

Ten-year analgesic utilization patterns and economic implications in Portugal

Nuno Duarte¹  | João Paulo Martins^{2,3}  | Jose-Ángel García-Pedraza^{4,5}  | Marlene Santos^{1,6} 

¹REQUIMTE/LAQV, Escola Superior de Saúde, Instituto Politécnico do Porto, Rua Dr. António Bernardino de Almeida, Porto, Portugal

²Escola Superior de Saúde, Instituto Politécnico do Porto, Rua Dr. António Bernardino de Almeida, Porto, Portugal

³CEAUL – Centro de Estatística e Aplicações, Faculdade de Ciências, Universidade de Lisboa, Portugal

⁴Laboratorio de Farmacología (Departamento de Fisiología y Farmacología), Facultad de Farmacia, Universidad de Salamanca, Salamanca, Spain

⁵Instituto de Investigación Biomédica de Salamanca, Paseo San Vicente 58-182, Salamanca, Spain

⁶Molecular Oncology & Viral Pathology, IPO-Porto Research Center, Portuguese Institute of Oncology, Porto, Portugal

Correspondence

Jose-Ángel García-Pedraza, Laboratorio de Farmacología (Departamento de Fisiología y Farmacología), Facultad de Farmacia, Universidad de Salamanca, Salamanca, Spain.
Email: joseagp@usal.es

Funding information

This work received financial support from FCT/MCTES (UIDP/50006/2020) through national funds.

Abstract

Aims: This study evaluated the 10-year consumption and economic patterns of classical analgesics, adjuvants and opioids in Portugal (2012-2022), and conducted a comparative analysis between Portugal, Spain and Denmark to explore the consumption patterns among these countries for 2022.

Methods: Data on sales and national health service (NHS) costs were obtained from the Portuguese National Authority of Medicines and Health Products. Sales data were converted to defined daily dose (DDD) per 1000 inhabitants per day according to the Anatomical Therapeutic Chemical (ATC) classification/DDD methodology, while comparisons between Spain and Denmark were evaluated with the chi-square test, when appropriate.

Results: The findings reveal that classical analgesics use in Portugal remained stable during the period 2012-2022, with ibuprofen being the most consumed. Adjuvants, specifically gabapentinoids, experienced an 84% increase in use, primarily attributed to pregabalin. Weak opioids, led by tramadol, witnessed a 117% rise in use, while strong opioid use, led by tapentadol, increased by 618%. Portugal presented the lowest overall opioid consumption when compared to Denmark and Spain in 2022. Economic trends indicated a heightened NHS expenditure on analgesics, primarily driven by increased opioid use. Notwithstanding, there was no significant burden on relative expenditure over the 10-year period.

Conclusions: Portugal presented a major increase in both weak and strong opioid prescriptions, aligning with the trends for Spain and Denmark. The development and approval of generic medicines and vigilant market monitoring are imperative strategies for managing the escalated costs resulting from heightened consumption, particularly concerning opioids.

KEYWORDS

analgesic usage patterns, chronic pain management, European drug consumption, healthcare expenditure, opioids

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Author(s). *British Journal of Clinical Pharmacology* published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.

1 | INTRODUCTION

The use of analgesics constitutes one of the most important therapeutic options when treating pain, whether acute or chronic, with a large over-the-counter (OTC) market available. The latest report of drug consumption in Portugal revealed that in 2022 the second most commercialized substance was paracetamol and the combination of tramadol with paracetamol ranked seventh, highlighting its significant utilization.¹ Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) are used in acute nociceptive pain and remain the first recommendation for osteoarthritis (OA) of the knee, hip and/or hand.^{2,3} Despite their popularity and widespread use, these drugs are responsible for a myriad of adverse drug reactions and should be avoided in the elderly and patients with congestive heart failure, reduced kidney function or at risk of developing gastritis and/or peptic ulcers.^{4,5}

As pain intensifies or becomes chronic, patients are prescribed other drugs with analgesic properties. This often includes opioids, which can be subdivided into weak and strong. The analgesic ladder, pioneered by the World Health Organization (WHO) in 1986 as a framework for cancer pain management, remains a fundamental paradigm in the scientific community's approach to pain relief strategies. For moderate pain, weak opioids, including [codeine](#), [hydrocodone](#) and [tramadol](#), are recommended, while strong opioids, including [morphine](#), [oxycodone](#), [tapentadol](#), [fentanyl](#), [buprenorphine](#) and [methadone](#), are recommended for very intense and severe pain.⁶ Although opioids are unquestionably valuable in managing cancer pain,⁷ the benefit provided in non-cancerous chronic pain of different origins is considered small, with increased risk of adverse drug reactions and less pain relief in long periods of treatment due to tolerance development. Furthermore, long-term opioid therapy may result in addiction and physical dependence, with patients continuing to use them only to avoid withdrawal symptoms.⁸ In the United States and Canada the "opioid epidemic" has been identified as a major public health issue, with a reported opioid-related death increase of 345% (by prescription or illicit use) between 2001 and 2016.⁹ The large number of opioid prescriptions, profit-oriented pharmaceutical advertisements, healthcare systems with fewer regulatory access restrictions and medical culture/patient expectations are identified as some of the main driving factors of this phenomenon.¹⁰

Adjuvant analgesics are drugs with other therapeutic indications, such as antiepileptics or antidepressants, that may be considered in combination with previously mentioned therapeutic agents. These are often the first line of treatment in pain of different aetiology, including neuropathic pain.¹¹ Gabapentinoids provide pain relief in post-herpetic neuralgia and diabetic neuropathic pain, albeit being extensively marketed for "off-label" use in other pain conditions, for which only limited evidence exists. [Gabapentin](#) and [pregabalin](#) consumption has been steadily rising in the United States since the start of the century, raising concern about their safety and potential for abuse and misuse.^{12,13} Despite being considered drugs with low abuse potential, increasing adjuvant analgesic co-prescription with opioids has been shown to raise the risk of opioid-related deaths.^{14–16}

What is already known about this subject

- Portugal has one of the highest rates of chronic pain among European countries.
- Opioid consumption in Europe has increased over the last decade, a trend that aligns with broader global patterns of use.
- Health expenditure on medication in Portugal has been rising steadily since 2013.

What this study adds

- Portugal has experienced a significant increase in opioid and gabapentinoid consumption, mirroring trends observed in other European countries.
- Relative analgesic national health service expenditure did not increase over the study period.
- Ongoing market surveillance, pricing strategies, and generic alternatives are key to maintaining rational opioid use and controlling public expenditure.

Drug utilization research is a key instrument for the detection of consumption trends that allows governments and policy makers to remove unsafe medications from the market, update guidelines and ensure their proper implementation in clinical practice. Moreover, when combined with expenditure data, these studies allow countries to decide on how to better allocate financial resources within their national health systems (NHSs), for example in reimbursement policies for different medications.¹⁷ Given that opioid prescription and consumption are on the rise in most European countries and deaths due to opioid overdose alone or combined with other substances are increasing, epidemiological studies are needed to understand and monitor these analgesics.^{18,19}

Portugal has a high rate of chronic pain as a result of several inter-related factors.²⁰ It has one of the largest aging populations in Europe,²¹ which increases the incidence of degenerative disc diseases, arthritis and osteoporosis. Socioeconomic factors such as education level disparities, low income and unemployment levels²⁰ as well as medical school curricula that do not adequately address chronic pain also influence its report and treatment.²² Furthermore, literature describing analgesic consumption trends is scarce, especially in the case of opioids. Considering this, the present study aimed to (i) analyse the consumption trends of analgesics in Portugal between 2012 and 2022, regardless of their intended use (acute, subacute, chronic pain with or without cancerous origin), with emphasis on opioids, (ii) evaluate correlations between strong opioid consumption and annual opioid death rates by overdose, annual cancer death rates and gross domestic product (GDP) annual growth rates, (iii) compare

Portuguese patterns of consumption with Spain and Denmark, and (iv) describe NHS expenditure with analgesic consumption over the defined period.

2 | METHODS

2.1 | Design and data sources

We retrospectively analysed analgesic package sales and associated costs from 2012 to 2022. Drugs of interest were identified using the Anatomical Therapeutic Chemical (ATC) classification. Additionally, the defined daily dose (DDD) proposed by the WHO for each drug in the study was used to determine the DDDs per 1000 inhabitants per day. Drug data were extracted from the National Authority of Medicines and Health Products (INFARMED) database, obtained in September 2023. This database provides detailed reporting on drug sales and costs specifically to community pharmacies, focusing exclusively on prescription medications. It includes information on each drug, encompassing various market presentations and available doses. Annual population was defined as the number of residents in Portugal at each year on 31 December. Estimates of the annual population were extracted from PORDATA – Base de dados de Portugal Contemporâneo.²³

For consumption comparison, drug sales data for Spain and Denmark were chosen with a focus on 2022. Spain was selected for comparison due to its cultural and social similarities with Portugal. Southern European countries are markedly different, culturally and socially, from northern European countries, hence the comparison with Denmark.²⁴ Data on analgesic consumption were obtained online from the Danish Health Data Agency (www.medstat.dk/) and from the National Health System and Pharmacy Authority – Ministry of Health of Spain (<https://www.sanidad.gob.es/areas/farmacia/consumoMedicamentos/home.htm>). Datasets from these countries also contained drug sales from community pharmacies exclusively by prescription (like INFARMED), as well as the calculated DDDs per 1000 inhabitants per day on an aggregated level.

2.2 | Analgesics classification and outcome metrics

The outcomes measured were analgesic consumption and NHS analgesic costs. Analgesic package sales data were used as a proxy for drug consumption. Analysis on an aggregated level was conducted using the following classification of analgesics: (i) classical analgesics, which includes NSAIDs (**ibuprofen**, **naproxen**, **ketoprofen**, **dexibuprofen**, **diclofenac**, **etodolac**, **aceclofenac**, **nimesulide**, **acetylsalicylic acid** and salts, **meloxicam**, **piroxicam**, **lornoxicam**, **acemetacin**, **indomethacin**, **etoricoxib** and **celecoxib**) and **paracetamol** (including fixed dose combinations except with opioids); (ii) antidepressant adjuvants (**amitriptyline**, **clomipramine**, **dosulepin**, **imipramine**,

maprotiline, **trimipramine**, **imipramine**, **venlafaxine**, **duloxetine**); (iii) antiepileptic adjuvants (**gabapentin**, **pregabalin**); (iv) weak opioids (**codeine** in fixed-dose combination with **paracetamol**, **tramadol** in monotherapy and in fixed-dose combination with **paracetamol**); and (v) strong opioids (**morphine**, **oxycodone**, including fixed dose combinations with **naloxone**, **fentanyl**, **hydromorphone** and **tapentadol**). Of note, **buprenorphine** at high doses (0.4 mg) and **methadone** were excluded since these substances are exclusively used to treat opioid dependence.

Data was expressed as DDDs per 1000 inhabitants per day (DDD/1000inhab/day) in accordance with the ATC/DDD methodology. The formula used for calculation was packages sold \times number of units per package \times dosage (in mg) \times 1000/(DDD (in mg) \times population size (last day of each year) \times 365 days).²⁵ According to the WHO, the DDD is “the assumed average maintenance dose per day for a drug used for its main indication in adults”, which is independent of the formulation used, assigned to an ATC code. DDDs were extracted from the WHO ATC/DDD index. For fixed-dose combinations, the DDD of the main active substance was used as stated in WHO guidelines.²⁶

NHS analgesics costs were expressed as the net ingredient cost (NIC) of dispensed analgesics in community pharmacies for all analgesic groups.

2.3 | Statistical analysis

Trends in analgesic consumption were expressed as the percentage of change between 2012 and 2022 for analgesic groups and the most common drugs within the group as appropriate. Simple linear regression was conducted when a linear relation was present. The annual rate of change (slope, m) and the baseline consumption level (intercept, c) estimated from regression models with associated P values were reported to provide a full picture of consumption trends. A qualitative analysis was undertaken when the linear relation was non-significant or assumptions were not met for linear regression (homoscedasticity and normally distributed residuals). Spearman's coefficient correlation was calculated to explore the correlation between annual opioid deaths by overdose, annual cancer death rates and GDP vs strong opioid consumption from 2012 and 2021. Significant correlations ρ were graded as weak ($0.10 < \rho < 0.40$), moderate ($0.50 < \rho < 0.80$) or strong ($\rho > 0.80$).²⁷ A qualitative and quantitative analysis of analgesic consumption between the three countries was performed. Chi-square tests were applied, and multiple comparisons were made using the Bonferroni correction. Cramer's V was used to measure the strength of the association.²⁸ Statistical tests were performed at a significance level of 5%, using IBM SPSS Statistics® 29 software.

Cost trends were expressed as the percentage of change of NIC between 2012 and 2022 for analgesic groups. Additionally, the overall cost burden of analgesics on total NHS medication expenditure was calculated in the defined period.

3 | RESULTS

3.1 | Consumption trends in Portugal

From 2012 until 2022, analgesic consumption in Portugal (measured in DDD/1000inhab/day) increased approximately 32% from 53 to 70. Classical analgesics (NSAIDs and paracetamol) were the most common analgesics dispensed. This remained stable throughout the 10-year period in the range of 37 to 39 DDD/1000inhab/day, except when it dropped to 33 DDD/1000inhab/day in 2020 (a 13% decrease relative to the previous year) during the COVID pandemic, with levels normalizing after this period (Figure 1).

All the analgesic groups displayed an increased consumption consistently over the 10-year period. Regarding pain adjuvants, antidepressant consumption increased almost two-fold from 10.12 to 19.20 DDD/1000inhab/day (90%) and antiepileptic consumption increased

approximately 84% from 3.54 to 6.51 DDD/1000inhab/day. Opioid overall consumption increased markedly on an aggregated level from 2.25 to 6.23 DDD/1000inhab/day (177%). Weak opioid consumption increased more than two-fold from 1.98 to 4.29 DDD/1000inhab/day (117%), while strong opioids registered the biggest increase in consumption from 0.27 to 1.94 DDD/1000inhab/day (618%).

3.2 | Classical analgesics

Qualitative analysis of individual analgesics was conducted for the six drugs in this group with the greatest consumption in the study period. As presented in Figure 2, the most consumed analgesic by DDD/1000inhab/day in 2022 was ibuprofen at 8.81 along with paracetamol at 6.76 and naproxen at 6.16. All of these had similar patterns of use from 2012 to 2022, increasing their consumption. Of note, in 2020 ibuprofen use

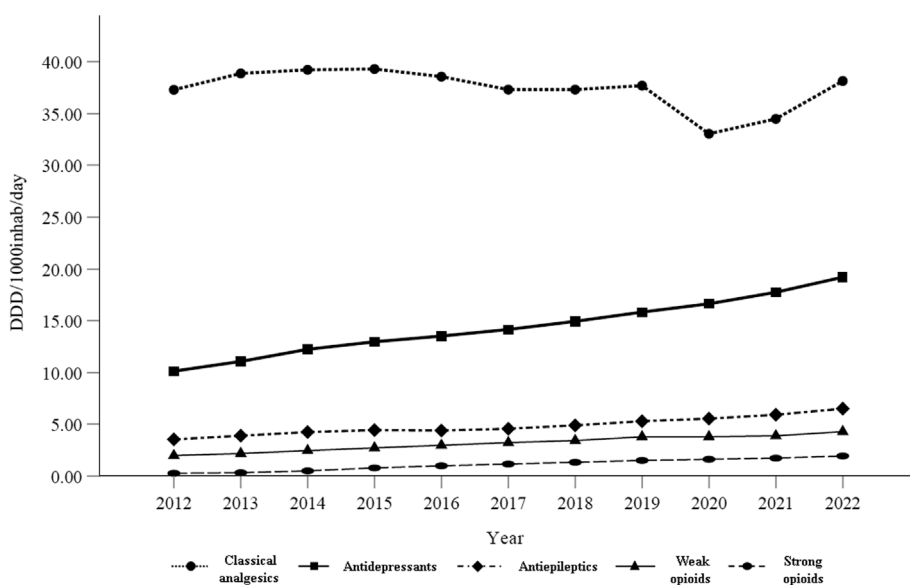


FIGURE 1 Analgesic consumption in Portugal, 2012-2022. DDD, defined daily dose; inhab, inhabitants.

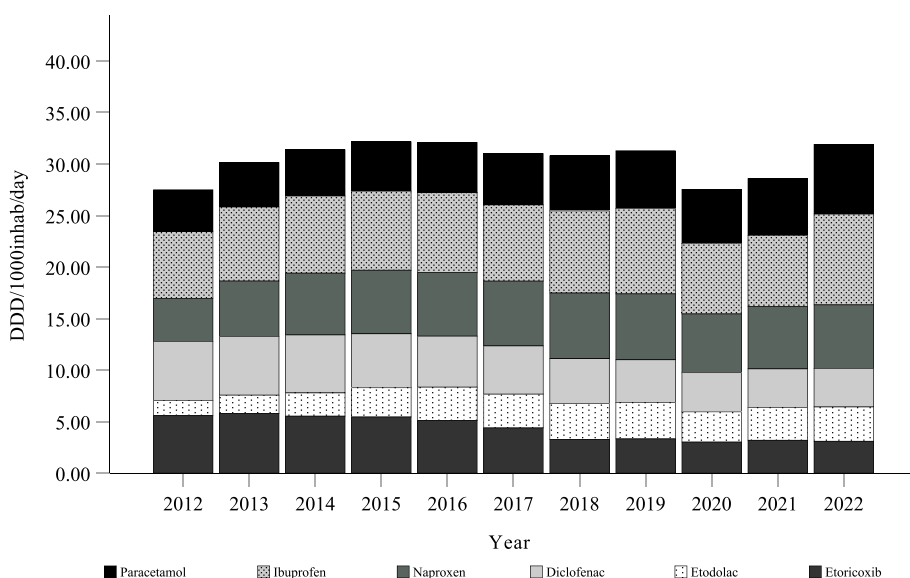


FIGURE 2 Classical analgesics consumption in Portugal, 2012-2022. DDD, defined daily dose; inhab, inhabitants.

decreased 17% and naproxen use dropped 11% while paracetamol use only reduced by 7%, followed by a recovery in 2021 and 2022 for the three substances. Acetic acid derivatives with more sales from 2012 to 2022 had different consumption patterns. Etodolac saw increased consumption of more than two-fold (125%) from 1.48 to 3.33 DDD/1000inhab/day. By contrast, diclofenac consumption decreased from 5.74 to 3.75 DDD/1000inhab/day (–35%). In the case of etoricoxib, a cyclooxygenase 2 (COX-2) selective inhibitor, its consumption dropped approximately 45% from 5.57 to 3.09 DDD/1000inhab/day.

3.3 | Analgesic adjuvants

Antidepressant adjuvant consumption is illustrated in Figure 3. Qualitative assessment was conducted for venlafaxine, amitriptyline and duloxetine. Venlafaxine was the most used antidepressant adjuvant, increasing 110% during the study period, followed by duloxetine, as the second

most consumed. However, duloxetine showed a stronger increase (151%) compared to venlafaxine. Amitriptyline, the only tricyclic antidepressant (TCA) analysed, also saw increased consumption, although to a much lesser extent (46%) than the previously mentioned substances.

In Figure 4 shows data for the consumption of antiepileptic adjuvants. The overall annual rate of consumption of pregabalin increased approximately 89% from 2.57 to 4.85 DDD/1000inhab/day between 2012 and 2022 ($m = 0.20$, $P < 0.001$ and $c = 2.32$). Gabapentin use during the same period also increased 71% ($m = 0.06$, $P < 0.001$ and $c = 0.94$) from 0.97 to 1.66, although this was not as pronounced as for pregabalin.

3.4 | Opioids

Weak opioids significantly increased in consumption between 2012 and 2022, as shown in Figure 5. Tramadol alone and in association with

FIGURE 3 Consumption of antidepressant adjuvants in Portugal, 2012–2022. DDD, defined daily dose; inhab, inhabitants.

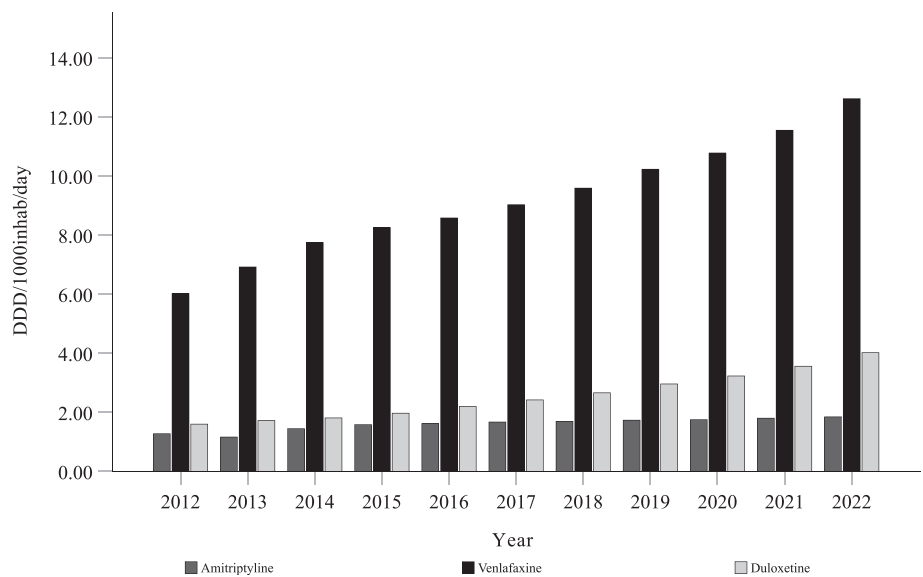
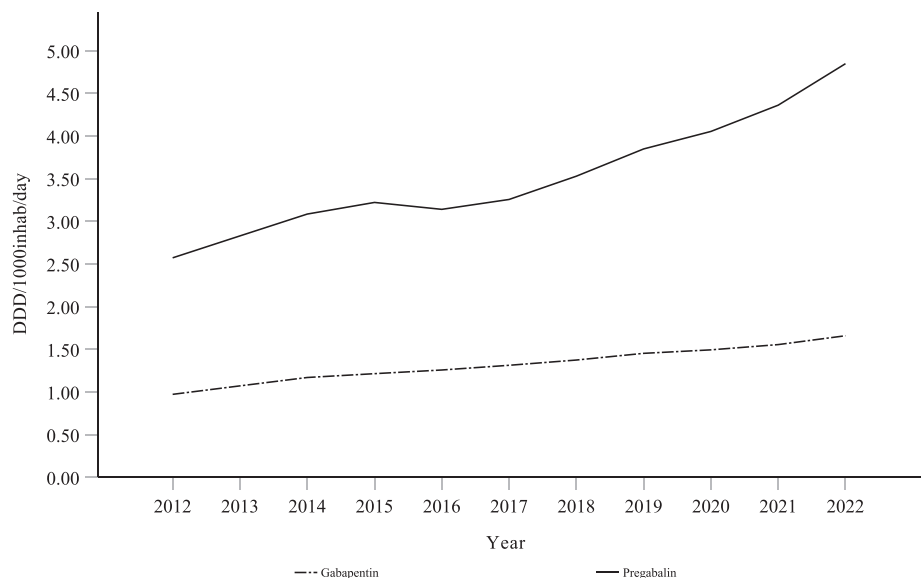


FIGURE 4 Consumption of antiepileptic adjuvants in Portugal, 2012–2022. DDD, defined daily dose; inhab, inhabitants. Linear regression: gabapentin, $P < 0.001$; pregabalin, $P < 0.001$.



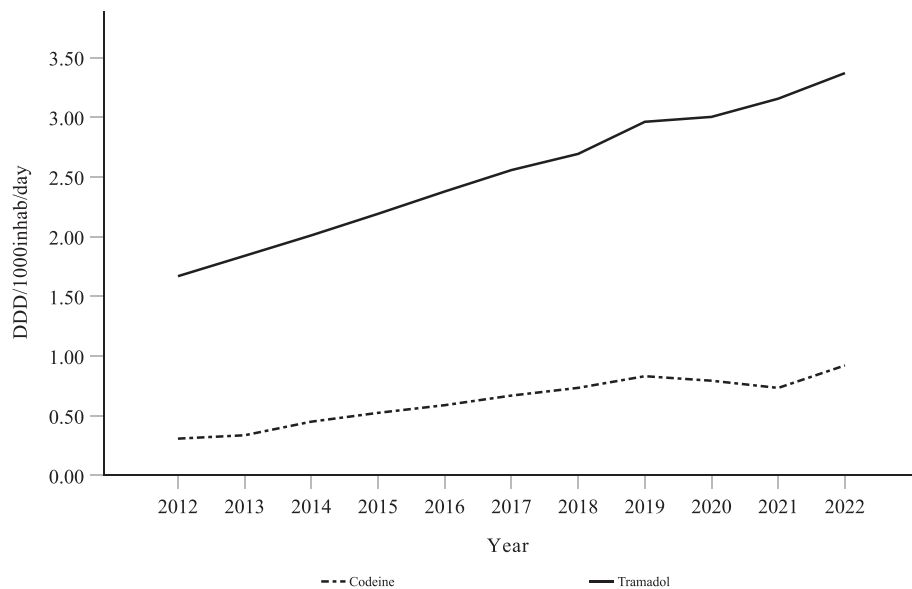


FIGURE 5 Consumption of weak opioids in Portugal, 2012-2022. DDD, defined daily dose; inhab, inhabitants. Linear regression: codeine, $P < 0.001$; tramadol, $P < 0.001$.

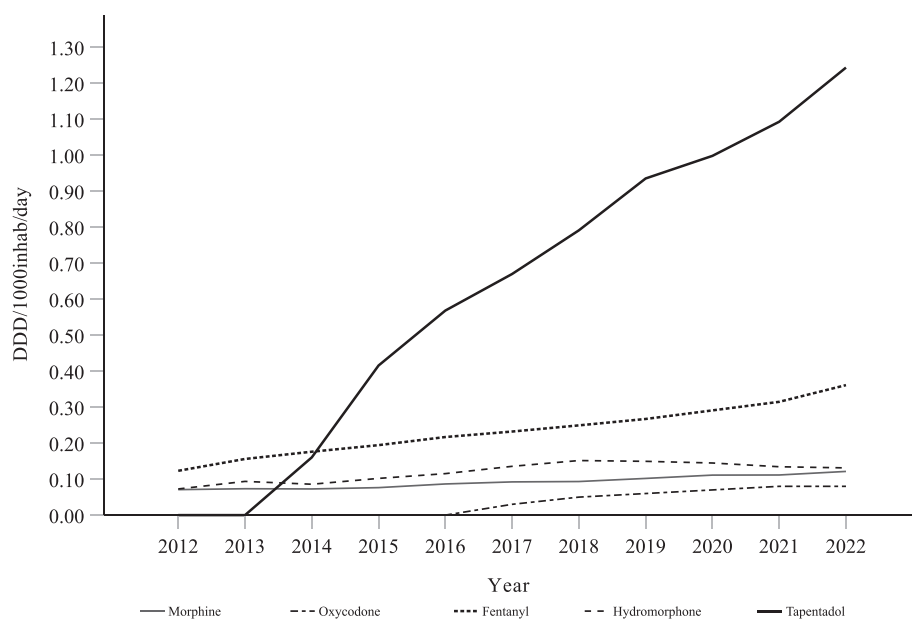


FIGURE 6 Consumption of strong opioids in Portugal, 2012-2022. DDD, defined daily dose; inhab, inhabitants. Linear regression: all opioids, $P < 0.001$. Hydromorphone showed a non-significant downward trend from 2018, $P = 0.056$. Oxycodone did not meet assumptions for linear regression.

other analgesics saw consumption increase two-fold from 1.67 to 3.37 DDD/1000inhab/day ($m = 0.17$, $P < 0.001$ and $c = 1.52$) and it was the most used weak opioid in Portugal during the time period evaluated. Use of codeine in fixed-dose combinations (the only presentation available for pain management in Portugal) increased by 196% from 0.31 to 0.92 DDD/1000inhab/day ($m = 0.059$, $P < 0.001$ and $c = 0.28$), although a slight decrease was visible between 2019 and 2021 (−12%).

The consumption trends for strong opioids are displayed in Figure 6. Tapentadol was the most dispensed strong opioid in Portugal during the evaluated period. It had a dramatic increase in use of 675% in DDD/1000inhab/day from 0.16 in 2013 to 1.24 in 2022 ($m = 0.125$, $P < 0.001$ and $c = -0.16$). Fentanyl was the second most sold substance, with an overall annual rate of change in the study period of 200% ($m = 0.021$, $P < 0.001$ and $c = 0.11$) from 0.12 to 0.36 DDD/1000inhab/day. Morphine, oxycodone and

hydromorphone were the less used opioids in this group during the 10-year study period. Nonetheless, morphine use increased 71% ($m = 0.005$, $P < 0.001$ and $c = 0.06$) from 0.07 to 0.12 DDD/1000inhab/day. Hydromorphone use increased by 114% from 0.07 to 0.15 DDD/1000inhab/day from 2012 ($c = 0.06$) to 2018 ($m = 0.012$, $P < 0.001$) and from 2018 ($c = 14.28$) to 2022 showed a non-significant decrease from 0.15 to 0.13 DDD/1000inhab/day ($m = -0.007$, $P = 0.056$). Oxycodone consumption analysis did not meet the assumptions for the regression model. Oxycodone was introduced in 2009 in the Portuguese market but until 2016 it had no sales presence. From 2017 to 2022 oxycodone use increased 147% (0.032 to 0.078 DDD/1000inhab/day) when considering presentations alone and in fixed-dose combinations with naloxone. Despite this growth, oxycodone remains the least used strong opioid in Portugal.

The bivariate correlation from 2012 to 2021 between strong opioids and annual opioid death rates by overdose, annual cancer death rates and GDP annual growth rates was also examined. Correlations between consumption and annual opioid death rates by overdose ($\rho = 0.82$, $P = 0.03$; **Supporting Information Figure S1**), as well as annual cancer death rates ($\rho = 0.92$, $P < 0.001$; **Supporting Information Figure S2**) were strong. In contrast, a non-significant correlation was found between GDP annual growth rate and strong opioid consumption ($\rho = 0.52$, $P = 0.128$; **Supporting Information Figure S3**).

3.5 | Comparison with Spain and Denmark in 2022

The comparison of analgesic consumption patterns between Portugal, Spain and Denmark in 2022 is displayed in Figure 7. Classical analgesics consumption in Portugal was lower than in the other countries included in the analysis, with a total of approximately 38 DDD/1000inhab/day, which is less than half of the total consumption in Spain (83 DDD/1000inhab/day) and about one-third of

Denmark's consumption (103 DDD/1000inhab/day). Patterns of use and country were moderately associated (Cramer's $V = 0.201$, $P < 0.001$; see Figure 10). Paracetamol consumption share was different between the three countries and was significantly lower in Portugal compared to Spain and Denmark (18%, 46% and 74% of the overall analgesic consumption, respectively, $P < 0.001$). The consumption share of ibuprofen was higher for Portugal when compared to Spain and Denmark (24%, 19% and 19%, respectively, $P < 0.001$). Naproxen consumption share was significantly higher in Portugal and Spain when compared to Denmark (16%, 15% and 2%, respectively, $P < 0.001$). Considering all other analgesics, consumption share was significantly different between any pair of these three countries ($P < 0.001$): it was higher in Portugal (43%), followed by Spain, with approximately 21%, and Denmark consumption was found to be residual (5%).

In Figure 8, opioid consumption is presented for the three countries. There is moderate association between patterns of consumption and country (Cramer's $V = 0.253$, $P < 0.001$). Spain had the highest overall consumption at 21 DDD/1000inhab/day, followed by

FIGURE 7 Consumption of classical analgesics in Portugal, Spain and Denmark, 2022. DDD, defined daily dose; inhab, inhabitants. Pairwise comparison (chi-square test) showed significant differences in consumption share for all classical analgesics ($P < 0.001$) between countries except for naproxen between Portugal and Spain.

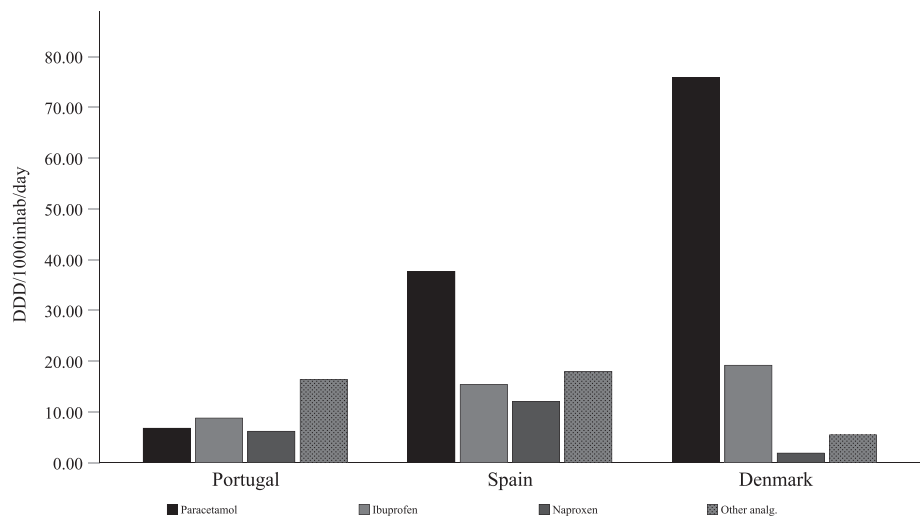
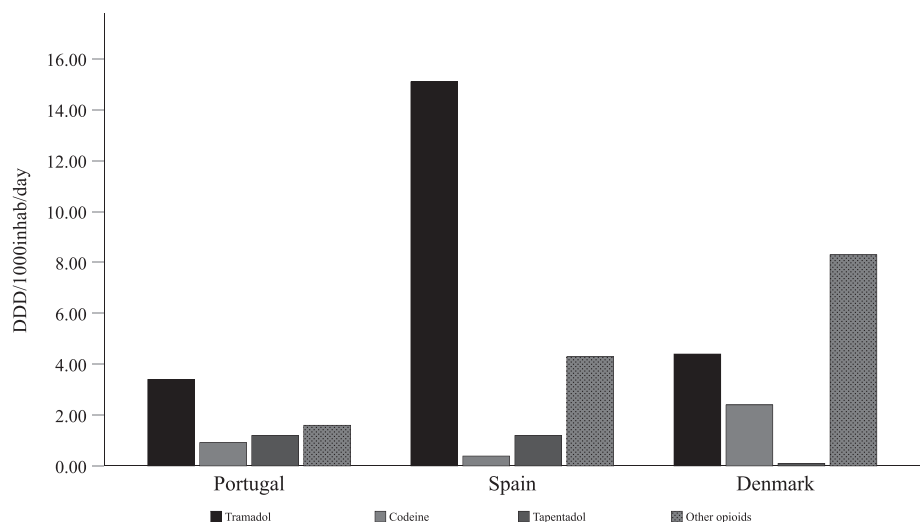


FIGURE 8 Consumption of opioids in Portugal, Spain and Denmark, 2022. DDD, defined daily dose; inhab, inhabitants. Pairwise comparison (chi-square test) showed significant differences in consumption share ($P < 0.001$) for all opioids.



Denmark at nearly 15 DDD/1000inhab/day and Portugal at 7 DDD/1000inhab/day. This value represents almost one-third of the consumption in Spain and half of the consumption in Denmark. Consumption share is different for all opioids between the three countries ($P < 0.001$). Tramadol was the most consumed opioid both in Portugal (47%) and Spain (72%), whereas in Denmark it was ranked second, with a 29% share ($P < 0.001$). Of note, the consumption share for tapentadol was 17% in Portugal, while in Spain it was 6% and in Denmark tapentadol was seldomly used, with a 0.67% share of total opioids ($P < 0.001$). Other strong opioids on an aggregated level had a 55% consumption share in Denmark compared to 23% in Portugal and 20% in Spain ($P < 0.001$). Codeine was the most consumed opioid in Denmark with 16% consumption share, similar to Portugal with 13%, while in Spain it had 2% market share ($P < 0.001$).

3.6 | NHS analgesic cost trends in Portugal

The aggregated cost analysis of analgesics is presented in Figure 9. Total annual costs increased from approximately 68 million euros to 79 million euros (16%) in the study period. Strong opioids were the most expensive analgesics in 2022, whereas in 2012 they were the second least expensive drugs. This represents a remarkable increase of 612% (4.17 to 29.7 million euros). In contrast, classical analgesics and antiepileptic adjuvants, the two most expensive groups in 2012, had the largest decrease in expenditure. Classical analgesics cost reduced from 25.3 to 17.6 million euros (−30%) while antiepileptic adjuvant cost reduced from 26.8 to 15.2 million euros (−43%). Antidepressants had a mild increase in expenditure of 20% (from 8.5 to 10.2 million euros). NHS costs for weak opioids also increased significantly (113%), from 3.2 to 6.8 million euros.

NHS expenditure on medication grew from 1173 million euros in 2012 to 1567 million euros in 2022 (Figure 10). The burden on NHS expenses of all analgesics NIC, ranged from its lowest value of

approximately 5% corresponding to 79 million euros in 2022 to its highest value in 2014, when it reached almost 7% with an identical value of 79 million euros (Figure 10).

4 | DISCUSSION

Analgesic consumption patterns in Portugal reveal a general increase over the 10-year study period. Classical analgesics consumption remained stable throughout the study period, while sales of other analgesics increased, including weak and strong opioids, with the latter having the biggest increase (Figure 1).

4.1 | Classical analgesics

Classical analgesic analysis was conducted for the six substances with the highest consumption. Ibuprofen was the most consumed classical analgesic drug when prescribed in Portugal, followed by paracetamol and naproxen in the 10-year study period (Figure 2). The higher consumption of ibuprofen may be correlated with the lower cost of this medicine and its wider range of applications, while paracetamol is useful for multiple mild to moderate pain conditions because of its antipyretic properties and is considered safer than NSAIDs, despite its liver toxicity.^{29,30} The high consumption of naproxen could be due to its long half-life, as well as perceived cardiovascular safety compared with selective COX-2 inhibitors, when used in long-term treatment, such as in OA and rheumatoid arthritis patients.^{31,32} This may also be the reason why etoricoxib consumption has been decreasing over the years, despite the availability of generic brands since 2015 and recent data reporting the non-inferiority of a COX-2 inhibitor when compared to naproxen³³ and ibuprofen³⁴ in high-risk cardiovascular patients. Etodolac, a rheumatic pain drug, registered significant consumption growth but did not demonstrated superiority compared to

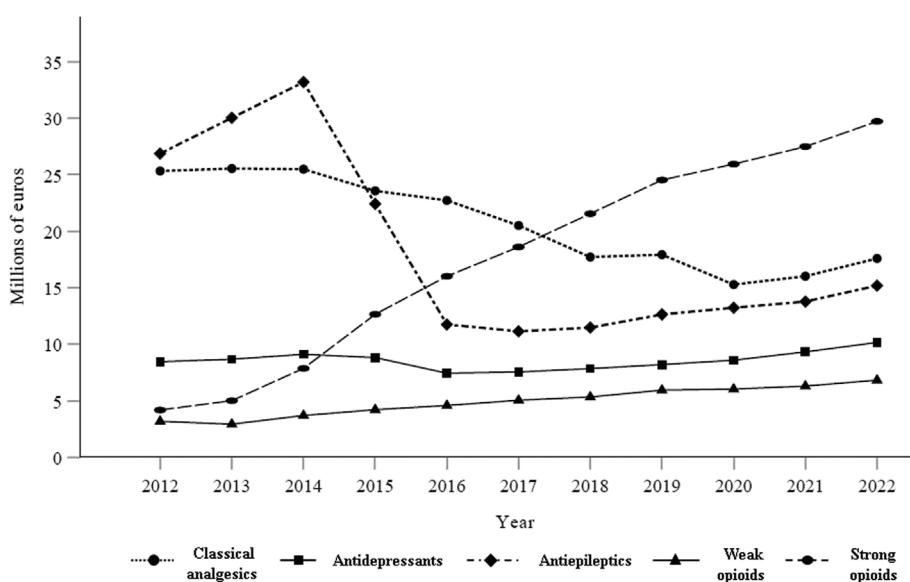
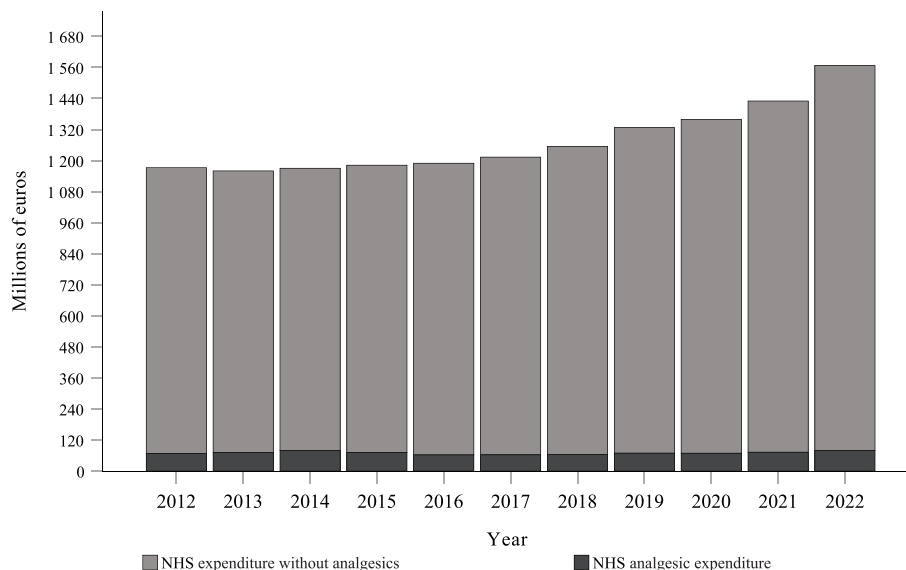


FIGURE 9 Analgesic costs in Portugal, 2012–2022.

FIGURE 10 Analgesic overall cost burden on the Portuguese national health service (NHS) expenditure (2012-2022).



other NSAIDs in this regard. Studies suggest etodolac has fewer gastrointestinal effects and higher tolerability,³⁵⁻³⁷ which may partially explain the increase in consumption. The cardiovascular safety of diclofenac was evaluated in 2013 by the European Medicines Agency (EMA), which concluded that its use has an increased risk of arterial thrombotic events, particularly at high doses and when taken in long-term treatments. Some of the recommendations from the EMA applied to product information amendment and risk minimization regarding cardiovascular risk.³⁸ Diclofenac consumption in Portugal has declined, probably due to the adoption of these regulatory actions, similar to what has happened in other European countries where a reduction in the initiation of diclofenac treatment was observed.³⁹ Interestingly, a sharp decline in classical analgesics consumption occurred in 2020 with a slight recovery in 2021 and back to normal in 2022. This period coincides with the COVID-19 pandemic when strong social restrictions were implemented in many countries, resulting in a global decline in influenza and other virus circulation among populations.⁴⁰ It is reasonable to assume that this decline in analgesic consumption could be linked to the declining virus circulation in the same period, since paracetamol and ibuprofen are heavily used to relieve flu and cold symptoms.⁴⁰ Furthermore, ibuprofen registered the highest decrease, which is most likely related to unsubstantiated concerns of worsening COVID-19 infection symptoms.^{41,42}

4.2 | Adjuvants

Results for adjuvant drugs demonstrated a considerable increase in consumption for both classes (antiepileptics and antidepressants), as seen in Figures 3 and 4. Venlafaxine was the most consumed antidepressant adjuvant and duloxetine registered the highest increment while amitriptyline use also grew, albeit less noticeably. It is noteworthy that these antidepressants, in particular amitriptyline due to its pleiotropic nature, have revolutionized pain management, especially pain of neurogenic origin.⁴³⁻⁴⁵ Many chronic pain conditions have a

neuropathic component, thus explaining the rise of these agents. Regarding antiepileptic adjuvants, pregabalin was the most consumed drug and had the highest enhancement relative to gabapentin, which also showed gradual increased use. Despite being available in the market for longer than pregabalin, gabapentin is not the first choice mostly because of a less favourable kinetic profile.⁴⁶ Of note, pregabalin use peaked in 2015, decreasing from this year to the next and resuming its increase in consumption in subsequent years. This was perhaps due to the availability of generic brands, which were approved for commercialization in 2014 but only gain market share after 2016, since they were not initially approved for neuropathic pain treatment.⁴⁷

Importantly, adjuvants are drugs whose main indication is not pain but are useful in specific clinical situations and can be added to pain treatment in any stage, according to the WHO pain ladder. Amitriptyline as well as other TCAs and gabapentinoids are recommended as first-line agents in chronic pain of neuropathic origin while antidepressants are recommended in some forms of neuropathic pain,^{11,48,49} particularly when it is accompanied by mood and sleep changes.⁵⁰ Nevertheless, it must be stated that reported consumption rates do not distinguish between non-analgesic and analgesic indications of these drugs. Studies conducted in European countries and Canada revealed a similar pattern, where TCAs are used for pain-related disturbances while other antidepressants are mainly used for depression, sleep disorders and anxiety.⁵¹⁻⁵³ In fact, according to the latest Eurobarometer on mental health, only 16% of respondents gave chronic pain as a reason for taking antidepressants.⁵⁴ This means that, most likely, only a fraction of the reported consumption of antidepressants, excluding TCAs, is used for pain relief specifically. Unlike antidepressants, gabapentinoids are more likely to be used in pain conditions since they are also approved to treat neuropathic pain. In addition, these drugs have been extensively used for other pain conditions, with some studies reporting off-label prescriptions of 35% in Sweden⁵⁵ and more than 50% in the United Kingdom.⁵⁶ Concerns about the abuse and misuse of gabapentinoids have been growing,

especially when combined with opioids. Studies report an increased mortality risk by overdose in combination with opioids and increased hospitalization with overuse of gabapentinoids alone.^{57,58} In Portugal, the consumption of gabapentinoids rose consistently over the study period along with opioids, warranting a close monitoring of the trend.

4.3 | Opioids

In the last decade, opioid consumption patterns and trends in Europe have been the focus of several studies due to rising medical use worldwide and concerns of a potential opioid crisis.^{18,59} Portuguese law is very strict concerning opioid commercialization. All opioids, including weaker ones, are prescription-only drugs. Moreover, strong opioids are schedule I and II controlled drugs due to their addictive and dependency potential. These drugs can only be obtained with a special prescription which requires pharmacies to electronically record the identification of both the patient and the individual who fills the prescription. In contrast, schedule III drugs, such as codeine, or schedule IV drugs represent less addictive and abuse potential, only requiring an ordinary prescription.⁶⁰ The most consumed opioid in Portugal was tramadol, followed by tapentadol, surpassing codeine in 2018 as the second most consumed (Figure 5). Another study conducted regionally in Lisbon and the Tagus Valley confirms these results.⁶¹ Tramadol was also the most consumed opioid in France, Ireland, Denmark and Sweden and the second most consumed in Norway, only surpassed by codeine.^{62–65} Despite being perceived as less prone to misuse and abuse, tramadol was identified as the primary opioid in analgesic-related deaths in France in 2018.⁶⁶ Furthermore, in the context of emergency hospital presentations, data from the Euro-DEN plus database showed that tramadol abuse was considered a significant burden on emergency departments, although substantial differences exist between countries.⁶⁷ In addition, “non-intended” use of tramadol, for sexual enhancement, premature ejaculation or simply to relieve stress, depression and headaches, has become a problem in Africa and Middle Eastern countries, despite regulatory actions to control the phenomenon.^{68,69} In Portugal, tramadol does not have the same access policy restrictions as strong opioids because it is a schedule IV classified drug that can be obtained with a normal medical prescription. This might change in the future since the latest review by the WHO Expert Committee on Drug Dependence recommended that tramadol should be used under surveillance. However, these recommendations were not immediately applied because they could limit access of this opioid in many low-income countries.⁷⁰

Tapentadol, first introduced in 2010, had a major surge in consumption between 2013 and 2022, surpassing all the other strong opioids (Figure 6). A substantial body of literature suggests that tapentadol has lower odds of adverse events compared to most active comparators.⁷¹ Moreover, the tapentadol summary of product characteristics (SmPC) and patient information leaflet (PIL) specifically referred to tapentadol as having lower risk of physical and psychological dependence when used as recommended in patients with chronic pain. This could be one of the

reasons why tapentadol consumption increased substantially. In addition, tapentadol is considered a safer and more effective choice in comparison with other strong opioids due to its kinetic profile, dual mechanism of action and low propensity for drug interactions.⁷² Unlike tramadol, which presents a similar dual mechanism of action, tapentadol is more rapidly absorbed, has a shorter half-life and no active metabolites produced by CYP2D6, making it highly predictable and less influenced by genetic polymorphisms. Tapentadol is also often regarded as a safer opioid compared to tramadol due to its lower risk of side effects related to serotonin inhibition reuptake, such as nausea, vomiting and serotonin syndrome.⁷³ Importantly, recent literature suggests that tapentadol may also have a lower potential for dependency and addiction.⁷⁴ These factors could explain shifts in prescribing practices favouring tapentadol over tramadol. The 2011 norm for the treatment of neuropathic pain in adults and elderly was released by the Portuguese General Health Directorate, recommending the use of tapentadol as a third-line choice for patients with peripheral neuropathic pain when the patient is not eligible for tramadol.⁷⁵ The unique characteristics of tapentadol, combined with national recommendations and possibly strong marketing of the drug when launched, may have contributed to the reported consumption. This may soon change, since a 2022 reevaluation by the EMA issued amendments to the SmPC and PIL regarding the potential for abuse and dependence of tapentadol, similar to other strong opioids.⁷⁶

All other opioids increased their consumption, with fentanyl being the second most consumed strong opioid, albeit not comparable to tapentadol. Morphine and hydromorphone use has been increasing as well, but when compared to fentanyl these opioids are minimally used. Fentanyl is used for long-term treatment in cancer and non-cancer chronic pain conditions and is considered safe and effective.⁷⁷ Its usefulness relies on the transdermal delivery system, which maintains constant blood levels for several hours.⁷⁸ The gradual increase in fentanyl consumption was expected since this trend has been seen in other European countries and can constitute a major problem due to its potency and possible abuse and misuse,⁷⁹ which warrants monitoring. Of note, oxycodone appeared on the Portuguese market in 2017 and in 6 years has approached morphine consumption. Despite its increasing consumption, it remains as the least used strong opioid. This could possibly be because there is a general consensus that oxycodone was the main driver of the opioid epidemic in the United States.⁸⁰

Overall, the increased consumption of opioids could influence other conditions. We explored the correlation between opioid consumption and opioid death rates, annual cancer death rates and GDP annual growth rates. These factors are, in the literature, some of the consequences most highly correlated with opioid consumption, and it is known to vary between regions and countries.⁵⁹ Our results show a strong positive correlation between increased opioid consumption and increased opioid death rates by overdose (**Supporting Information Figure S1**), as well as cancer death rates (**Supporting Information Figure S2**). From 2019 to 2021 deaths by opioid overdose seemed to stabilize despite the correlation with increased opioid consumption and the increased use of illegal substances during this period.⁸¹

Rather, this fact maybe linked to policies regarding the illegal drug use and support given to users in Portugal. Abuse of illegal substances such as opioids is not criminalized but managed as a health problem.⁸² Drug users can overcome their addiction with the assistance of health institutions and more recently the availability of drug consumption rooms allows for safe injections, with the support of healthcare professionals and social workers who help combat the stigma surrounding this social problem.⁸³ In the same period, cancer death rates dropped, coinciding with the COVID-19 pandemic. It is well known that social restriction measures during the pandemic negatively affected diagnosis and treatment in healthcare systems, particularly in the case of cancer,⁸⁴⁻⁸⁷ a well-documented event that might be the root of the decline in cancer diagnosis and treatment during the COVID-19 pandemic seen in Portugal. These findings are in line with other studies reporting strong associations between these factors and increased opioid consumption.^{88,89} In contrast, GDP annual growth rates were only moderately associated with increased opioid consumption, as seen in **Supporting Information Figure S3**. Reports from other studies reveal that GDP was a factor for increased consumption even though it had a small contribution to the phenomenon when compared with other social and economic factors, thus explaining our findings.^{90,91} In addition, a major contributing factor was chronic pain prevalence in Portugal which is considerably higher than estimations in Spain and Denmark.⁹² Opioid usefulness is counterbalanced by their safety profile, associated risks and adverse events, but this should not stop its prescription when pain does not respond to other approaches.⁹³ Portugal is considered a low opioid consuming country. To incentivize the safe prescription and rational use of these drugs, national guidelines were released in 2008,⁹⁴ although an update is needed to include the more recent opioids available in the Portuguese market.

4.4 | Comparison with Spain and Denmark in 2022

When considering total analgesic consumption, Portugal had the lowest use of analgesics, followed by Spain and Denmark (approximately 45, 104 and 118 DDD/1000inhab/day, respectively). A higher DDD/1000inhab/day of paracetamol was observed comparing to other analgesics in Denmark relative to other analgesics (Figure 7). This trend was expected since most Nordic countries display higher paracetamol consumptions.⁹⁵ Furthermore, in 2013, legislative change restricted the sales of large package sizes of paracetamol without prescription in Denmark, following major public concerns about overdoses.⁹⁶ This may have prompted higher paracetamol prescription. The difference in paracetamol consumption between Spain and Portugal is difficult to address due to the paucity of drug utilization literature in these countries. In Portugal, many OTC preparations with paracetamol are available and our data only capture prescribed medication. This might explain Portugal's apparent low paracetamol consumption compared with both countries. The consumption of OTC preparations might be lower in Spain, and this may justify the differences in consumption between the two countries. Ibuprofen use is

comparable between Portugal, Spain and Denmark. Portugal and Spain use naproxen in similar proportions, whereas Denmark consumes much less of the drug. The OTC market for analgesics in Denmark is notably strict, with only paracetamol, ibuprofen and acetylsalicylic acid (with combinations) available due to concerns related to toxicity and adverse effects. This restriction influences prescription habits, as Danish physicians tend to have more experience with these drugs, which may lead to a lower prescription rate of alternatives such as naproxen.⁹⁷ Additionally, Denmark also has a lower prevalence of chronic pain compared to Portugal and Spain, reducing the overall demand for a broader range of analgesics.⁹² These factors combined likely contribute to the disparities observed between Denmark and the Iberian countries. The latter clearly have more similarities due to healthcare policy and regulation, but also culture and behaviour towards pain management.

Analysing opioid consumption, Spain ranks first, followed by Denmark and Portugal (21, 15 and 7 DDD/1000inhab/day), as demonstrated in Figure 8. In Spain and Portugal, opioid use is mainly driven by tramadol, a growing and concerning trend in Europe.⁹⁰ Tramadol consumption in Denmark has decreased from 2017 onwards. Awareness from the media about the increasing use of tramadol among Danish teenagers and its addiction potential led to regulatory action by the Danish Medicines Agency.⁹⁸ Since early 2018, tramadol has the same prescription restrictions as other stronger opioids, such as morphine or oxycodone, which has led to a marked decrease in its use.⁹⁹ In comparison, Portugal and Spain increased their tramadol consumption over these years. In Spain, since 2012 government policies have affected the funded by the health system of codeine-containing products, which explains the low use of this drug nowadays, and simultaneously led to the shift to tramadol, a similar drug for pain control.¹⁰⁰ Regarding tapentadol, Portugal has the largest market share of the three European countries by far. In Spain, tapentadol consumption is rapidly increasing, and it was the most prescribed strong opioid between 2019 and 2020.¹⁰¹ In contrast, in Denmark consumption of this drug is negligible, which can be explained by the 2019 Danish guidelines underlining the use of morphine as the first-line opioid for chronic pain management, despite general discouragement of opioid use.¹⁰² This prioritization of morphine combined with the absence of specific mention of tapentadol in the guidelines likely influences prescription habits in Denmark. Danish opioid consumption shares some similarities to that in Spain and Portugal, but a clear distinction must be made relative to strong opioids. Excluding tapentadol, the consumption of strong opioids in Denmark increased markedly and represents now more than half of the total opioid use in the country. Overall, increasing opioid consumption is expected in the three countries due to demographic, social and life-expectancy factors, among others.

Comparisons between the three countries did not include adjunct antidepressants since, as previously mentioned, only a fraction of these drugs are used for pain management. Similarly, the main indication for gabapentinoids is the control of seizures in epilepsy despite it being approved for pain conditions such as neuropathic pain or post-herpetic neuralgia.

4.5 | Cost trends

The analysis of analgesic costs reveals an increased expenditure with all opioids, reflecting the increased consumption of these drugs, as presented in Figure 9. Strong opioids had the most significant rise in expenditure, mainly due to tapentadol. The high consumption of this drug from 2013 onwards and its considerable high price compared to other analgesic drugs, coupled with the fact that generic brands were not available in the market until recently, were the main drivers for the higher expenditure. Additionally, regulatory health policies introduced in 2008 recognized the public health interest of these drugs in the management of chronic cancer pain¹⁰³ and chronic non-cancer pain.¹⁰⁴ This legislation allowed for a greater reimbursement of opioids when prescribed in certain conditions to patients suffering from moderate to severe pain of cancer and non-cancer origin, and consequently higher expenditure with opioids. The increasing expenditure with strong opioids raises other concerns, namely the potential for long-term costs related to opioid adverse effects and dependency. It is well documented that strong opioids can induce constipation, nausea and vomiting, and respiratory depression, among other effects, leading to greater healthcare needs and treatment programs.¹⁰⁵ This is particularly relevant in patients with long-term exposure to opioids,¹⁰⁶ who are at higher risk of dependency and subsequent costs associated with rehabilitation and addiction services. It is therefore important to note that although the direct impact on NHS expenditure over the 10-year period has not been significantly burdensome, the potential for future costs linked to opioid-related complications demands careful consideration.

In the case of adjuvants, antiepileptics were the costliest analgesics at the start of the study period, decreasing drastically from 2014 to 2016, when their use bottomed out. This aligns with the previously mentioned period when generic medicines of pregabalin were made available in the market. Furthermore, Portugal has an established reference pricing system for medicine reimbursement. In the Portuguese model, when generic medicines become available, patients can still opt for the original brand medicine, paying the extra value associated with choosing of a costly medicine.¹⁰⁷ Over time, the model incentivizes patients and prescribers to choose the cheaper generic alternatives, reducing drug expenditure.¹⁰⁸ This reimbursement system and the fact that until 2016 generic medicines of pregabalin could not be prescribed for neuropathic pain, may be responsible for the major drop in costs seen with gabapentinoids. In the case of antidepressants, there was an overall small increase in costs over the 10-year period, despite most of them having cost depreciation. The only drugs with cost increases were amitriptyline and venlafaxine, which are used off-label for pain.

Classical analgesics were the second costliest analgesics despite the gradual decrease in costs of classical analgesics over the study period. Myriad factors could be responsible for this decrease. Generic medicines of many of these analgesics were released into the market over the years, which made them cheaper to acquire and less onerous to the NHS. Prescribing habits also changed, with prescribing of piroxicam, nimesulide and diclofenac dropping due to safety

evaluations.^{38,109,110} Finally, most of these drugs saw a drop in price and very few had price increases (eg, acetaminophen, paracetamol or etodolac), while aggregated consumption remained stable.

Considering total NHS expenditure (Figure 10), analgesics costs increased nominally, albeit they maintained their burden in relative terms in 2022 when compared to 2012. Strong opioids were the main drivers of this higher expenditure, whereas classical analgesics and adjuvants offset the costs. A recent study estimated an opioid cost increase of 222% for Spain between 2010 and 2029 considering only OA patients.¹¹¹ The Portuguese population is one of the oldest populations in Europe, has low fertility rates and has increasing physical disability among older adults.¹¹² Similar to Spain, it is expected that consumption of opioids, particularly strong opioids, will continue to rise due not only to demographic factors like those mentioned, but also increasing prevalence of chronic pain.

4.6 | Limitations and strengths

This study was conducted using sales and costs data from national databases, but some limitations must be addressed when using it. These databases do not capture OTC sales or hospital consumption, only prescribed analgesics sales in outpatients. Also, sales data were used as a proxy for consumed doses. The proportion of the drugs that was in fact used cannot be determined since patients usually do not consume the full package. Another aspect is the use of the ATC/DDD methodology to calculate dose consumption, which may not reflect real doses taken by patients. The DDD is the assumed standard dose for a drug used for its main indication in adults but in many conditions doses must be adjusted to obtain significant pain relief. Moreover, drugs such as antidepressants and antiepileptic adjuvants have DDDs that do not correspond to their off-label use for pain. Finally, we could not ascertain the proportion of adjuvant consumption used for pain management, especially antidepressants, which are used less than antiepileptics for pain relief. One of the strengths of this study was the use of reliable data in primary care from national databases. National data regarding opioid deaths by overdose, annual cancer death rates and GDP annual growth rates were used to explore correlations between these factors and opioid consumption. To our knowledge, this is the first study which presents these correlations and the first to characterize consumption trends in a 10-year study period in Portugal. Considering our results, it would be of great interest to explore the consumption of analgesics in different population groups, stratifying it by factors like age, type of pain presented and mental health status.

5 | CONCLUSION

Analgesic consumption patterns from 2012 to 2022 in Portugal revealed an increased use of all drug classes, apart from classical analgesics, where use remained relatively stable. Opioids registered the biggest increase, with tramadol and tapentadol as the most consumed

drugs. Furthermore, adjuvants also increased, following a tendency seen in many developed countries. High chronic pain prevalence, national guidelines and regulation incentivizing and facilitating the use of opioids, as well as prescribers' willingness to address clinical situations where pain is refractory to classical analgesics probably contributed to this trend. The analgesic preferences in the three countries were most likely related to differences in pain management, prescription policies and national guidelines, but also highlight the different cultural and social backgrounds of the Nordic and Iberian countries.

Strong opioid consumption was, in this study, correlated with opioid overdose deaths. Although other factors can contribute to this outcome, it is still a major point for further exploration. Additionally, strong opioid acquisition constitutes the main reason for increased costs of analgesics in Portugal over the 10-year period under evaluation. It is imperative that policy makers and other stakeholders are aware of this trend to provide closer monitoring of strong opioid consumption. Strategies for reimbursement systems, such as the referencing pricing system, generic medicines development and approval, should continue to be implemented to reduce the expected expenditure increase. Furthermore, studies of drug utilization trends and close monitoring by government authorities could be key in preventing uncontrolled dispensing and spending, and possibility to prevent the associated opioid overdose deaths.

AUTHOR CONTRIBUTIONS

N.D.: Data curation; formal analysis; methodology; writing—original draft; writing—review and editing. J.P.M.: Data curation; formal analysis; writing—review and editing. J.A.G.-P.: Conceptualization; methodology; supervision; writing—original draft; writing—review and editing. M.S.: Conceptualization; formal analysis; funding acquisition; supervision; writing—original draft; writing—review and editing. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

This work received support and help from FCT/MCTES (LA/P/0008/2020 DOI [10.54499/LA/P/0008/2020](https://doi.org/10.54499/LA/P/0008/2020), UIDP/50006/2020 DOI [10.54499/UIDP/50006/2020](https://doi.org/10.54499/UIDP/50006/2020) and UIDB/50006/2020 DOI [10.54499/UIDB/50006/2020](https://doi.org/10.54499/UIDB/50006/2020)).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during the current study are available from the corresponding author upon reasonable request.

ORCID

Nuno Duarte  <https://orcid.org/0000-0002-9690-0374>

João Paulo Martins  <https://orcid.org/0000-0002-0474-1397>

Jose-Ángel García-Pedraza  <https://orcid.org/0000-0002-5252-9470>

Marlene Santos  <https://orcid.org/0000-0001-5020-5942>

REFERENCES

1. INFARMED IP. *Meio Ambulatório*. Monitorização Do Consumo de Medicamentos.; 2022.
2. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the Management of Osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2020;72(2):149-162. doi:[10.1002/acr.24131](https://doi.org/10.1002/acr.24131)
3. *Osteoarthritis in over 16s: diagnosis and management NICE guideline*. 2022. Accessed October 27, 2023. www.nice.org.uk/guidance/ng226
4. Hörl WH. Nonsteroidal anti-inflammatory drugs and the kidney. *Pharmaceuticals*. 2010;3(7):2291-2321. doi:[10.3390/ph3072291](https://doi.org/10.3390/ph3072291)
5. Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 updated AGS beers criteria[®] for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674-694. doi:[10.1111/jgs.15767](https://doi.org/10.1111/jgs.15767)
6. Anekar AA, Hendrix JM, Cascella M. WHO Analgesic Ladder. [Updated 2021 May 18]. In: *StatPearls [internet]*. StatPearls Publishing; 2021. Accessed October 29, 2023. <https://www.ncbi.nlm.nih.gov/books/NBK554435/>
7. Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO clinical practice guidelines. *Ann Oncol*. 2018;29-(Suppl 4):iv166-iv191. doi:[10.1093/annonc/mdy152](https://doi.org/10.1093/annonc/mdy152)
8. Busse JW, Wang L, Kamaledin M, et al. Opioids for chronic noncancer pain. *Jama*. 2018;320(23):2448-2460. doi:[10.1001/jama.2018.18472](https://doi.org/10.1001/jama.2018.18472)
9. Gomes T, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. The burden of opioid-related mortality in the United States. *JAMA Netw Open*. 2018;1(2):e180217. doi:[10.1001/jamanetworkopen.2018.0217](https://doi.org/10.1001/jamanetworkopen.2018.0217)
10. Fischer B, Keates A, Bühringer G, Reimer J, Rehm J. Non-medical use of prescription opioids and prescription opioid-related harms: why so markedly higher in North America compared to the rest of the world? *Addiction*. 2014;109(2):177-181. doi:[10.1111/add.12224](https://doi.org/10.1111/add.12224)
11. Moulin D, Boulanger A, Clark A, et al. Pharmacological Management of Chronic Neuropathic Pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag*. 2014;19(6):328-335. doi:[10.1155/2014/754693](https://doi.org/10.1155/2014/754693)
12. Goodman CW, Brett AS. Gabapentin and pregabalin for pain — is increased prescribing a cause for concern? *N Engl J Med*. 2017;377(5):411-414. doi:[10.1056/NEJMp1704633](https://doi.org/10.1056/NEJMp1704633)
13. Johansen ME. Gabapentinoid use in the United States 2002 through 2015. *JAMA Intern Med*. 2018;178(2):292-294. doi:[10.1001/jamainternmed.2017.7856](https://doi.org/10.1001/jamainternmed.2017.7856)
14. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs*. 2017;77(4):403-426. doi:[10.1007/s40265-017-0700-x](https://doi.org/10.1007/s40265-017-0700-x)
15. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: a population-based nested case-control study. *PLoS Med*. 2017;14(10):e1002396. doi:[10.1371/journal.pmed.1002396](https://doi.org/10.1371/journal.pmed.1002396)
16. Lynn E, Cousins G, Lyons S, Bennett KE. A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland. *Drug Alcohol Depend*. 2020;206:107741. doi:[10.1016/j.drugalcdep.2019.107741](https://doi.org/10.1016/j.drugalcdep.2019.107741)
17. WHO International Working Group for Drug Statistics Methodology. *WHO collaborating Centre for Drug Statistics Methodology, & WHO collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services. Introduction to drug utilization research*. World Health Organization; 2003.
18. Pierce M, van Amsterdam J, Kalkman GA, Schellekens A, van den Brink W. Is Europe facing an opioid crisis like the United States? An analysis of opioid use and related adverse effects in 19 European countries between 2010 and 2018. *Eur Psychiatry*. 2021;64(1):e47. doi:[10.1192/j.eurpsy.2021.2219](https://doi.org/10.1192/j.eurpsy.2021.2219)

19. European monitoring Centre for Drugs and Drug Addiction. *European drug report: trends and developments 2019*. Publications Office of the European Union; 2019.
20. Azevedo LF, Costa-Pereira A, Mendonça L, Dias CC, Castro-Lopes JM. Epidemiology of chronic pain: a population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. *J Pain*. 2012;13(8):773-783. doi:10.1016/j.jpain.2012.05.012
21. European Commission. *Population structure and ageing*; 2024. <https://ec.europa.eu/eurostat/statisticsexplained/>
22. Cristóvão I, Reis-Pina P. Chronic pain education in Portugal: perspectives from medical students and interns. *Acta Med Port*. 2019; 32(5):338-347. doi:10.20344/amp.10773
23. FFMS. *PORDATA - Estatísticas gráficos e indicadores de MP e E. População Residente: Total e Por Sexo*; 2022. Accessed May 9, 2024. www.pordata.pt
24. Börsch-Supan A, Hank K, Jürges H. A new comprehensive and international view on ageing: introducing the "survey of health, ageing and retirement in Europe". *Eur J Ageing*. 2005;2(4):245-253. doi:10.1007/s10433-005-0014-9
25. Hollingworth S, Kairuz T. Measuring medicine use: applying ATC/DDD methodology to real-world data. *Pharmacy*. 2021;9(1):60. doi:10.3390/pharmacy9010060
26. WHO Collaborating Centre for Drug Statistics Methodology. *ATC classification index with DDDs*, 2023. Accessed October 24, 2023. https://www.whocc.no/atc_ddd_index_and_guidelines/atc_ddd_index/
27. Akoglu H. User's guide to correlation coefficients. *Turk J Emerg Med*. 2018;18(3):91-93. doi:10.1016/j.tjem.2018.08.001
28. Dai J, Teng L, Zhao L, Zou H. The combined analgesic effect of pregabalin and morphine in the treatment of pancreatic cancer pain, a retrospective study. *Cancer Med*. 2021;10(5):1738-1744. doi:10.1002/cam4.3779
29. Varrassi G, Pergolizzi JV, Dowling P, et al. Ibuprofen safety at the Golder anniversary: are all NSAIDs the same? A narrative review. *Adv Ther*. 2020;37(1):61-82. doi:10.1007/s12325-019-01144-9
30. Freo U, Ruocco C, Valerio A, Scagnol I, Nisoli E. Paracetamol: a review of guideline recommendations. *J Clin Med*. 2021;10(15):3420. doi:10.3390/jcm10153420
31. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs. *Circulation*. 2007;115(12):1634-1642. doi:10.1161/CIRCULATIONAHA.106.181424
32. Barcella CA, Lamberts M, McGettigan P, et al. Differences in cardiovascular safety with non-steroidal anti-inflammatory drug therapy—a nationwide study in patients with osteoarthritis. *Basic Clin Pharmacol Toxicol*. 2019;124(5):629-641. doi:10.1111/bcpt.13182
33. Chan FKL, Ching JYL, Tse YK, et al. Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial. *Lancet*. 2017;389(10087):2375-2382. doi:10.1016/S0140-6736(17)30981-9
34. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;375(26):2519-2529. doi:10.1056/nejmoa1611593
35. Neustadt DH. Double blind evaluation of the long-term effects of etodolac versus ibuprofen in patients with rheumatoid arthritis. *J Rheumatol Suppl*. 1997;47:17-22.
36. Dore R, Ballard I, Constantine G, McDonald P. Efficacy and safety of etodolac and naproxen in patients with osteoarthritis of the knee: a double-blind, placebo-controlled study. *Clin Ther*. 1995;17(4):656-666. doi:10.1016/0149-2918(95)80042-5
37. Liang TH, Hsu PN. Double-blind, randomised, comparative trial of etodolac SR versus diclofenac in the treatment of osteoarthritis of the knee. *Curr Med Res Opin*. 2003;19(4):336-341. doi:10.1185/030079903125001866
38. European Medicines Agency. *New safety advice for diclofenac—new measures aim to minimise cardiovascular risks*. 2013. Accessed December 19, 2023. https://www.ema.europa.eu/en/documents/referral/diclofenac-article-31-referral-new-safety-advice-diclofenac_en.pdf
39. Morales DR, Morant SV, MacDonald TM, et al. Impact of EMA regulatory label changes on systemic diclofenac initiation, discontinuation, and switching to other pain medicines in Scotland, England, Denmark, and the Netherlands. *Pharmacoepidemiol Drug Saf*. 2020; 29(3):296-305. doi:10.1002/pds.4955
40. Bonacina F, Boëlle PY, Colizza V, Lopez O, Thomas M, Poletto C. Global patterns and drivers of influenza decline during the COVID-19 pandemic. *Int J Infect Dis*. 2023;128:132-139. doi:10.1016/j.ijid.2022.12.042
41. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir*. 2020;8(4):e21. doi:10.1016/S2213
42. Laughery W, Lodhi I, Pennick G, et al. Ibuprofen, other NSAIDs and COVID-19: a narrative review. *Inflammopharmacology*. 2023;31(5):2147-2159. doi:10.1007/s10787-023-01309-7
43. Valverde O, Micó JA, Maldonado R, Mellado M, Gibert-Rahola J. Participation of opioid and monoaminergic mechanisms on the antinociceptive effect induced by tricyclic antidepressants in two behavioural pain tests in mice. *Prog Neuropsychopharmacol Biol Psychiatry*. 1994;16(6):1073-1092. doi:10.1016/0278-5846(94)90132-5
44. Pancrazio JJ, Kamatchi GL, Roscoe AK, Lynch C. Inhibition of neuronal Na⁺ channels by antidepressant drugs. *J Pharmacol Exp Ther*. 1998;284(1):208-214.
45. Tura B, Tura SM. The analgesic effect of tricyclic antidepressants. *Brain Res*. 1990;518(1-2):19-22. doi:10.1016/0006-8993(90)90948-B
46. Joshi I, Taylor CP. Pregabalin action at a model synapse: binding to presynaptic calcium channel α -2 δ subunit reduces neurotransmission in mice. *Eur J Pharmacol*. 2006;553(1-3):82-88. doi:10.1016/j.ejphar.2006.09.019
47. INFARMED IP. *Circular Informativa Conjunta N°2/INFARMED/SPMS de 13/03/2015*; 2015. Accessed December 20, 2023. <https://www.infarmed.pt/documents/15786/1147844/img-313214002-0001.pdf/db7a5940-525d-4789-b1d2-66637a41fb66>
48. Bates D, Schultheis BC, Hanes MC, et al. A comprehensive algorithm for management of neuropathic pain. *Pain Med*. 2019;20(Suppl 1):S2-S12. doi:10.1093/pm/pnz075
49. Centre for Clinical Practice at NICE (UK). *Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings*. National Institute for Health and Care Excellence, (UK); 2013. Accessed November 29, 2023. www.nice.org.uk/guidance/cg173
50. IsHak WW, Wen RY, Naghdechi L, et al. Pain and depression: a systematic review. *Harv Rev Psychiatry*. 2018;26(6):352-363. doi:10.1097/HRP.0000000000000198
51. Patten SB, Esposito E, Carter B. Reasons for antidepressant prescriptions in Canada. *Pharmacoepidemiol Drug Saf*. 2007;16(7):746-752. doi:10.1002/pds.1385
52. Noordam R, Aarts N, Verhamme KM, Sturkenboom MCM, Stricker BH, Visser LE. Prescription and indication trends of antidepressant drugs in the Netherlands between 1996 and 2012: a dynamic population-based study. *Eur J Clin Pharmacol*. 2015;71(3):369-375. doi:10.1007/s00228-014-1803-x
53. Camacho-Arteaga LF, Gardarsdottir H, Ibañez L, et al. Indications related to antidepressant prescribing in the Nivel-PCD database and the SIDIAP database. *J Affect Disord*. 2022;303:131-137. doi:10.1016/j.jad.2022.02.001

54. European Commission. *Special Eurobarometer 345 mental health. Part 1: report.*; 2014. Accessed December 20, 2023. http://data.europa.eu/88u/dataset/S898_73_2_EBS345
55. Wettermark B, Brandt L, Kieler H, Bodén R. Pregabalin is increasingly prescribed for neuropathic pain, generalised anxiety disorder and epilepsy but many patients discontinue treatment. *Int J Clin Pract.* 2014;68(1):104-110. doi:10.1111/ijcp.12182
56. Montastruc F, Loo SY, Renoux C. Trends in first gabapentin and pregabalin prescriptions in primary care in the United Kingdom, 1993-2017. *Jama.* 2018;320(20):2149-2151. doi:10.1001/jama.2018.12358
57. Peckham AM, Fairman KA, Sclar DA. All-cause and drug-related medical events associated with overuse of gabapentin and/or opioid medications: a retrospective cohort analysis of a commercially insured US population. *Drug Saf.* 2018;41(2):213-228. doi:10.1007/s40264-017-0595-1
58. Evoy KE, Sadrameli S, Contreras J, Covvey JR, Peckham AM, Morrison MD. Abuse and misuse of pregabalin and gabapentin: a systematic review update. *Drugs.* 2021;81(1):125-156. doi:10.1007/s40265-020-01432-7
59. Ju C, Wei L, Man KKC, et al. Global, regional, and national trends in opioid analgesic consumption from 2015 to 2019: a longitudinal study. *Lancet Public Health.* 2022;7(4):e335-e346. doi:10.1016/S2468-2667(22)00013-5
60. Decreto lei 15/93, de 22 de Janeiro; regime Jurídico do Tráfico e Consumo de Estupefacientes e Psicotrópicos; 1993.
61. Caldeira D, Broeiro P, Cimadeira F, et al. Opioids prescribing trend between 2013 and 2017 in the Lisbon and Tagus Valley region, Portugal. *Int J Clin Pharmacol.* 2021;43(2):323-327. doi:10.1007/s11096-020-01199-7
62. Daveluy A, Micallef J, Sanchez-Pena P, et al. Ten-year trend of opioid and nonopioid analgesic use in the French adult population. *Br J Clin Pharmacol.* 2021;87(2):555-564. doi:10.1111/bcp.14415
63. Moriarty F, Bennett K, Fahey T. Opioid and analgesic utilization in Ireland in 2000 and 2015: a repeated cross-sectional study. *Pharmacol Res Perspect.* 2022;10(1):e00899. doi:10.1002/prp2.899
64. Nissen SK, Pottgård A, Ryg J. Trends of opioid utilisation in Denmark: a nationwide study. *Drugs Real World Outc.* 2019;6(4):155-164. doi:10.1007/s40801-019-00163-w
65. Muller AE, Clausen T, Sjøgren P, Odsbu I, Skurtveit S. Prescribed opioid analgesic use developments in three Nordic countries, 2006-2017. *Scand J Pain.* 2019;19(2):345-353. doi:10.1515/sjpain-2018-0307
66. Roussin A, Soeiro T, Fouque C, et al. Increase of high-risk tramadol use and harmful consequences in France from 2013 to 2018: evidence from the triangulation of addictovigilance data. *Br J Clin Pharmacol.* 2022;88(8):3789-3802. doi:10.1111/bcp.15323
67. Layne KA, Dargan PI, Dines AM, et al. Acute toxicity related to misuse (nonmedical use) of tramadol: experience of the European drug emergencies network plus. *Br J Clin Pharmacol.* 2021;87(4):1668-1675. doi:10.1111/bcp.14408
68. Salm-Reifferscheidt L. Tramadol: Africa's opioid crisis. *Lancet.* 2018;391(10134):1982-1983. doi:10.1016/S0140-6736(18)31073-0
69. Fawzi MM. Some medicolegal aspects concerning tramadol abuse: the new Middle East youth plague 2010. An Egyptian overview. *Egypt J Forensic Sci.* 2011;1(2):99-102. doi:10.1016/j.ejfs.2011.04.016
70. WHO ECDD. *WHO expert committee on drug dependence forty-first report*; 2019. Accessed December 28, 2023. <https://iris.who.int/bitstream/handle/10665/325073/9789241210270-eng.pdf?sequence=10>
71. Freynhagen R, Elling C, Radic T, et al. Safety of tapentadol compared with other opioids in chronic pain treatment: network meta-analysis of randomized controlled and withdrawal trials. *Curr Med Res Opin.* 2021;37(1):89-100. doi:10.1080/03007995.2020.1832977
72. Zajączkowska R, Przewłocka B, Kocot-Kępska M, Mika J, Leppert W, Wordliczek J. Tapentadol – a representative of a new class of MOR-NRI analgesics. *Pharmacol Rep.* 2018;70(4):812-820. doi:10.1016/j.pharep.2018.01.005
73. Roulet L, Rollason V, Desmeules J, Piguat V. Tapentadol versus tramadol: a narrative and comparative review of their pharmacological, efficacy and safety profiles in adult patients. *Drugs.* 2021;81(11):1257-1272. doi:10.1007/s40265-021-01515-z
74. Barbosa J, Leal S, Pereira FC, Dinis-Oliveira RJ, Faria J. Tramadol and Tapentadol induce conditioned place preference with a differential impact on rewarding memory and incubation of craving. *Pharmaceuticals.* 2023;16(1):86. doi:10.3390/ph16010086
75. *Direção Geral da Saúde. Tratamento Farmacológico Da dor Neuropática no Adulto e Idoso Médicos do Sistema de Saúde*; 2011.
76. European Medicines Agency. *Tapentadol: scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)*; 2022.
77. Mystakidou K, Befon S, Tsilika E, Dardoufas K, Georgaki S, Vlahos L. Use of TTS fentanyl as a single opioid for cancer pain relief: a safety and efficacy clinical trial in patients naive to mild or strong opioids. *Oncology.* 2002;62(1):9-16. doi:10.1159/000048241
78. Skaer TL. Transdermal opioids for cancer pain. *Health Qual Life Outcomes.* 2006;4(1):24. doi:10.1186/1477-7525-4-24
79. Mounteney J, Giraudon I, Denissov G, Griffiths P. Fentanyls: are we missing the signs? Highly potent and on the rise in Europe. *Int J Drug Policy.* 2015;26(7):626-631. doi:10.1016/j.drugpo.2015.04.003
80. Van Zee A. The promotion and marketing of OxyContin: commercial triumph, public health tragedy. *Am J Public Health.* 2009;99(2):221-227. doi:10.2105/AJPH.2007.131714
81. Fernandes S, Sosa-Napolskij M, Lobo G, Silva I. Impact of the COVID-19 pandemic in the Portuguese population: consumption of alcohol, stimulant drinks, illegal substances, and pharmaceuticals. *PLoS ONE.* 2021;16(11):e0260322. doi:10.1371/journal.pone.0260322
82. Rêgo X, Oliveira MJ, Lameira C, Cruz OS. 20 years of Portuguese drug policy - developments, challenges and the quest for human rights. *Subst Abuse Treat Prev Foreign pol.* 2021;16(1):59. doi:10.1186/s13011-021-00394-7
83. Pinto de Oliveiraa A, Gautier D, Nunes P, et al. First year of implementation of a drug consumption room in Lisbon: the client's profile. *Eur J Public Health.* 2020;30(Supplement_5):ckaa166.403. doi:10.1093/eurpub/ckaa166.403
84. Peacock HM, Tambuyzer T, Verdoodt F, et al. Decline and incomplete recovery in cancer diagnoses during the COVID-19 pandemic in Belgium: a year-long, population-level analysis. *ESMO Open.* 2021;6(4):100197. doi:10.1016/j.esmoop.2021.100197
85. Decker KM, Feely A, Bucher O, et al. New cancer diagnoses before and during the COVID-19 pandemic. *JAMA Netw Open.* 2023;6(9):e2332363. doi:10.1001/jamanetworkopen.2023.32363
86. Patt D, Gordan L, Diaz M, et al. Impact of COVID-19 on cancer care: how the pandemic is delaying cancer diagnosis and treatment for American seniors. *JCO Clin Cancer Inform.* 2020;4:1059-1071. doi:10.1200/CCI.20.00134
87. Jacob L, Loosen SH, Kalder M, Luedde T, Roderburg C, Kostev K. Impact of the COVID-19 pandemic on cancer diagnoses in general and specialized practices in Germany. *Cancers (Basel).* 2021;13(3):1-11. doi:10.3390/cancers13030408
88. Bohnert ASB. Association between opioid prescribing patterns and opioid overdose-related deaths. *Jama.* 2011;305(13):1315-1321. doi:10.1001/jama.2011.370
89. Sun M, Lin JA, Chang CL, Wu SY, Zhang J. Association between long-term opioid use and cancer risk in patients with chronic pain: a propensity score-matched cohort study. *Br J Anaesth.* 2022;129(1):84-91. doi:10.1016/j.bja.2022.04.014

90. Jayawardana S, Forman R, Johnston-Webber C, et al. Global consumption of prescription opioid analgesics between 2009-2019: a country-level observational study. *EClinicalMedicine*. 2021;42:101198. doi:10.1016/j.eclinm.2021.101198
91. Liu X, Luo C, Dai H, Fang W. Consumption trends and prescription patterns of opioids from 2011 to 2016: a survey in a Chinese city. *BMJ Open*. 2019;9(3):e021923. doi:10.1136/bmjopen-2018-021923
92. Todd A, McNamara CL, Balaj M, et al. The European epidemic: pain prevalence and socioeconomic inequalities in pain across 19 European countries. *Eur J Pain (United Kingdom)*. 2019;23(8):1425-1436. doi:10.1002/ejp.1409
93. Häuser W, Morlion B, Vowles KE, et al. European* clinical practice recommendations on opioids for chronic noncancer pain – part 1: role of opioids in the management of chronic noncancer pain. *Eur J Pain (United Kingdom)*. 2021;25(5):949-968. doi:10.1002/ejp.1736
94. Direção Geral da Saúde. *Utilização dos Medicamentos Opióides fortes Na dor Crónica Não Oncológica*. Médicos Do Sistema Nacional de Saúde; 2008.
95. Wastesson JW, Martikainen JE, Zoëga H, Schmidt M, Karlstad Ø, Pottegård A. Trends in use of paracetamol in the Nordic countries. *Basic Clin Pharmacol Toxicol*. 2018;123(3):301-307. doi:10.1111/bcpt.13003
96. Morthorst BR, Erlangsen A, Chaine M, et al. Restriction of non-opioid analgesics sold over-the-counter in Denmark: a national study of impact on poisonings. *J Affect Disord*. 2020;268:61-68. doi:10.1016/j.jad.2020.02.043
97. Gaster N, Hallas J, Pottegård A, Friis S, Schmidt M. The validity of danish prescription data to measure use of aspirin and other non-steroidal anti-inflammatory drugs and quantification of bias due to non-prescription drug use. *Clin Epidemiol*. 2021;13:569-579. doi:10.2147/CLEP.S311450
98. Lægemiddelstyrelsen. *Ny udleveringsstatus for visse opioider træder i Kraft den 1*. 2018. Accessed January 22, 2024. <https://laegemiddelstyrelsen.dk/da/nyheder/2017/ny-udleveringsstatus-for-visse-opioider-traeder-i-kraft-den-1-januar-2018/>
99. Sørensen AMS, Rasmussen L, Ernst MT, et al. Use of tramadol and other analgesics following media attention and risk minimization actions from regulators: a Danish nationwide drug utilization study. *Eur J Clin Pharmacol*. 2021;77(4):617-624. doi:10.1007/s00228-020-03016-6
100. Xie J, Strauss VY, Collins GS, et al. Trends of dispensed opioids in Catalonia, Spain, 2007-19: a population-based cohort study of over 5 million individuals. *Front Pharmacol*. 2022;13:912361. doi:10.3389/fphar.2022.912361
101. Regueras Escudero E, Guzmán JL. Prescriptions of opioid medicines in Spain between 2019 and 2020: what medical specialities are prescribing them and in what indications. *Multidiscip Pain J*. 2021;1:5-12.
102. The Danish Health Authority. *Smerteguide*.; 2019. Accessed September 2, 2024. <https://www.sst.dk/-/media/Udgivelser/2019/Smerteguide.ashx>
103. *Despacho 10279/2008 de 11 Março D.R. II Série 69*; 2008.
104. *Despacho 10280/2008 de 11 Março D.R. II Série. 69*; 2008.
105. Shafi S, Collinworth AW, Copeland LA, et al. Association of opioid-related adverse drug events with clinical and cost outcomes among surgical patients in a large integrated health care delivery system. *JAMA Surg*. 2018;153(8):757-763. doi:10.1001/jamasurg.2018.1039
106. Davies E, Phillips CJ, Jones M, Sewell B. Healthcare resource utilisation and cost analysis associated with opioid analgesic use for non-cancer pain: a case-control, retrospective study between 2005 and 2015. *Br J Pain*. 2022;16(2):243-256. doi:10.1177/20494637211045898
107. Portela C. Reference pricing system in Portugal - supply, demand, and the effect of reimbursement level. *Int J Healthc Manag*. 2014;7(2):120-126. doi:10.1179/2047971913Y.0000000062
108. Dylst P, Vulto A, Simoens S. Reference pricing systems in Europe: characteristics and consequences. *GaBI J*. 2012;1(3-4):127-131. doi:10.5639/gabij.2012.0103-4.028
109. European Medicines Agency. *Questions and answers on the review of piroxicam*; 2007. Accessed January 4, 2024. https://www.ema.europa.eu/en/documents/referral/questions-and-answers-review-piroxicam_en.pdf
110. European Medicines Agency. *Questions and answers on the outcome of the review of Nimesulide-containing medicines*; 2009. Accessed January 4, 2024. https://www.ema.europa.eu/en/documents/referral/questions-and-answers-outcome-review-nimesulide-containing-medicines_en.pdf
111. Rejas-Gutierrez J, Sicras-Mainar A, Darbà J. Future projections of opioid use and cost in patients with chronic osteoarthritis pain in Spain. *Ther Adv Musculoskelet Dis*. 2021;13:1759720X211010599. doi:10.1177/1759720X211010599
112. Lopes DG, Mendonça N, Henriques AR, Branco J, Canhão H, Rodrigues AM. Trajectories and determinants of ageing in Portugal: insights from EpiDoC, a nationwide population-based cohort. *BMC Public Health*. 2023;23(1):1564. doi:10.1186/s12889-023-16370-8

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Duarte N, Martins JP, García-Pedraza JA, Santos M. Ten-year analgesic utilization patterns and economic implications in Portugal. *Br J Clin Pharmacol*. 2024;1-16. doi:10.1111/bcp.16333