there is an important need to set out strategies and protocols that promote and guarantee their safe use and minimize the above risk situations [21] and to redirect the knowledge that prescribers, dispensers, patients and researchers have about the use of this active principle. France is one of the countries that is already reporting on the risks of fentanyl misuse [22]. AEMPS (Spanish Agency for Medicines and Health Products) [2] stresses the importance of respecting the conditions of use authorized for each of the pharmaceutical forms described for fentanyl in order to minimize the risk of abuse and dependence, especially in its pharmaceutical forms providing immediate release (patches), and in particular, in those patients who use fentanyl for the treatment of non-cancer pain [2]. In Ontario (Canada) control plans have been promoted for fentanyl by offering a new fentanyl patch for each one used as an incentive, which has allowed the Canadian health system to carry out a pharmacotherapeutic monitoring (SFT) on this active principle [23]. In Israel, the increased consumption of fentanyl and the decrease in morphine prescriptions have justified the initiation of national programs aimed at ensuring the safe use of opioids in the treatment of chronic pain [7].

The role of the community pharmacist in the direct care/monitoring of opioid user patients and in the detection of risk situations has been analyzed by various authors who all agree on positioning the pharmacist as one of the main contributors in the approach to the correct use of opioid medication [24-27]. Dispensing provides the community pharmacist with a multitude of opportunities for interaction with the patient and the verification of the correct and safe use of medicines [26], as well as the ability and opportunity to identify and respond to problems derived from its use [27]. However, there is still significant scope for increasing confidence in the response to opioid-related problems, an opportunity that should not be overlooked by the community pharmacy. Pharmaceutical care is the individual care for the medicine-using patient and is aimed at improving the patients' outcomes, including quality of life. There is a clear need and the value has been proven. Pharmaceutical care offers especially to pharmacists the real possibility of being responsible healthcare professionals [28]. Pharmacotherapy follow-up is based on the increased implication of the pharmacist in the monitoring and systematic documentation of the treatment received by the patient [29]. Nevertheless, poor communication of pharmacists with and between elderly patients, caregivers and other healthcare providers is one of the most important causes of drug-related problems (DRP). Pharmacists need to cooperate with patients and other healthcare providers in designing, implementing and monitoring a care plan aimed at preventing and resolving DRP [30].

Once this Pharmaceutical Care opportunity has been detected, the community pharmacy should become a strategic link for the development of action plans on the safe use of fentanyl to generate dispensing protocols and pharmacotherapeutic monitoring that favor the optimization of therapeutic results and the minimization of risks associated with this molecule.

### **Aim of the Study**

The present study aims to investigate the use and user profile of the analgesic fentanyl in a community pharmacy in Tenerife.

### **Methodology**

This is a retrospective observational study in a community pharmacy in Tenerife of the 72 dispensations of fentanyl to 47 patients in 2018 and 2019. The NIXFARMA® pharmaceutical management program was used for the study and the following variables were studied using data collection questionnaires: sex, age, pharmaceutical form, origin of prescription, PDD, posology and concomitant treatments with potentially dangerous interactions.

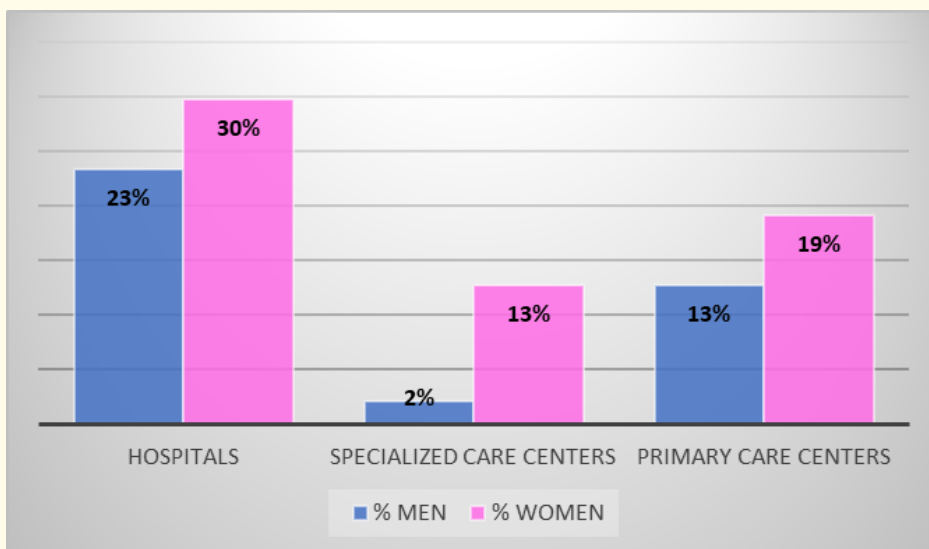
The data analysis was performed with the statistical package IBM SPSS Statistics 25. Hypothesis contrasts were performed with a significance level of 5% and confidence intervals at 95%. Qualitative variables were compared using the Chi-square test or Fisher's exact

test in the case that the number of cells with an expected count less than 5 accounted for more than 20% of the total. Quantitative variables were compared between two groups using the Mann-Whitney nonparametric U test and between more than two groups with the Kruskal-Wallis nonparametric H test. If this last test was significant, a Mann-Whitney post-hoc analysis was performed to identify which groups the differences were in.

### Results and Discussion

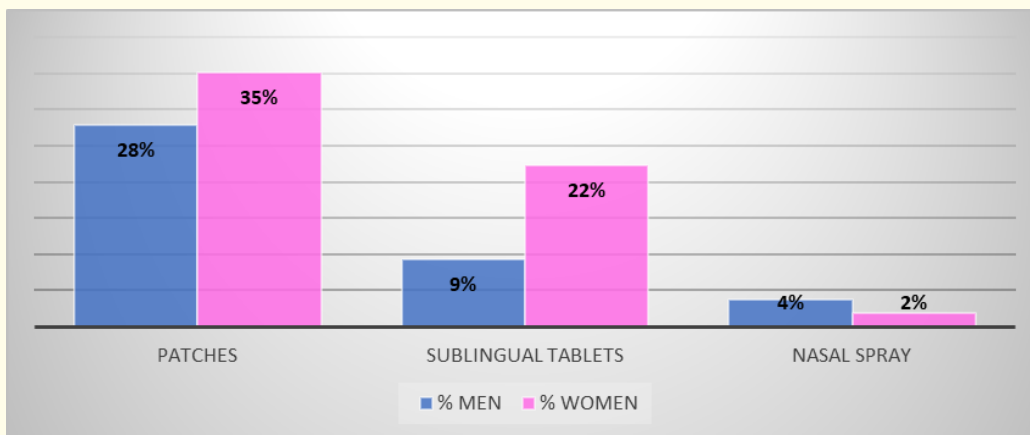
For both sexes, the predominant age range for fentanyl users is over the age of 70 in the case of 45% of the sample (30% women and 15% men). They are followed by the age ranges of 61 - 70, 24% of the sample (13% women and 11% men) and of 51 - 60, 22% of the sample (11% women and 11% men). The remaining 10% are patients aged between 31 and 50.

Regarding the origin of the prescription and the health level, 53% of the fentanyl prescriptions dispensed have a hospital origin. Prescriptions prescribed in primary care account for 32% of prescriptions and those from specialized care centers account for 15% of prescriptions (Figure 1).



**Figure 1:** Origin of de fentanyl prescription according to the user's gender.

As regards the pharmaceutical forms of fentanyl (Figure 2), most of the prescriptions are patches (63% of the total), with a similar distribution between women (35%) and men (28%). Sublingual tablets were prescribed in 31% of cases but with a significant difference between women (22%) and men (9%). Fentanyl nasal spray accounted for only 6% of the total prescriptions, although none of these prescriptions were in primary care, so it could be concluded that the prescription of fentanyl nasal spray in our community is restricted to pain specialists. Furthermore, it is noteworthy that the fentanyl nasal spray is combined in all cases with the use of sublingual fentanyl tablets.

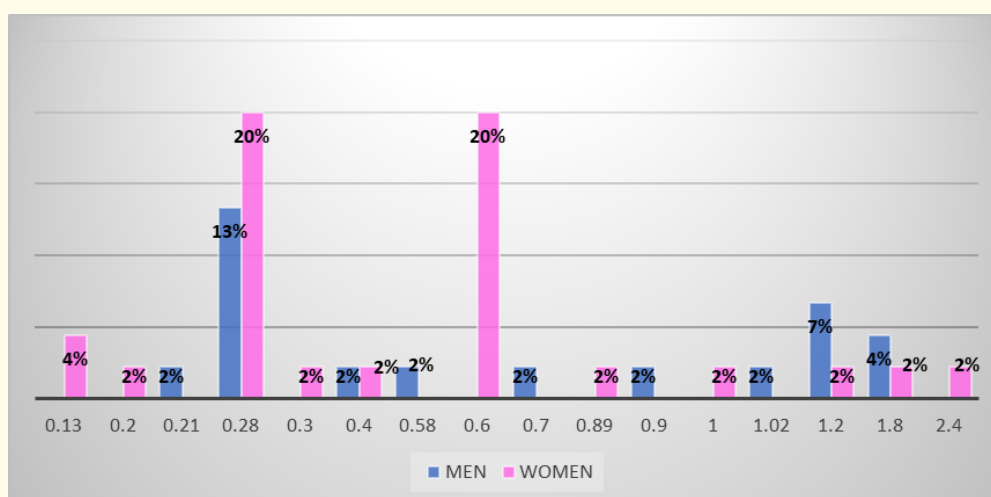


**Figure 2:** Prescribed and dispensed pharmaceutical forms of fentanyl.

Drug consumption can be expressed in cost, number of units, number of prescriptions or by the physical quantity of drugs. However, these variables can vary between regions and countries over time. This limits comparisons of drug consumption, at an international level. To address this, a technical unit of measurement, the defined daily dose (DDD) was created by the WHO Collaborating Center for Drugs Statistics Methodology [31] and defined as “the assumed average maintenance dose per day for a drug used for its main indication in adults”. DDDs are only assigned for medicines with an ATC code. The DDD for fentanyl has been set at 0.6 mg via the nasal route, 0.6 mg via the sublingual, buccal, or mucosal route, and at 1.2 mg via the transdermal route every 24 hours.

It is important to underline that the DDD is a technical unit (fixed unit of measurement) and does not necessarily correspond to the recommended or prescribed daily dose (PDD) which is defined as the average dose prescribed according to a representative sample of prescriptions. The PDD can be determined from studies of prescriptions, medical or pharmacy records, and it is important to relate the PDD to the diagnosis which the drug is used for. The PDD will give the average daily amount of a drug that is actually prescribed. When there is a substantial discrepancy between the PDD and the DDD, it is important to take this into consideration when evaluating and interpreting drug utilization.

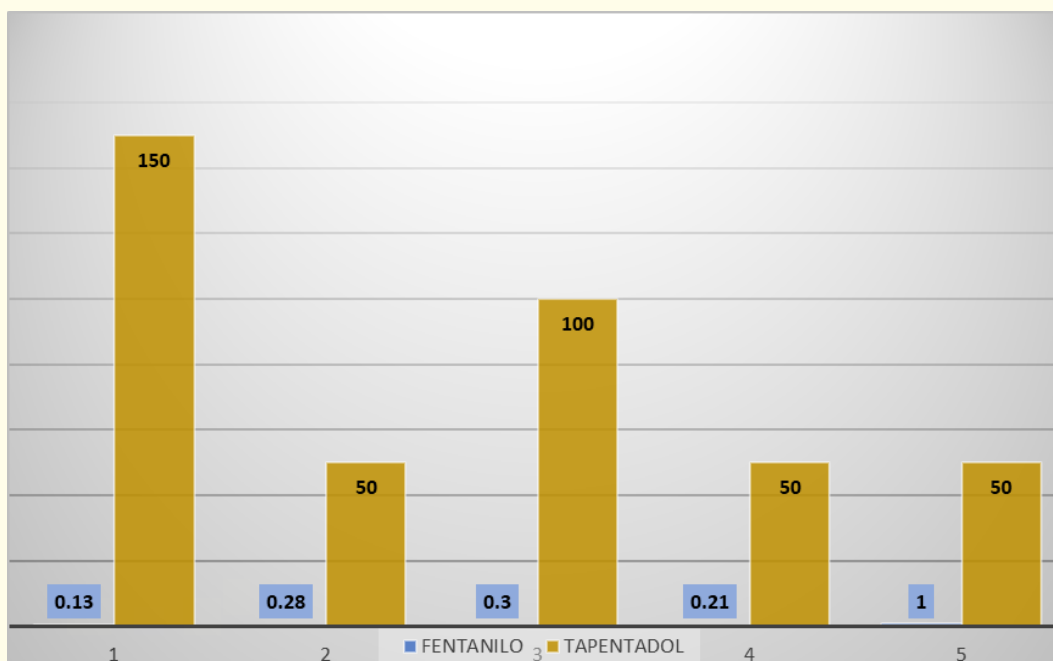
In the present study, the PDD for fentanyl ranges from 0.13 to 2.4 mg/day with 0.28 mg/day and 0.6 mg/day being the most common PDD in women accounting for 20% of the prescriptions and in the case of men the PDD ranges from 0.28 mg/day (13%) and 1.2 mg/day (7%) (Figure 3).



**Figure 3:** Prescribed daily dose (mg) of fentanyl according to sex.

A total of 8.5% of the patients studied who use fentanyl exceed the DDD of 1.8 mg when they use more than one pharmaceutical form of fentanyl in combination, specifically patches (sustained release) whose DDD is 1.2 mg/day together with sublingual tablets (of rapid release) whose DDD is 0.6 mg/day. It is noteworthy that 3 of the 4 fentanyl users who exceed the DDD went to the community pharmacy with “repeat” prescriptions generated in a health center. Only one of them came with a prescription generated in a hospital. As mentioned in the introduction, the continuous training of prescribing doctors in the knowledge of this and other active principles would reduce these risk situations [21].

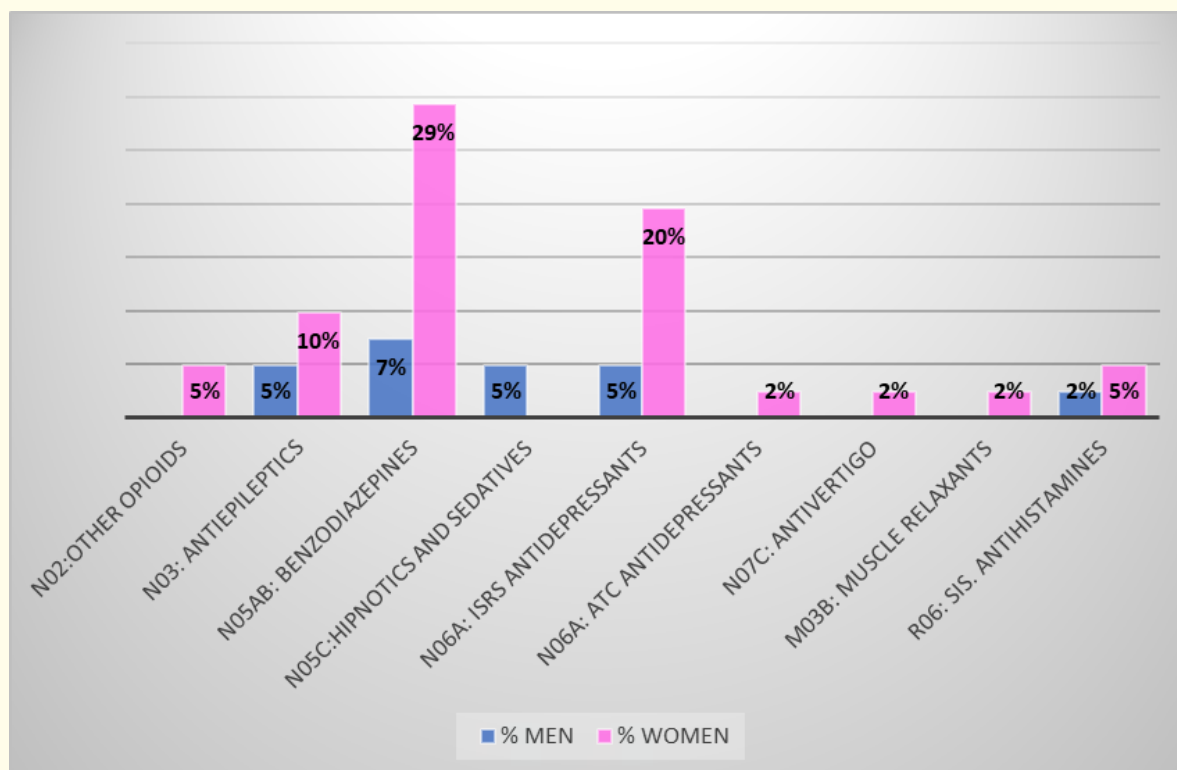
The synergistic prescription of fentanyl with other opioids has also been studied. As discussed below, 5% of the fentanyl users are treated simultaneously with other opioid pain relievers. Five of the 47 patients were treated concomitantly with different doses of fentanyl + Tapentadol. The dispensed combinations of fentanyl + Tapentadol (mg/day + mg/day) were 1 + 50; 0.28 +50; 0.3 +100; 0.21 +50 and 0.13 +150 (Figure 4).



**Figure 4:** Patients treated concomitantly with fentanyl and tapentadol (N = 5).

Fentanyl has potentially dangerous interactions with other commonly prescribed drugs. While the interaction with centrally acting drugs, CNS depressants, alcohol, BZP, antihistamines, anesthetics and other opioids increases the risk of cardiorespiratory depression, the fentanyl-MAOI interaction enhances the effect of fentanyl and its serotonergic effect. In addition, all these interactions increase the incidence of adverse reactions of medium high frequency, among which are: drowsiness, dizziness, headaches; nausea, vomiting, constipation; insomnia, depression, confusional states, hallucinations; vertigo, palpitations; high blood pressure; diarrhea, dry mouth; tolerance and withdrawal syndrome. Undoubtedly, dispensing is an ideal time to detect and prevent these interactions, and the community pharmacist should intervene by referring the prescribing physician for a reevaluation of the benefit-risk balance of the prescribed combination therapy.

Figure 5 shows the active treatments that are simultaneously prescribed and delivered to the patients in this study. Considering the drugs prescribed in concomitance with fentanyl, it should be noted that 36% of the fentanyl users here are treated with BZP (29% women and 7% men), 25% of the fentanyl users here are treated with SSRIs (20% women and 5% men), 15% of the fentanyl users are treated with antiepileptics (10% women and 5% men), 5% of the fentanyl users are treated with other opioid analgesics, 5% of the fentanyl users are treated with sedative-hypnotics. The percentage of fentanyl users treated concomitantly with other medications such as ADT (2%), antivertigos (2%), muscle relaxants (2%), and antihistamines (2%) is low although this data helps to characterize the profile of the fentanyl users studied here and identify the need to implement and offer collateral assistance services to address these health problems from the community pharmacy.



**Figure 5:** Concomitant treatments with relevant interactions in fentanyl users.

According to gender, the potential interactions between concomitant treatments in women aged 51-70 years is noteworthy, since they are treated simultaneously with fentanyl and BZP (12%), minor opioid analgesics (4%), antiepileptic drugs (4%) and SSRIs (4%). Female fentanyl users over 70 years of age are also a group susceptible to interactions as they use Fentanyl concomitantly with BZP (15%), SSRIs (8%) and minor opioid analgesics (4%). Female fentanyl users aged 61 - 70 years are also treated with antiepileptic drugs (8%), BZP (4%) and SSRI (4%) (Figure 6).

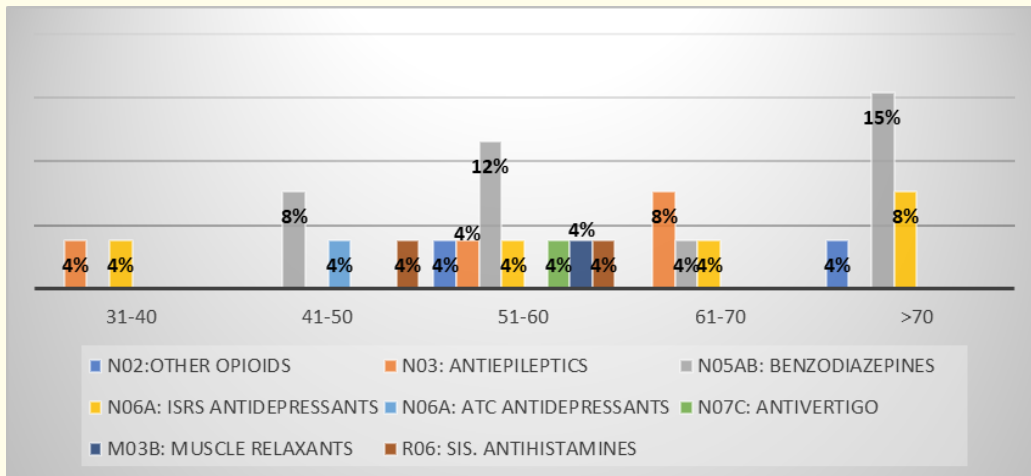


Figure 6: Concomitant treatments in women treated with fentanyl according to age range.

In the case of men, the group over 60 years of age is the one with the highest number of potential interactions between fentanyl and other active treatments. Thus, this group is prescribed fentanyl concomitantly with: BZP (33%), SSRIs (17%), antiepileptic drugs (8%), hypnotic/sedatives (8%) and antihistamines (8%). Among 41 - 50-year-old men 8% use hypnotic/sedative drugs together with fentanyl. Eight percent of men aged 51 - 60 use SSRIs together with fentanyl and 8% of male fentanyl patients between 61 - 70 also use antiepileptic drugs (Figure 7).

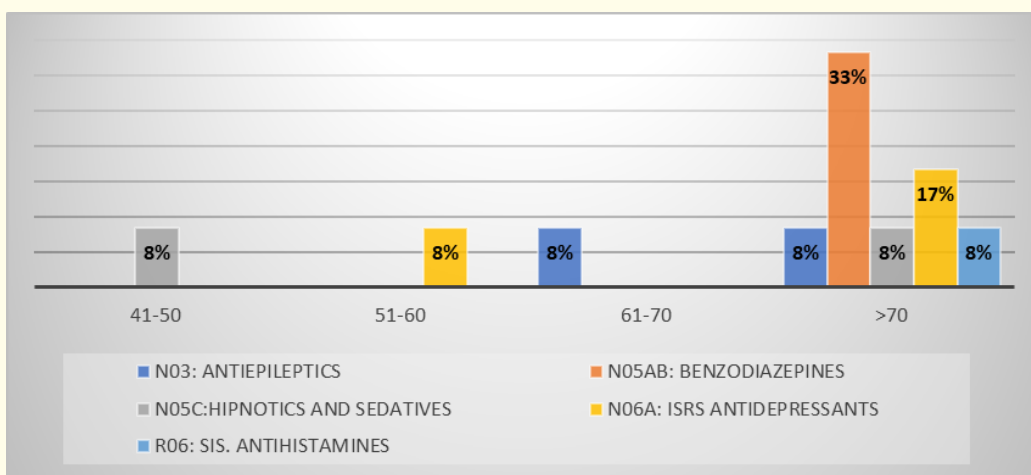
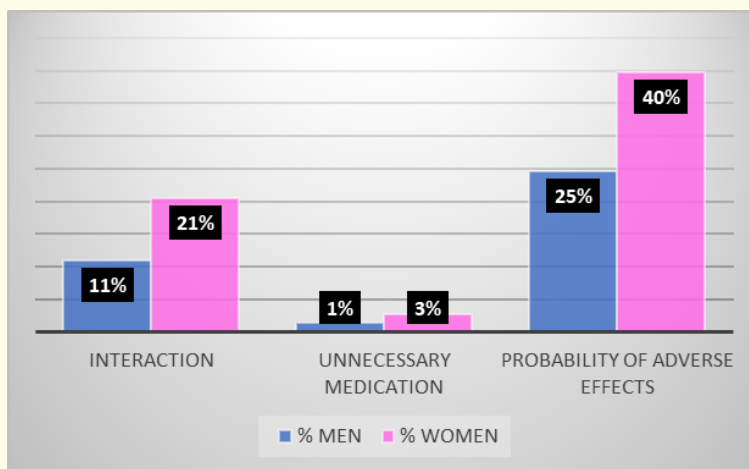


Figure 7: Concomitant treatments in men treated with fentanyl according to age range.



This significant difference according to the gender of the patient in the consumption of drugs with relevant interactions shows that the female gender may need more health care and specifically a personalized pharmaceutical care.

There is a significant difference between women and men regarding the risk of presenting drug related problems (DRP) during treatment with fentanyl. Thus, while 62% of women have suspected DRP, only 38% of men show this risk. The types of DRP detected are probability of adverse effects (65%), interaction (33%) and unnecessary medication (4%) (Figure 8).



**Figure 8:** Types of DRP observed in fentanyl users.

One of the activities derived from pharmaceutical care is pharmacotherapeutic follow-up (PFU), which can be defined as the professional practice in which the pharmacist is responsible for the needs of the patient related with their medication by the continuous, systematic and documented detection, prevention and resolving of DRP, in collaboration with the patients themselves and other health professionals, with the aim of achieving concrete results which will improve the quality of life of the patient. The results of PFU have been demonstrated in different scenarios of pharmaceutical professional practice, achieving an effective solution of DRP [32].

After analyzing the results of the present study, the authors believe that the design and implementation of pharmacotherapeutic follow-up for female users of fentanyl with other active treatments would increase the safety of the use of fentanyl. The pharmacist's intervention is the activity should be aimed at modifying certain features of the treatment, the behavior of the patient receiving it, or the conditions of use, and with the purpose of resolving a DRP/NMO [29].

Although health systems and society in general recognize that the community pharmacy is a health center close to and accessible to drug users, in the case of fentanyl users, the present study shows that attracting frequent patient visits to the community pharmacy to receive pharmaceutical care and especially pharmacotherapeutic follow-up is a challenge yet to be overcome. Only 5% of female fentanyl users visit the community pharmacy more than 20 times in a period of two years. The patients who visit the pharmacy between 6-10 times/24 months are distributed in the following are 9% of men and 5% of women. The majority of women (52%) and men (30%) only visit the community pharmacy between 1 and 5 times/24 months for the withdrawal of fentanyl (Figure 9). Taking into account this low rate of visits, it is worth highlighting the notable opportunity of community pharmacies to intervene and provide patients on Fentanyl, with pharmacotherapeutic follow-up programs.

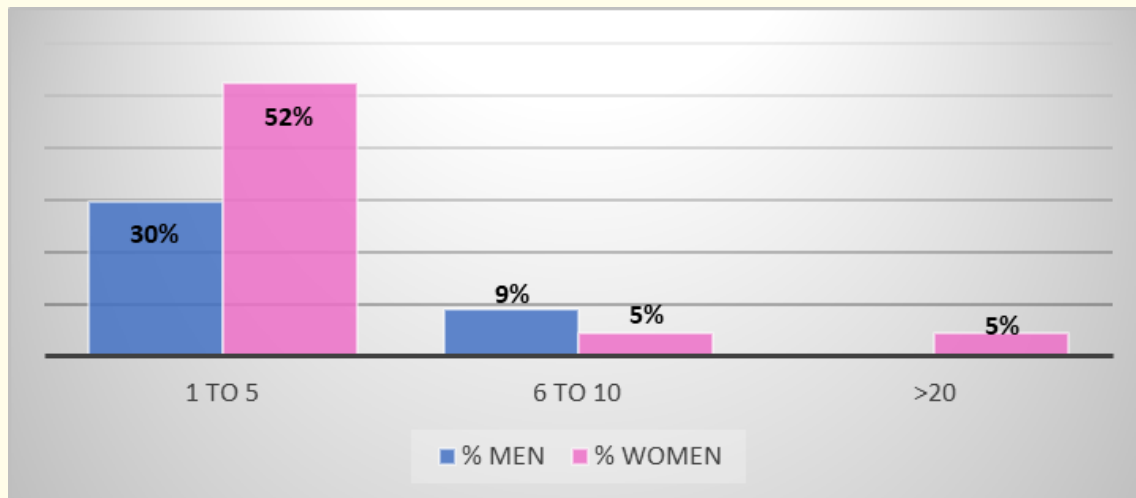


Figure 9: N<sup>o</sup> of visits to a pharmacy in 24 months by fentanyl users according to gender.

## Conclusion

Fentanyl is dispensed in the community pharmacy to patients with diverse profiles, thus pharmaceutical care during dispensation should respond to the individual characteristics of the patient. The dispensing of fentanyl occurs on presentation of a medical prescription for fentanyl for its use in the treatment of cancer pain and severe chronic pain of varied etiology. The fentanyl users studied here are usually elderly patients who use it safely since the prescribed and dispensed doses and therapeutic guidelines are in accordance with the authorized recommendations. However, in the case of dispensing the intranasal fentanyl pharmaceutical form, the DDP exceeds the DDD when there is the concomitant use of intranasal fentanyl with fentanyl formulated in another pharmaceutical form, which suggests the need to offer a pharmacotherapeutic follow-up service to supervise the safe use and the absence of negative medication outcomes due to overdose in these patients. No patient has presented symptoms of abuse or illicit use. However, unsafe situations have been detected due to the simultaneous prescription of fentanyl with other opioids, especially Tapentadol, and due to potentially dangerous interactions derived from the concomitance of other active treatments such as BZP, SSRIs and antiepileptics, among others. Among the noteworthy DRPs detected and preventable with Pharmaceutical Care are the probability of adverse effects, interaction with other medications and the consumption of unnecessary medication. The female gender is worth mentioning for its combination therapy and for presenting a higher prevalence of DRP caused by interactions between different drugs. Therefore, females could be identified as a target group to receive and benefit from personalized pharmaceutical care while using fentanyl. It is undoubtedly necessary to study aspects in greater depth such as the knowledge that the patient has about fentanyl and its use before and during treatment and in the optimization of the dispensing protocols and pharmacotherapeutic monitoring according to the differential characteristics of the different patients. The community pharmacist plays an essential role together with the other health professionals in the detection and resolution of ineffective and unsafe situations that arise during fentanyl treatment and in understanding the health needs of the users of this drug.

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