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Risk indicators in tapentadol use: opportunities to improve outcomes with a personal pharmaceutical care approach in community pharmacies

Abstract

Opioids have historically been the pharmacological choice in the treatment of moderate to severe pain of oncological and chronic origin but they have also become a growing and controversial tool in the treatment of non-oncological pain that requires a risk/benefit evaluation. The present study focuses on the opioid tapentadol, the newest opioid considered highly effective in treating cancer and non-cancer pain. According to the WHO Collaborating Center for Drugs Statistics Methodology, the stated Tapendatol Defined Daily Dose (DDD) for oral administration is 400 mg but the prescribed doses range from 100 mg/day in patients without previous opioid treatments up to a maximum of 600 mg/day. However, the DDD is a unit of measurement that does not have to reflect the prescribed daily dose (PDD) because therapeutic doses usually differ from DDDs by taking into account individual patient considerations and pharmacokinetic conditions.

This retrospective observational study in a community pharmacy on the island of Tenerife (Canary Islands, Spain) is based on the 471 dispensations of opioids for the year 2020, of which 213 correspond to tapentadol (45.2%). In 2020, among the 62 patients using opioids, 58% (36) were treated with tapentadol. For both genders, the predominant age range among tapentadol users is over 61 years, accounting for 70% of the sample (50% women and 20% men). Regarding the origin of the prescription of tapentadol, 68% of the prescriptions were originated in Primary Care services and only 14% were prescribed at a Hospital. Recorded tapentadol PDDs range from 25 mg/day to 500 mg/day but the most prescribed PDD in both women (22%) and men (11%) was 100 mg/day. When studying the polymedication of tapentadol users we observed that 36% of them are also treated with benzodiazepines (34% women and 2% men), 34% also use SSRI antidepressants (32% women and 2% men), 15 % take antiepileptic drugs (13% women and 2% men) and 8% receive TCA antidepressants. The tapentadol dispensing was also recorded in synergy with other major opioids. Thus, 3.2% of patients (women over 61 years of age) receive a combination of oral tapentadol (150 mg and 200 mg) and oral sublingual fentanyl (0.13 mg - 0.4 mg/day). Therefore, the authors believe that in any pharmaceutical care intervention on opioids treatment users, especially dispensing and follow up, is an ideal time to promote a safer user of Tapentadol and to detect and to avoid potential drug related problems (DRP) and negative medicine outcomes (NMO).

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Introduction

Chronic pain is presented as one of the serious problems in the world today. It affects approximately 20% of the adult European population, especially the female gender and advanced ages.[1] In the United States; it is considered the main cause of disability, which implies not only a social burden but also a cost for public health due to expenses derived from diagnosis, treatment and sick leave.[1] The International Association for the Study of Pain (IASP: International Association for the Study of Pain) defines chronic pain as the pain that persists beyond the normal time for tissue healing, generally considered to last approximately 3 months.[2] Pain affects mental health, reduces quality of life and even affects the individual in decision-making.[3] Despite its ubiquity, chronic pain is an invisible epidemic that accompanies various diseases and conditions, including cancer. Chronic pain affects more than 60% of those over 65 years of age, especially nociceptive musculoskeletal pain, generated by degenerative joint diseases.[4]

Opioids have historically been the choice in the treatment of severe to moderate pain of oncological and chronic origin and are a growing therapeutic tool in the treatment of non-oncological pain of diverse etiology. In these cases, the current trend is to use prolonged-release pharmaceutical forms, which implies the use of lower doses, better pain control, better adherence and a lower risk of tolerance and abuse.[5] The WHO 'analgesic ladder' suggests treatment based on the intensity of pain, from no drug in case of no pain (step 0) to strong opioids (step III) for moderate to severe pain.[6]

However, the use of opioids in the treatment of chronic pain is controversial and requires a correct evaluation between the benefits of pain relief and the possible risks among which the side effects, the tolerance, the dependence and the abuse outstand. This therapeutic group is known to present a higher overdose rate in men compared to women,[5] which highlights the importance of the gender variable in studies on their use and in informational and educational actions prior to and during the treatment.

While there is evidence of the safety of the short-term use of opioids, the long-term use in the treatment of non-cancer pain and in musculoskeletal conditions continues to generate debate not only regarding the limited evidence on its efficacy but also derived from the high individual variability and the serious side effects that may be observed.[1,2] Furthermore, the increase in the use of opioids in the

treatment of chronic pain has been associated with an increase in the number of deaths related to their use.[7]

Sedation, nausea, vomiting, and constipation are commonly recognized as classic opioid side effects but opioid-induced changes in endocrine function are also common and have been recognized for more than a century. Hypogonadism may be the most common toxicity associated with long-term opioid treatment Other issues that may also be associated with chronic opioid use include peripheral edema and immune suppression. Controversial case reports suggest that patients taking opioids for non-cancer chronic pain may develop hyperalgesia and exacerbated central sleep apnea, particularly when benzodiazepines are co-administered.[8] Studies registered in MEDICAID have concluded that 40% of opioids users presented at least one risk indicator such as high prolonged-release PDDs or overlap with other treatments such as benzodiazepines.[1]

Drug consumption can be evaluated and compared using different variables such as number of packages sold or number of prescriptions, among others. However, these variables are not usually shared between regions, which may be a limitation when comparing data at an international level.[9] This is why recent drug use studies resort to the use of the Defined Daily Dose (DDD), "*The average daily maintenance dose assumed for one day of a drug used for its main indication in adults"* (WHO Collaborating Center for Drugs Statistics Methodology), used for drugs with ATC classification.[10] The assigned DDD is based on the average adult dose recommended for the main indication as reflected by the ATC code. When setting the DDD, the recommended maintenance dose (long term therapeutic dose) is usually preferred. DDDs provide a fixed unit of measurement enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups.[11]

However, the DDD is a unit of measurement that does not have to reflect the prescribed daily dose (PDD). Therapeutic doses usually differ from DDDs by taking into account individual patient considerations and pharmacokinetic conditions. The DDD is rarely used as a prescribed daily dose (PDD) as in some cases, it could be the mean average of two or more commonly used doses.

The present study focuses on the opioid tapentadol, the newest opioid since it combines agonist properties of the mu opioid receptors and the inhibition of noradrenaline reuptake generating a synergy in terms of efficacy and reduction of possible adverse effects.[7] In the USA the increase in the use of tapentadol, especially the immediate-release forms, has registered a growing trend since June 2009.[12] Tapentadol is known to be highly effective in treating cancer and non-cancer pain of the nociceptive, neuropathic and mixed types[13] but few randomized controlled trials have been reported regarding its use in the treatment of long-term neuropathic pain. Moreover, the period of time of the studies usually oscillates between 3-6 months.[14] The safe and effective use of tapentadol has been reported in the treatment of non-cancer pain for periods of between 3 or 4 months, with it also being well tolerated and effective in therapies of up to 2 years, but it has not been studied beyond this period of time.[3]

Despite its novel action mechanism, the doses that have been reported in studies range from 100 mg in patients without previous opioid treatments up to a maximum of 600 mg in divided doses, in immediate-release forms.[15] However, the recommended initial doses are 50, 75 or 100 mg every 4-6 hours according to the intensity of the pain. According to the technical data sheets of the Spanish Drug Agency Total daily doses greater than 500 mg of tapentadol have not been included in safety studies of prolonged-release pharmaceutical forms.[16] In the case of tapentadol, the stated DDD according to the WHO Collaborating Center for Drugs Statistics Methodology is 400 mg for oral administration.

According to the American Association of Poison Control Centers, during the therapeutic dosing of tapentadol the most frequently reported adverse effects are nausea, dizziness, vomiting, headache, and a high rate of drowsiness.[14] Like in all mu opioid receptor agonists, excessive amounts of tapentadol can cause alterations in the central nervous system and respiratory depression, as has been demonstrated even with the ingestion of this substance in a single dose in children.[17] However, little is known about the effects of tapentadol in overdose, although there is a recording of death due to intravenous injection of tapentadol.[14]

Concomitant administration of tapentadol with serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and any agent that alters the central metabolism, including triptans, can be life-threatening as a result of the development of serotonin syndrome, respiratory depression, hypotension, deep sedation, coma or death.[18]

Drug-related problems (DRP) are one of the cornerstones of pharmaceutical care[19] and it is any event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes or negative medicine outcomes (NMOs), defined as patient health outcomes not suited to the objectives of pharmacotherapy and associated or potentially associated with drug use, without a doubt, there is a need to improve the use of Tapentadol and its health outcomes, especially in specific subpopulations specially females.[2,5,20] Thus, the pharmaceutical care and the follow-up of patients are now consolidated as tools of great impact for the prevention and minimization of the potential risks associated with the consumption of drugs.[3,21,22] This study aims to evaluate the need and the opportunity of collaborative pharmaceutical care in the multidisciplinary team of healthcare professionals that assists patients using tapentadol for the optimization of the drug outcomes and the minimization of its risks.

Method

A retrospective observational study was developed in a community pharmacy on the island of Tenerife (Canary Islands, Spain). A total of 471 dispensations of opioids for the year 2020, of which 213 correspond to the active principle tapentadol (45.2%), were evaluated. The data were obtained using the NIXFARMA® pharmaceutical management program. The data collection questionnaires included several variables: sex, age, pharmaceutical form, origin of prescription, PDD, posology and concomitant treatments with potentially dangerous interactions, among others. 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 event that the number of cells with an expected count of less than 5 accounted for more than 20% of the total.

Results and discussion

In 2020, 62 patients were opioid users with a total of 471 prescriptions dispensed at our community pharmacy. Fifty-eight percent (36) of these users were treated with tapentadol. For both genders, the predominant age range among tapentadol users is over 61 years, accounting for 70% of the sample (50% women and 20% men). This is followed by the age range of 51 to 60 years of age, with 22% of the sample (19% women and 3% men). Only 9% of the sample (only women) are in the age range between 30 and 50 years (Figure 1).

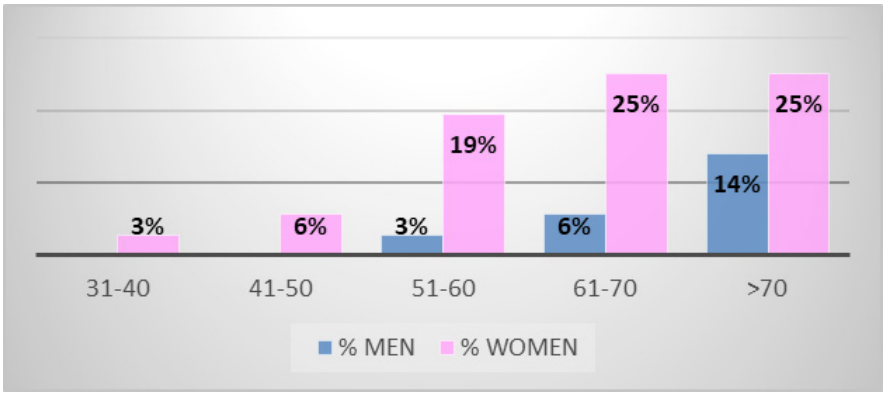

Figure 1 Tapentadol user´s age by gender.

Regarding the origin of the prescription of tapentadol, 68% of the prescriptions were originated in primary care services (67% women and 19% men) and only 14% come from hospital centers (11% women and 3% men) (Figure 2). There are no prescriptions to be dispensed from specialized care centers. This is an unexpected result as it shows that tapentadol is mostly prescribed by non-specialist doctors outside hospital settings or specialized care centers. This trend is contrary to that previously observed by our team with fentanyl, where most of the prescriptions were generated in hospitals (53%), specialized care centers (15%) and only 32% come from primary care health services.[23]

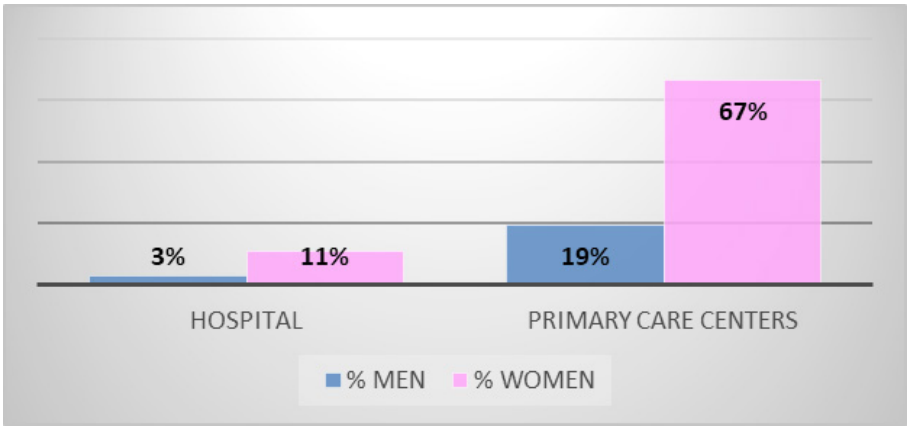

Figure 2 Origin of the tapentadol prescription according to the user´s gender.

Registered tapentadol PDDs range from 25 to 500 mg/day. The most prescribed PDD in both women (22%) and men (11%) was 100 mg/day. While 12% of the tapentadol users received a PDD greater than 250 mg/day and 3% received a PDD of 500 mg/day, all of these dispensations were for females (Figure 3). It should be remembered that the technical data sheet authorized by the AEMPS (Spanish Agency for Drugs and Health Products) for tapentadol states that doses >500 mg/day are not safe in prolonged-release pharmaceutical forms as there are no safety studies.[16]

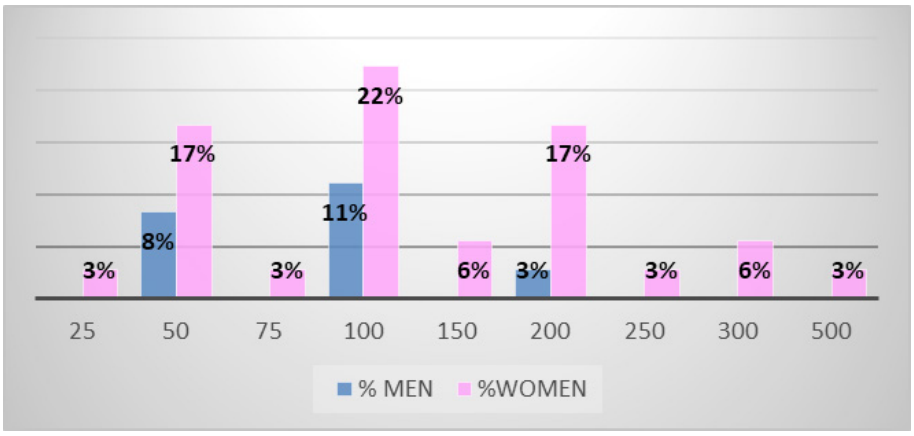

Figure 3 Tapentadol Prescribed Daily Dose (PDD) by gender and age groups.

Citation: García VH, Armas DA, Bethencourt IS, et al. Risk indicators in tapentadol use: opportunities to improve outcomes with a personal pharmaceutical care approach in community pharmacies. *Pharm Pharmacol Int J.* 2021;9(3):81–87. DOI: 10.15406/ppij.2021.09.00331

The tapentadol prescription was also dispensed in synergy with other major opioids. Thus, 3.2% of patients (women over 61 years of age) are treated with a combination of oral tapentadol (150mg and 200mg) and oral sublingual fentanyl (0.13mg-0.4mg/day). In addition, concomitant use of benzodiazepines, SSRIs and antiepileptics is also observed in these women over 61 years of age treated synergistically with both opioids. This has been identified as a potentially dangerous interaction with observed or potential MNO (medicine Negative Outcomes) that should be detected and/or prevented by a pharmaceutical care intervention suggesting a reevaluation of the benefit/risk balance of the combined medication by the prescribing doctor.

When studying the polymedication of tapentadol users, 36% of them are also treated with benzodiazepines (34% women and 2% men), 34% also use SSRI antidepressants (32% women and 2% men), 15 % take antiepileptic drugs (13% women and 2% men) and 8% receive TCA antidepressants (6% women and 2% men) (Figure 4). Furthermore, it is differentially observed that tapentadol users also receive prescription and dispensing of other opioids (2%), hypnotics and sedatives (2%), antivertiginous products (2%) and muscle relaxants (2%) (Figure 4). Again, as mentioned before, dispensing at the community pharmacy is an ideal time to detect and prevent these potentially risky interactions and the pharmacist should follow up the patients in order to observe the appearance of any MNO and if needed to refer the patient to the prescribing physician (19) for a reevaluation of the benefit-risk balance of the prescribed polymedication.

Considering that the technical specifications of the medicines containing tapentadol approved by the AEMPS indicate that the concomitant use of tapentadol with sedative medicines such as benzodiazepines or other respiratory or CNS depressants (other opioids, antitussive or substitution treatments, barbiturates, antipsychotics, H1 antihistamines, alcohol) is a potentially dangerous interaction because the risk of sedation, respiratory depression, coma or death is increased due to the additive depressant effect of the CNS. Therefore, it is important that, in those patients in whom a combined treatment of tapentadol with a depressant is prescribed, the pharmacists check that patient knows the instructions to safely use all the medicines included in the treatment. Additionally, based on the potential risks, the pharmacist could refer the patient to the prescribing physician suggesting a reduction in the dose of one or both drugs and limiting the duration of concomitant use. These interventions are already listed by the PCNE (Pharmaceutical Care Network Europe Association) classification for Drug-Related Problems V9.1 in 2020 either at the prescriber level (Intervention proposed to prescriber) and at patient level (Patient (drug) counselling; Patient referred to prescriber; Spoken to family member/caregiver.

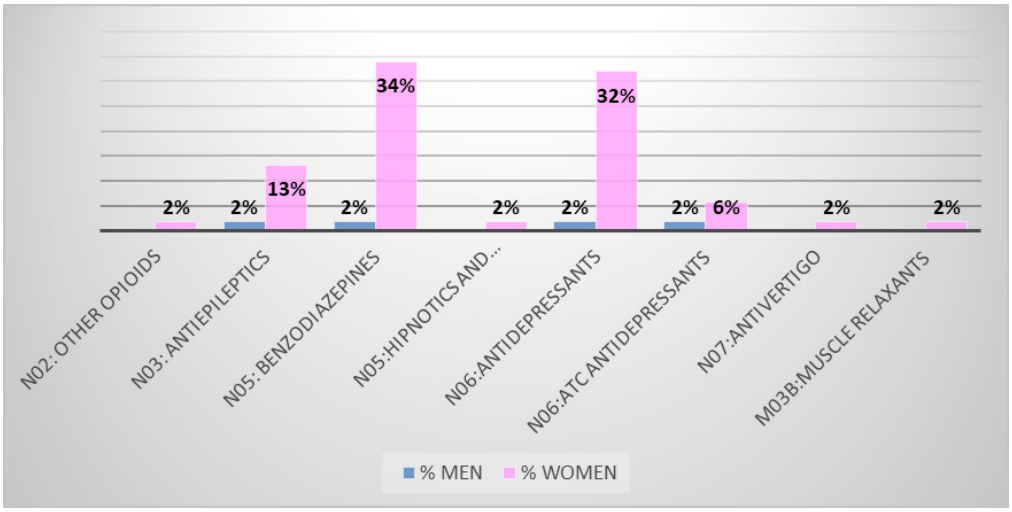

Figure 4 Concomitant treatments with relevant interactions in tapentadol users.

In addition, both the prescribing physician and the dispensing pharmacist should remember that tapentadol may cause seizures and increase the potential for seizures of selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), antidepressant tricyclics, antipsychotics, and other medications that lower the seizure threshold.[16] Therefore, during the follow up of the treatment a special attention to this negative outcome must be paid.

The present study shows that the use of tapentadol in women over 61 years of age stands out for its potential interactions with BZP (22%), SSRI antidepressants (20%), antiepileptic drugs (8%), hypnotics and sedatives (2%), other opioids (2%), TCA antidepressants (2%) and muscle relaxants (2%) (Figure 5). These results contribute to the characterization of the profile of tapendadol users and suggest the need to design and offer personalized and innovative Pharmaceutical Care services with gender and age approaches. This particularity of greater prescription of concomitant drugs in female suggests that the implementation of pharmaceutical care protocols addressing the differences and specificities of gender could lead to greater safety and knowledge in the patient during the use of tapentadol.

In the case of men, the group over 61 years of age is also the one with the most potentially dangerous interactions due to concomitant use with other drugs. Thus, concomitance of tapentadol in males has been recorded with BZP (25%), antiepileptics (25%), SSRI antidepressants (25%) and TCA antidepressants (25%). There is no concomitance of risk treatments in male users under 60 years of age (Figure 6).

As previously observed for fentanyl (9), we believe these results will contribute to fill some of the gaps detected in the design of Pharmaceutical Care dispensing and follow up protocols for chronic use of Tapentadol.

Considering the Drug Related Problems (DRPs) a significative difference in the occurrence was observed between genders during

tapentadol treatment. While 49% of women present potential DRP only 15% of men treated with tapentadol show potential DRPs (Figure 7). The most relevant DRPs detected in almost 50% of patients are the probability of adverse effects and the potential interactions among polymedication. Once again, the difference according to gender is noteworthy. There is a risk of DRP derived from interactions with other drugs used concomitantly in 43% of women compared to 7% in men. The same figures are true for the DRP associated with the risk of the appearance of adverse effects, since 43% women and 7% men treated with tapentadol are exposed to suffering diverse NMO because of these side effects DRP (Figure 8).

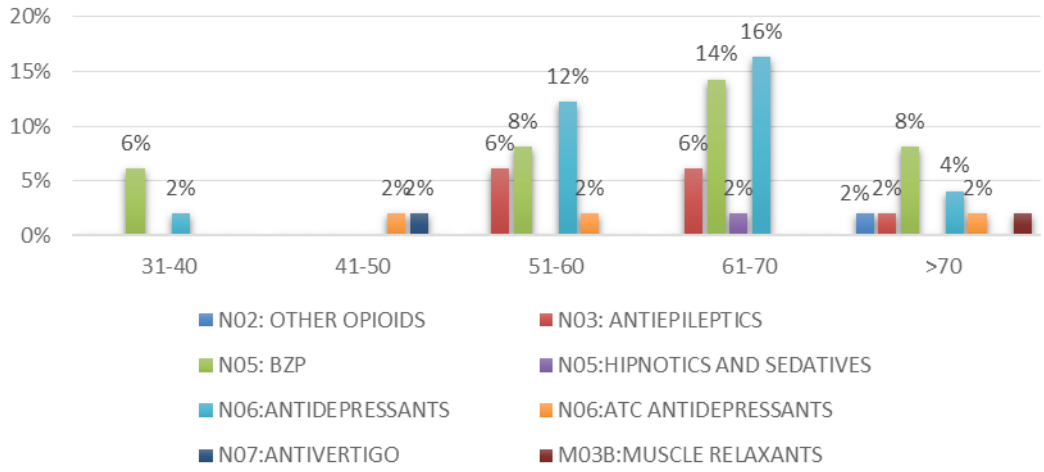

Figure 5 Concomitant treatments in women treated with tapentadol according to age range.

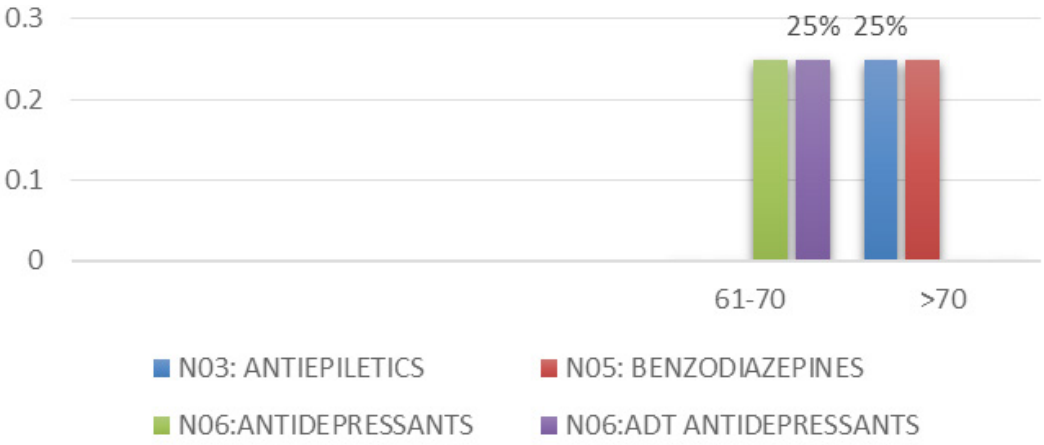

Figure 6 Concomitant treatments in men treated with tapentadol according to age range.

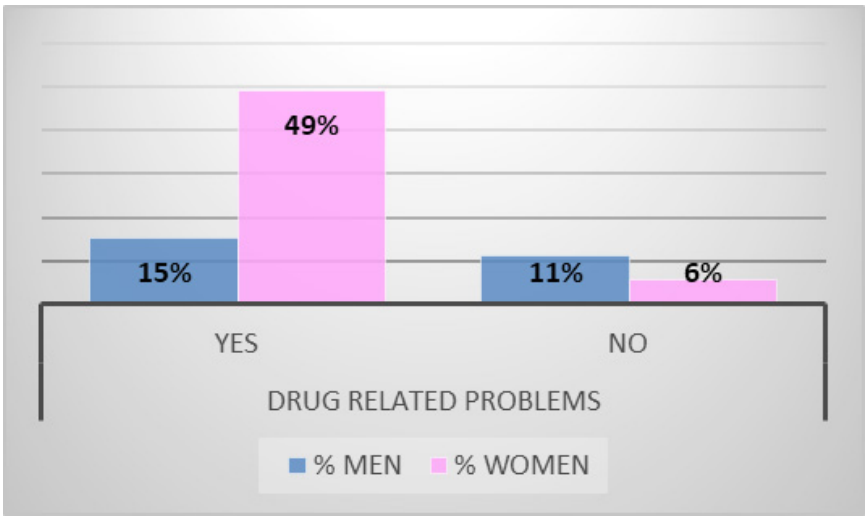

Figure 7 Drug Related Problems (DRP) occurrence in tapentadol users.

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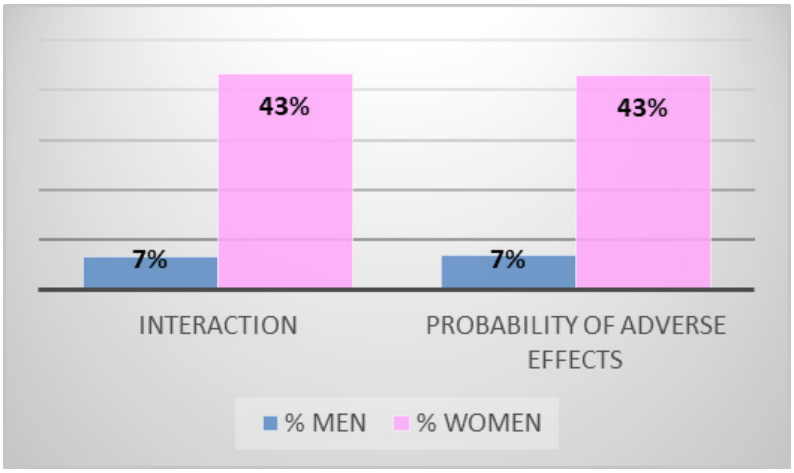

Figure 8 Main Drug Related Problems (DRP) observed in tapentadol users.

The pharmacist's intervention with the purpose of resolving a DRP/NMO and the aim of modifying certain features of the treatment, the behavior of the patient receiving it or the conditions of use, is considered essential during the treatment with Tapentadol. Therefore, the Pharmacotherapeutic follow-up (PFU), 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, is pointed out as the best tool to improve the safe use of Tapentadol. The results of PFU have been demonstrated in different scenarios of pharmaceutical professional practice, achieving an effective solution of DRP.[23]

Even though the community pharmacy is recognized by health systems and society as accessible health centers, the present study confirms the challenge of improving the frequency of visits by these patients to the community pharmacy. While only 6% of tapentadol users visit their community pharmacy more than 15 times a year (3% women, 3% men), the majority of users (65%) only visit between 1 and 5 times a year (54% women and 11% men) to receive their tapentadol dispensation (Figure 9).

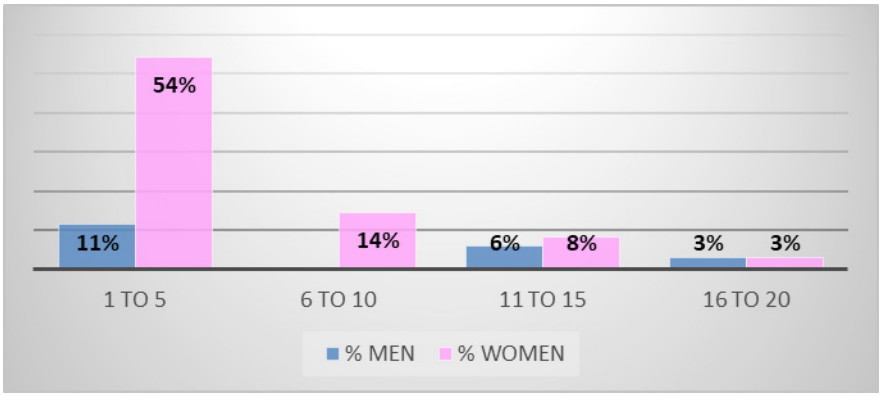

Figure 9 No. of visits to the community pharmacy in 12 months by tapentadol users according to gender.

Conclusion

Tapentadol is dispensed in community pharmacies to a diverse patient profile, although with a higher percentage to women over 60 years of age. Tapentadol dispensing is always carried out, with a medical prescription, for the treatment of chronic pain of high intensity and varied etiology. The prescription guidelines conform to those recommended in the Spanish Drug Agency technical sheets and a safe use of tapentadol is observed with no abuse situations detected. Nevertheless, the high prevalence of prescriptions from primary care centers raises our concern about whether the patients are periodically reviewed by specialized medical services in pain treatment such as oncologists, orthopedists or pain units, among others.[24-28]

Unsafe situations are detected when tapentadol is prescribed with other centrally acting drugs (BZP, SSRI and antiepileptic drugs) that could generate potentially dangerous drug related problems (DRP) derived of these drug interactions.

A high percentage of tapentadol users who synergistically take other opioids has been observed. 3.2% of tapentadol female users over 60 years used tapentadol combined with fast-release fentanyl along with other centrally acting treatments. It is noteworthy that the females stand out for receiving combined therapies and polymedication with a higher prevalence of DRP and a higher risk for NMO when using tapentadol.

Our results suggest the need and the opportunity to promote and offer a personalized pharmacotherapeutic follow-up for (PFU) along with a collaborative work with other health professionals. In those situations where potentially negative medicine (Tapentadol) outcomes are observed or expected, the pharmacist's intervention would need

to include the referral of the patient to the prescribing physician for the reevaluation of the treatment along with a promotion of a greater frequency of visits to the pharmacy to monitor the safety of the treatment with Tapentadol.

The authors have identified some "red flats" for Tapentadol. Among these risk indicators for DRP and NMO outstand being older than 65, consuming high doses of Tapentadol, chronic use of Tapentadol and the presence of polymedication susceptible of generating potentially risk interactions.

It can be stated that community pharmacists may play an essential role, together with other health professionals, in both the detection and resolution of unsafe situations that could arise during the use of tapentadol. The lack of specific protocols for the chronic use of opioids and Tapentadol makes of this study a novel approach for the design of pharmaceutical care personalized services along with the understanding of the profile and needs of tapentadol users.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

References

1. Morrone LA, Scuteri D, Rombolà L, et al. Opioids Resistance in Chronic Pain Management. *Curr Neuropharmacol*. 2017;15(3):444–456.
2. Jayawardhana J, Abraham AJ, Young HN, et al. Opioids in Georgia Medicaid: Gender and Insurance Disparities in Utilization and Potential Inappropriate Prescribing Practices. *J Pharm Health Serv Res*. 2018;9(2):101–108.
3. Pergolizzi JV, Taylor R, LeQuang JA, et al. Tapentadol Extended Release in the Treatment of Severe Chronic Low Back Pain and Osteoarthritis Pain. *Pain Ther*. 2018;7(1):37–57.
4. Freo U, Romualdi P, Kress HG. Tapentadol for neuropathic pain: a review of clinical studies. *J Pain Res*. 2019;12:1537–1551.
5. Lyra DP, Rocha CE, Abriata JP, et al. Influence of Pharmaceutical Care intervention and communication skills on the improvement of pharmacotherapeutic outcomes with elderly Brazilian outpatients. *Patient Education and Counseling*. 2007;68(2):186–192.
6. Corli O, Floriani I, Roberto A, et al. Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids. *Ann Oncol*. 2016;27(6):1107–1115.
7. Borys D, Stanton M, Gummin D, et al. Tapentadol toxicity in children. *Pediatrics*. 2015;135(2):e392–e396.
8. Tzschentke TM, Christoph T, Kögel BY. The mu-opioid receptor agonist/noradrenaline reuptake inhibition (MOR-NRI) concept in analgesia: the case of tapentadol. *CNS Drugs*. 2014;28(4):319–329.
9. Rubio C, Armas DA, Bethencourt IS, et al. Risk in Fentanyl Use: Opportunities to Improve with a Personal Pharmaceutical Care Approach in Community Pharmacies. *EC Pharmacology and Toxicology*. 2021;9(4):104–116.
10. WHO. *Collaborating Centre for Drug Statitics Methodology*; 2021.
11. Rubio C, Armas DA, Pérez Dieppa MA, et al. Benzodiazepines Drug Consumption Trends in a Community Pharmacy. Assessment of the Dispensed Daily Dose. *EC Pharmacology and Toxicology.* 2020;8(2):01–09.
12. Dart RC, Bartelson BB, Adams EH. Nonmedical use of tapentadol immediate release by college students. *Clin J Pain*. 2014;30(8):685–692.
13. Romualdi P, Grilli M, Canonico PL, et al. Pharmacological rationale for tapentadol therapy: a review of new evidence. *J Pain Res*. 2019;12:1513–1520.
14. Homma M, Kokubun H, Okuwaki K, et al. Pharmacokinetic Analysis, Analgesic Effects, and Adverse Effects of Tapentadol in Cancer Patients with Pain. *Biol Pharm Bull*. 2020;43(6):1000–1006.
15. Cantrell FL, Mallet P, Aldridge L, et al. A tapentadol related fatality: Case report with postmortem concentrations. *Forensic Sci Int*. 2016;266:e1–e3.
16. Agencia Española del Medicamento. Fichas Técnicas.
17. Wade WE, Spruill WJ. Tapentadol hydrochloride: a centrally acting oral analgesic. *Clin Ther*. 2009;31(12):2804–2818.
18. Molina KC, Fairman KA, Sclar DA. Concomitant use of opioid medications with triptans or serotonergic antidepressants in US office-based physician visits. *Drug Healthc Patient Saf*. 2018;10:37–43.
19. PCNE. The PCNE Classification for Drug-Related Problems. *Pharmaceutical Care Network Europe Association*. 2020;9(1):1–10.
20. Vinks TH, de Koning HP, de Lange TM, et al. Identification of potential drug-related problems in the elderly: the role of the community pharmacist. *Pharm World Sci*. 2006;28(1):33–38.
21. Yamada M, Matsumura C, Jimaru Y, et al. Effect of Continuous Pharmacist Interventions on Pain Control and Side Effect Management in Outpatients with Cancer Receiving Opioid Treatments. *Biol Pharm Bull*. 2018;41(6):858–863.
22. *Estrategia en cuidados paliativos del Sistema nacional de Salud*. Ministerio de Sanidad; 2011. 72 p.
23. Armando P, Semería N, Tenllado M, et al. Pharmacotherapeutic Follow-up of Patients in Community Pharmacies. *Aten Primaria*. 2005;36(3):129–136.
24. Merchant S, Noe L, Howe A, et al. Budget impact analysis of tapentadol extended release for the treatment of moderate to severe chronic noncancer pain. *Clin Ther*. 2013;35(5):659–672.
25. Corli O, Floriani I, Roberto A, et al. Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids. *Ann Oncol*. 2016;27(6):1107–1115.
26. Brennan MJ. The effect of opioid therapy on endocrine function. *Am J Med*. 2013;126(3 Suppl 1):S12–S18.
27. Guías Fisterra. Tapentadol; 2021.
28. Pharmaceutical Care Forum. Consensus document January 2008. 58 p.