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# Impact of a Community Pharmacy Pharmacotherapy Follow-up (PTF) service in patients using opioid analgesic

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ABSTRACT

The use of prescribed major opioid analgesics (fentanyl, tapentadol, morphine and oxycodone and combinations) for non-cancer chronic pain is fraught with risks that may generate Negative Medicine Outcomes (NMO). Among the factors associated with these risks, those related to the patient's characteristics and aberrant behavior, the treatment conditions, and the prescription health settings should be evaluated with the aim of minimizing unsafety during the health care process. The present study addresses, from a community pharmacy, the analysis of Drug Related Problems (DRP) and Negative Medicine Outcomes (NMO) in patients using these major opioid analgesics while it aims to demonstrate the role of pharmaceutical care interventions in promoting safety during the use of these molecules. A three step Pharmacotherapeutic Follow-up (PFT) protocol was designed to prevent, detect, and solve DRP and NMO associated with the use of opioid analgesics. 74.6% of the patients used opioid analgesics to treat musculoskeletal pain. Polypharmacy with benzodiazepines (61.9%); antidepressants (57.1%) and antiepileptics (30.2%) was detected in patients using these opioids. The Morisky-Green Adherence test revealed that 30.2% were nonadherent. It was observed, with statistical significance, that in all patients (63), the impact of the 14-week PFT supervised by the community pharmacist achieved an overall reduction in the prevalence of DRP and NMO. While the reduction in the number of DRPs reached 66.7%. Community pharmacies are a strategic point to promote and implement effective opioid stewardship due to both their central role in healthcare services and frequent interaction with patients.

## 1. Introduction

At present, there is almost an obligation, both legal and moral, to prevent patients from suffering pain, not only for a matter of improving health conditions, but to avoid the suffering derived from the decrease in the ability to perform one's daily life, the affectation of the relationship with their peers and the impact at an employment and economic level, among others. When patients undergo painful processes for a period of more than six months, a deterioration is observed both in their quality of life and in their emotional and psychological well-being. Pain is a common, disabling, and exacerbating condition that affects quality of life and interferes in the performance of daily life, work, and family activities.

The 2016 Global Burden of Disease Study reaffirmed that the high prominence of pain and pain-related diseases is the leading global cause of disability and disease burden. Worldwide, the burden caused by chronic pain is growing: 1.9 billion people were found to be affected by recurrent tension-type headaches, which were the most common symptomatic chronic condition. Measuring years lived with disability, low back and neck pain have consistently been the leading causes of disability around the world, with other chronic pain conditions featuring prominently in the top ten causes of disability.[1]

In recent decades, the prevalence of pain has been extensively studied and it is globally described as high and highly variable. Chronic pain is considered a public health problem, and it should be approached as a priority due to its high prevalence.[2] The prevalence and impact of

*Abbreviations:* DDI, Drug Drug Interactions; DRP, Drug Related Problems; Max, Maximum; Min, Minimum; NMO, Negative Medicines Outcomes; No, Number; PCNE, Pharmaceutical Care Network Europe Association; PCS, Pharmaceutical Clinical Services; PTF, Pharmacotherapy Follow-up; US, United Station; WHO, World Health Organization.

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pain in US adults is high, with an estimated 20.4% (50 million) of adults experiencing chronic pain, and 8% of US adults (19.6 million) living with high-impact chronic pain.[3] Similar figures are observed in Europe regarding chronic pain, where the most recent estimates suggest that up to 40% of the European population experience chronic back pain. Recent data suggests that in Denmark, one million working days are lost each year due to chronic pain.[4] In Spain, it is estimated that one in six Spaniards (17%), suffers from some form of chronic pain process.[5]

Medicines have been and will be the most widely used therapeutic tools for solving health problems. In addition to reporting enormous benefits, their use entails, in parallel, associated risks not only derived from the medication itself, but related to its consumption and to the patients themselves. Approximately one quarter of primary care consultations involve chronic pain consultations, with patients often dissatisfied with treatment plans, particularly those involving opioid analgesic treatment.[6]

Opioids are widely used, have a narrow therapeutic index and can be associated with toxicity. Among their associated risks, tolerance, dependence, constipation, dry mouth and increased depressive states stand out.[7] Drug Related Problems (DRPs) are those situations that cause or may cause the appearance of negative medicine outcomes (NMOs). While DRPs are elements of the process that entail an increased user experience of suffering an NMO, with the latter being those patient health results not suited to the objectives of pharmacotherapy and associated or potentially associated with drug use.[8] The Pharmaceutical Care Network Europe Association (PCNE) describes a DRP as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes[9].

In general, major opioids (those placed on the third rung of the WHO analgesic ladder,[10,11] morphine, fentanyl, oxycodone and tapentadol), are generally safe drugs that show a good safety profile. Nevertheless, pharmacokinetic drug-drug interactions (DDIs) involving opioid analgesics can be problematic along with some aberrant patient behaviors.

The social and health precedents that have led to the so-called *"Opioid Crisis"* in the US since the 1990s should be mentioned. The misuse of prescribed opioids has reached epidemic proportions.[12,13,14,15,16,17]. Among the factors associated with these epidemic risks of opioid analgesics, the duration of the treatments (> 60 days) has been identified as a major factor. According to Kurteva et al.,[18] the highest risk is observed among those patients who present a history of opioid/benzodiazepines use and high initial daily opioid dose.

For all these reasons, regular monitoring and evaluation of the risks and drug-related aberrant behaviors are necessary.[19] Community pharmacists are one of the most accessible health care providers[20] and they are a strategic point to promote effective opioid stewardship due to both their central role in healthcare teams and frequent interaction with patients[14,21,22]

The role of pharmacists has grown considerably, going beyond the mere dispensing to providing patients with a comprehensive health service.[23,24] In many countries community pharmacists are becoming increasingly patient oriented by offering professional services and increasing safety, efficacy, and efficiency.[25] Pharmaceutical Clinical Services (PCS) can optimize the process of pharmacotherapy ([26]; MSSSI, 2015[27];). The provision of PCS is one of the strategies for improving health outcomes in patients and promoting the safety of their treatment.[28] Furthermore, practice-based research networks have been established to support collaborative research and knowledge translation in community pharmacies.[29]

## 2. Objectives

The present study aims to: a) address the analysis of DRP/NMO in patients using major opioid analgesics from a community pharmacy, b) to design and implement a pharmaceutical care service (PCS) on opioid analgesics based on pharmacotherapeutic follow-up (PTF) and c) to analyze the impact of the pharmaceutical intervention on the patients' health and behavior with respect to the opioid analgesics.

## 3. Method

Observational, descriptive, cross-sectional prospective study, based on a pharmaceutical care follow-up (PTF) program in a community pharmacy, on patients with a medical prescription for major opioid analgesics (fentanyl, tapentadol, morphine and oxycodone and combinations).

The criteria for including patients in the study established that 100% of patients of both sexes, over 18 years of age, without impaired communication and/or decision-making abilities, and who requested the dispensation of a major opioid analgesic would be included in the study. After being informed about the study and its protocol, every patient was requested to sign the informed consent form. Considering the protocol, every patient requesting the dispensation of a major opioid analgesic was referred to the community pharmacist responsible for the study to receive the provision of the pharmaceutical care service (PCS) for major opioids.

Following an incidental and non-probabilistic sampling, the sample size was estimated considering the data collection period (April 2021–February 2022 = 10 months) for the study and the last two years of the community pharmacy opioid dispensing registry (125 patients in 24 months = 52 patients ((125·10)/24 = 52) every ten months).

The pharmaceutical care follow-up (PTF) program was designed to have a mean follow-up time per patient of 14 weeks. Data collection was carried out through three clinical interviews using different questionnaires and each interview separated in time by a minimum period of six weeks. A comparison was made of the data obtained in the initial (baseline status) data collection questionnaire and the final data collection questionnaire for the study of the impact of pharmacotherapeutic follow-up,.

Multiple variables related to sociodemographic parameters, characteristic of the opioid treatment (polypharmacy, interactions, adverse effects, etc.), patient behavior (adherence, etc.), among others, were collected to detect and solve the several DRPs and NMOs through individualized pharmaceutical interventions.

The interventions included in the program ranged from personalized medicine information (PMI), health care education, referring to the physician reporting the DRP/NMO, referring to the physician proposing changes in treatment, reporting to pharmacovigilance services, among others.

No complementary clinical analysis tests were requested from the patients since the pharmaceutical care service for opioid analgesics designed for the study did not include any clinical parameter to meet the objectives.

For the statistical analysis (SPSS 24.0™ from IBM Co. ®), all the contrasts of hypotheses used in the comparisons were bilateral at a level of statistical significance $p \leq 0.05$. Qualitative variables were compared using the Chi-square test or Fisher's exact test if the number of cells with an expected count of less than five accounted for >20% of the total.

Numerical scale variables that did not follow a normal distribution were analyzed with the Mann-Whitney *U* test between the same group at two different times with the Wilcoxon sign and rank test and between more than two independent groups with the H test. Kruskal-Wallis with post hoc U Mann-Whitney was used to identify at the expense of which groups the difference occurs if the global test offered significance.

## 4. Results

Sixty-three patients were finally included in the study (84.1% were female; 15,9% male). Patients were stratified by age in younger than 65 years (46%) and older than 65 years (54%).

The most prescribed opioid among the participating patients was tapentadol (50.7%), followed by fentanyl (33.8%). Minority prescriptions were detected for morphine (7%); oxycodone-naloxone

(5.6%) and oxycodone (2.8%). While the use of opioid analgesics was motivated by non-oncological causes in 74.6% of the patients, mainly musculoskeletal pain, 22.2% of patients used opioid analgesics for cancer pain.

The results of the Morisky-Green Adherence test revealed that 30.2% of the patients presented a poor adherence attitude to the opioid treatment at the baseline interview. Among the side effects observed and reported by the patients, constipation (16%), dry mouth (14.7%) and feeling depressed (10.9%) stand out.

Benzodiazepines (61.9%); antidepressants (57.1%) and antiepileptics (30.2%) stand out as concomitant treatments during the opioid analgesics use. All these drugs are usually adjuvant treatments in the guidelines for the treatment of non-cancer chronic pain. It should also be noted that some patients using major opioid analgesics keep on consuming some of the minor analgesics such as tramadol or codeine (5.8%) prescribed previously to the major opioid treatments.

After a 14-week pharmacotherapeutic follow-up it was observed that the pharmaceutical intervention of the community pharmacists achieved an overall reduction in the number of NMOs ($p < 0.001$). These results confirm that pharmaceutical care services offered to patients who use opioid analgesics has a verifiable and direct impact on the results expected of the treatment. The reduction in the prevalence of NMOs after the pharmacotherapeutic follow-up (PTF) (Tables 1 and 2) occurs in all three categories of NMOs, safety, effectiveness, and necessity.

The prevalence of NMO increases, with statistical significance, when the patient is under a polypharmacy status and is prescribed, together with the opioid analgesic, any of the following therapeutic groups: antidepressants ($p < 0.05$); antiepileptics ($p < 0.01$); benzodiazepines (BZD) ($p < 0.01$) and H1 antihistamines ($p < 0.05$) (Table 3).

Results show that, while the occurrence of NMOs increases with statistical significance when the patients suffer confusion and dry mouth as side effects, the prevalence of NMO also increases, without statistical significance, if the patient reports headache as a side effect (Table 4).

The analysis of the results between the baseline interview and final interview shows that the community pharmacists' intervention and the PTF service impact the expected results in health of the opioid treatment by reducing, with statistical significance, the initial number of DRPs suffered by the patient (Tables 5 & 6).

The predominant DRP at the PTF baseline interview was the probability of adverse effects (85.7%), followed by the DRP derived from interactions with other drugs (polypharmacy) (76.2%) and those DRPs associated with the personal characteristics of the patients themselves (34.9%). The occurrence of DRPs increases, with statistical significance, when the patient is under polypharmacy and is prescribed, together with the opioid analgesic, any of the following therapeutic groups: antidepressants ($p < 0.01$); antiepileptics ($p < 0.05$); benzodiazepines (BZD) ($p < 0.01$) (Table 7).

The number of DRP increases, with statistical significance, with constipation, confusion, and body falls ($p < 0.05$). An increase in the DRP occurrence is also observed in the presence of drowsiness, dizziness, headaches, dizzying sensation, dry mouth, and depressive sensation (Table 8).

When considering the different categories of DRP, it is observed that DRP derived from non-adherence behavior, the DRPs caused by drug interactions and the DRPs associated with the occurrence of opioid analgesic side effects are the ones with the best regression rate after pharmaceutical follow-up program.

Pharmacotherapeutic adherence to the opioid analgesic treatment was measured using the Morisky-Green test.[16] Before the PTF (baseline situation), non-adherent patients constituted 30.2% of the total sample. At the end of the pharmaceutical care follow up, only 1.6% of the patients remained not adherent. This improvement is related to the different actions proposed during the pharmacist intervention along 14 weeks of follow-up. Statistically significant improvement in medication adherence in intervention groups has been previously reported.[30]

**Table 1**
Comparison of the occurence (%) of NMO by category (safety, effectiveness, and necessity) between the baseline *and* final stages of the PTF.

| NMO category | | Occurrence (%) at PTF baseline | Occurrence (%) at PTF Final |
|---|---|---|---|
| Safety | Non-quantitative unsafety | 15.9 | 11.1 |
| | Quantitative unsafety | 30.2 | 22.2 |
| Necessity | No-need of the medication | 100 | 98.4 |
| Effectiveness | Non-quantitative ineffectiveness | 98.4 | 92.1 |
| | Quantitative ineffectiveness | 96.8 | 69.8 |

NMO: Negative Medicines Outcomes; PTF: Pharmacotherapy Follow Up.

## 5. Discussion

The impact of the 14-week PTF shows that, for the total sample of patients, between the baseline interview and the final interview, the community pharmacists' intervention during the PTF service provided reduced the occurrence of DRPs and NMOs in patients using opioid analgesics. Therefore, not only is a positive impact on therapeutic results of these drugs expected but there is also a minimization in the risks associated with prescribed opioids.

It has been observed that polypharmacy including combined use of antidepressants/antiepileptics/BZDs, lack of adherence and side effects such as headaches and confusion may be modifiable risk factors affecting the occurrence of NMOs during treatment with opioid analgesics. Polypharmacy as the combined use of the opioid analgesic with other drugs may expose the patient to potential drug interactions. Polypharmacy not only has a high prevalence among patients using opioids analgesics, but it has been identified as a hazard since it may risk the expected therapeutic results[31]. The risks of drug interactions with an opioid in polypharmacy situations are largely determined by which enzyme system metabolizes the opioid.[32] Opioids metabolized by the cytochrome P450 (CYP450) system (oxycodone y fentanyl) are associated with numerous DDIs that can result in either a reduction or excess in the opioid effects.[33] According to Kurteva et al.,[18] the highest risk is observed among those patients who present a history of opioid/benzodiazepines use and high initial daily opioid dose. Poor medication adherence is considered a potential contributor to disparities in health outcomes[34] and patients who are nonadherent to their medicine 50% of the time.[35] Improving medication adherence through pharmaceutical care may contribute to optimizing therapeutic results and preventing therapeutic failures or prolonged treatments.

Considering that approximately one quarter of primary care consultations involve chronic pain consultations, with patients often dissatisfied with treatment plans, particularly those involving opioid analgesic treatment[6] and knowing that while hospital admissions related to NMOs have been reported to reach 28.2%, visits to emergency services related to NMOs account for >35% of overall hospital visits,[21,36,37] the results here support the evidence on pharmaceutical intervention through PTF services which may benefit the health care system and public health. Furthermore, DRPs have been identified as one of the main causes of harm to the patient and one of the problems that generate the highest costs for healthcare systems [21,37,38]leading to substantial morbidity and mortality and increased healthcare costs.

The authors believe that the provision of healthcare in patients treated with opioid drugs needs to be redesigned to minimize the risks derived from the process of using these drugs. These patients should be configured as a group of patients with special monitoring at all levels of care, from prescription to dispensing. The awareness and instruction of patients about medications, health education, is a tool of great value to minimize risks and optimize health results. Since in the act of dispensing and in the professional pharmacotherapeutic follow-up care service the

**Table 2**
Statistical significance of the PTF impact (baseline versus final status) on the reduction of the occurrence of NMOs along the PTF.

| NMO category | | Occurrence (%) at PTF baseline | Occurrence (%) at PTF final | Reduction (%) | *p*-value |
|---|---|---|---|---|---|
| Safety | Non-quantitative unsafety | 15.9 | 11.1 | 4.8 | <0.01 |
| | Quantitative unsafety | 30.2 | 22.2 | 7.9 | <0.01 |
| Necessity | No-need of the medication | 100 | 98.4 | 1.6 | 0.98 |
| Effectiveness | Non-quantitative ineffectiveness | 98.4 | 92.1 | 6.3 | 0.97 |
| | Quantitative ineffectiveness | 96.8 | 69.8 | 27 | 0.08 |

NMO: Negative Medicines Outcomes; PTF: Pharmacotherapy Follow Up.

**Table 3**
Association between NMO occurrence (no.) and other active treatments (polypharmacy).

| Other treatments | NMO occurence (no.) median (MIN-MAX) | | *p*-Value |
|---|---|---|---|
| | Non combined use of the opioid analgesic with the following drugs | Combined use of the opioid analgesic with the following treatments | |
| Antiepileptics | 2(1–3) | 3(2–4) | <0.01 |
| Benzodiazepines | 1(0–2) | 2(1–3) | <0.01 |
| Antihistamines | 2(1–3) | 3(2–4) | <0.05 |
| Antidepressants | 1(0–2) | 2(1–3) | <0.05 |
| Second Opioid | 2(1–3) | 2(1–3) | 0.15 |
| Antipsychotics | 2(1–3) | 2(1–3) | 0.53 |
| Monoamine oxidase inhibitors | 2(1–3) | 2(1–3) | 0.98 |
| Muscle Relaxants | 2(1–3) | 2(1–3) | 0.60 |
| Antivertiginous | 2(1–3) | 3(2–4) | 0.15 |

NMO: Negative Medicines Outcomes; Min: minimum; Max: maximum; No: number.

**Table 4**
Correlation between the occurrence (no.) of NMOs and the presence of opioid analgesic side effects.

| Side effect | NMO occurence (no.) Median (MIN-MAX) | | *p*-Value |
|---|---|---|---|
| | Side effect: no | Side effect: yes | |
| Mental confusion | 2(1–3) | 3(2–4) | <0.05 |
| Dry mouth | 2(1–3) | 2(1–3) | <0.05 |
| Drowsiness | 2(1–3) | 2(1–3) | 0.10 |
| Dizziness | 2(1–3) | 2(1–3) | 0.10 |
| Headache | 2(1–3) | 3(2–4) | 0.08 |
| Constipation | 2(1–3) | 2(1–3) | 0.06 |
| Vertigo | 2(1–3) | 2(1–3) | 0.07 |
| Palpitations | 2(1–3) | 2(1–3) | 0.20 |
| Fatigue | 2(1–3) | 2(1–3) | 0.43 |
| Falls | 2(1–3) | 2(1–3) | 0.40 |
| Depressive Feeling | 2(1–3) | 2(1–3) | 0.12 |

NMO: Negative Medicines Outcomes; Min: minimum; Max: maximum; No: number.

**Table 5**
Comparison of the occurence (%) of the different types of DRP between the baseline *and* final stages of the PTF.

| DRP category | % Baseline DRP Occurrence | % Final DRP occurrence |
|---|---|---|
| Personal Characteristics | 63.5 | 61.9 |
| Interactions | 33.3 | 23.8 |
| Probability of adverse effects | 17.5 | 11.1 |
| Non compliance | 98.4 | 71.4 |
| Other health problems affecting the treatment | 100 | 9.2 |
| Insufficiently treated health problem | 96.8 | 93.7 |

NMO: Negative Medicines Outcomes; PTF: Pharmacotherapy Follow Up.

**Table 6**
Statistical significance of the PTF impact (baseline versus final status) on the reduction of the different types of DRP occurrence along the PTF.

| DRP | % Baseline DRP occurrence | % Final DRP occurrence | % reduction | *p*-Value |
|---|---|---|---|---|
| Personal Characteristics | 63.,5 | 61.9 | 1.6 | <0.01 |
| Interactions | 33.3 | 23.8 | 9.5 | <0.01 |
| Probability of adverse effects | 17.5 | 11.,1 | 6.3 | <0.01 |
| Non compliance | 98.4 | 71.4 | 27 | 0.29 |
| Other health problems affecting the treatment | 100 | 9.2 | 4.8 | 0.24 |
| Insufficiently treated health problem | 96.8 | 93.7 | 3.2 | 0.99 |

DRP: Drug Related Problems; PTF: Pharmacotherapy Follow Up.

**Table 7**
Correlation between the occurrence (no.) of DRPs and the presence of other active treatments (polypharmacy) along with the opioid analgesic.

| | DRP occurrence (n°) median (Min-Max) | | *p*-Value |
|---|---|---|---|
| | Non combined use of the following treatment | Combined use of the following treatment | |
| Antidepressants | 2(1–3) | 3(2–4) | **<0.01** |
| Benzodiazepines | 2(1–3) | 3(2–4) | **<0.01** |
| Antiepileptics | 2(1–3) | 3(2–4) | **<0.05** |
| Second Opioid | 2(1–3) | 2(1–3) | 0.74 |
| Antipsicotics | 2(1–3) | 3(2–4) | 0.05 |
| Antihistamines | 2(1–3) | 3(2–4) | 0.06 |
| Monoamine oxidase inhibitors | 2(1–3) | 3(2–4) | 0.13 |
| Muscle Relaxants | 2(1–3) | 3(2–4) | 0.44 |
| Antivertiginuous | 2(1–3) | 3(2–4) | 0.39 |

DRP: Drug Related Problems; Min: minimum; Max: maximum; no: number.

**Table 8**
Correlation between the occurrence (no.) of DRPs and the prevalence of opioid side effects.

| Side effect | DRP occurrence (no.) median (MIN-MAX) | | *p*-Value |
|---|---|---|---|
| | Non presence of side effect | Presence of side effect | |
| Constipation | 2(1–3) | 3(2–4) | **<0.05** |
| Mental Confusion | 2(1–3) | 3(2–4) | **<0.05** |
| Falls | 2(1–3) | 3(2–4) | **<0.05** |
| Drowsiness | 2(1–3) | 3(2–4) | 0.16 |
| Dizziness | 2(1–3) | 3(2–4) | 0.16 |
| Headache | 2(1–3) | 3(2–4) | 0.08 |
| Vertigo | 2(1–3) | 3(2–4) | 0.11 |
| Palpitations | 2(1–3) | 2(1–3) | 0.77 |
| Fatigue | 2(1–3) | 2(1–3) | 0.58 |
| Dry mouth | 2(1–3) | 3(2–4) | 0.07 |
| Depressive Feeling | 2(1–3) | 3(2–4) | 0.22 |

DRP: Drug Related Problems; Min: minimum; Max: maximum; no: number.

patient is instructed in the knowledge of opioid analgesic, the community pharmacy should be understood and valued as a healthcare level of great value not only for monitoring treatments with opioid analgesics and DRPs and NMOs but also for complementing the health education and drug awareness provided in other levels of care. In many countries, community pharmacists are becoming increasingly patient oriented by providing professional services and increasing safety, efficacy, and efficiency[25]. Pharmaceutical Clinical Services (PCS) can optimize the process of pharmacotherapy ([26]; MSSSI, 2015[27]). The provision of PCS is one of the strategies for improving health outcomes in patients and promoting the safety of their treatment.[28] Finally, health systems may also benefit from integrating the registry of pharmaceutical interventions in the patients' medical records.

## 6. Conclusions

Patients under opioid analgesic treatment benefit from pharmacotherapeutic follow up (PTF) and community pharmacies are optimal health care centers for the provision of this service since it has been demonstrated that they decrease not only the prevalence of negative medicine outcomes, but also the occurrence of drug related problems. Community pharmacies are a strategic point to promote and implement effective opioid stewardship due to both their central role in healthcare services and frequent interaction with patients. Nevertheless, the characterization of the patient at risk of an NMO and a DRP during the use of opioid analgesics is a key factor in guiding the pharmaceutical intervention and any pharmacotherapeutic follow-up service. Finally, pharmaceutical care services contribute to adding value to the pharmaceutical profession but further studies on the newest opioids such as tapentadol are needed to build a robust, translatable evidence base.

## Ethics

The study has been endorsed and classified (code: VER-TAP-2020-02) by the Spanish Agency for Medicines and Health Products; approved by the Ethics Committee for Drug Research (CEIm) of the Hospital Universitario de Canarias (HUC) and authorized by the Pharmacy Regulation Department of the Canary Islands Government.

## Credit authorship contribution statement

**V. Hernández-García:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **C. Rubio-Armendáriz:** Writing -review and editing, Visualization, Supervision, Methodology, Formal analysis, Conceptualization. **D. Alberto-Armas:** Visualization, Investigation, Formal analysis, Conceptualization. **A. Hardisson-de la Torre:** Validation, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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