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Use and misuse of psychoactive medicines: a descriptive cross-sectional study in a densely populated region of Portugal

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ABSTRACT

Introduction: Although psychoactive medicines (PMed) are needed in several psychiatric conditions, their use and misuse bear risks. We aimed at estimating the prevalence of PMed use and misuse.

Methods: Data on all PMed prescribed in 2017 and dispensed in community pharmacies of the Lisbon and Tagus Valley region of Portugal (ARSLVT) were extracted from ARSLVT medicines' dispensing database. For 21 PMed among prescription opioids, benzodiazepines and z-drugs (BZDR), antidepressants (AD) and anticonvulsants (AC), we estimated the number of users of each PMed, and assessed PMed misuse by a set of proxy indicators for studying this practice: chronic use (use of ≥180 DDD during the study period) of PMed intended for short-term treatments, concomitant use of several PMed, in particular if involving long-term (≥ 30 days) opioid analgesic (OA) use, and doctor shopping (patients consulting several physicians in order to have access to a quantity higher than intended by each prescriber). Data were analysed using descriptive statistics and hypothesis testing, and multivariate logistic regression was used to explore potential factors affecting long-term concomitant treatment of chronic OA with other PMed.

Results: PMed use prevalence was 21.7%: 6.6% for OA, 12.7% for benzodiazepines (BZD), 5.3% for AD and 2.8% for AC. BZDR were mainly prescribed in primary care and OA in hospital outpatients. Chronic use of PMed was observed in 25%, especially with sertraline and buprenorphine for opioid use disorder (long-term treatment), and lorazepam (short-term treatment). About 56.6% of OA chronic users were long-term concurrent users with other PMed, mainly BZDR. Risk of abuse was low for BZDR, whilst

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four opioids had meaningful doctor shopping indicators – fentanyl, opioid use disorder buprenorphine, morphine and hydromorphone.
Conclusions: BZD are the main PMed used in ARSLVT, often chronically, especially lorazepam. Prevalence of OA use is low, although with higher risk of misuse than BZDR. Concomitant use of several PMed is frequent.

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Introduction

Psychoactive drugs with therapeutic use – psychoactive medicines (PMed) – play an important role in the treatment and symptomatic relief of many mental health disorders like depression, psychosis, and anxiety, as well as in epilepsy and pain. However, despite their clinical benefits, PMed constitute a unique group of medicinal products given their high risk of misuse. The concept of medicines' misuse varies in the literature (Barrett et al., 2008), namely as non-medical use (consumption of a medication not prescribed, or in a manner not intended by the prescriber [Araújo et al., 2022, 2023; Novak et al., 2016; Smith et al., 2017), abuse (intentional excessive use accompanied by harmful physical or psychological effects [European Medicines Agency, 2017]) and doctor shopping (intentional use of a dose higher than prescribed by seeking multiple clinicians to obtain several prescriptions [Biernikiewicz et al., 2019]). Chronic use of medicines intended for short-term treatments was also considered in our definition of misuse.

Misuse of PMed is a recognised public health problem (Motta-Ochoa et al., 2017; Worley & Thomas, 2014), namely in the United States of America (USA) (Wood & Dargan, 2021), where there is growing concern about the opioid crisis (Friedman & Shover, 2023). In addition to prescription and synthetic illegal opioids, other central-nervous system (CNS) medications like benzodiazepines (BZD) and anticonvulsants (Haukka et al., 2018; Simonsen et al., 2020) are also misused. The United Nations Office on Drugs and Crime has alerted about the increased risk of prescription opioid deaths by polydrug use of opioids and other CNS-acting drugs (Hockenhull et al., 2021; United Nations Office on Drugs and Crime, 2017b). Antidepressants like bupropion (Schifano et al., 2018), venlafaxine (Schifano et al., 2018) and paroxetine, also seem to have relevant withdrawal and dependence potential (Chiappini et al., 2022), although evidence is limited. Clonazepam is frequently detected in fatal poisonings (Haukka et al., 2018), and gabapentinoids – pregabalin and gabapentin – are reported to have significant misuse potential (Hägg et al., 2020).

In Europe, literature on PMed misuse is more limited (Araújo et al., 2022, 2023; Bramness & Person, 2014; Casati et al., 2012; van Amsterdam & van den Brink, 2015) and differences between national guidelines, prescribing

practices, health systems' organisation and availability of PMed hamper its evaluation (Araújo et al., 2023). Data available in Portugal essentially refer to consumption, pointing to high levels of antidepressant and especially BZD use (Conselho Nacional de Saúde 2019; Coordenação Nacional da Estratégia do Medicamento e dos Produtos de Saúde, 2017; INFARMED, 2017, 2020; OECD, 2020, 2023; Faria Vaz et al., 2017a). Recognising this problem, the National Health Plan has included a primary care monitoring indicator to tackle BZD excessive prescribing in the elderly (Administração Central dos Sistemas de Saúde, 2012), in most cases considered inappropriate (2023 American Geriatrics Society Beers Criteria® Update Expert Panel, 2023; O'Mahony et al., 2023) because their harmful consequences are more likely to occur in this age group. Nevertheless, BZD use is frequent also in younger individuals (INFARMED, 2017), including in substance users that may use BZD to self-medicate, for example for anxiety, or to provide relief from opioid withdrawal symptoms or adverse effects from alcohol or cocaine use (EMCDDA, 2023).

Guidelines aiming at reducing prescribing of BZD and therapy duration have been issued (Direção Geral da Saúde, 2015). A study looking at BZD consumption in the Lisbon and Tagus Valley region of Portugal (ARSLVT) (Gomes et al., 2023), has shown a decrease in BZD use between 2013 and 2020, aside with switching to other PMed, like antidepressants and gabapentinoids (pregabalin and gabapentin).

Prescription or reimbursement databases, containing data on prescribed drugs over a period of time allow the assessment of consumption patterns in real-life dispensing conditions. The magnitude of medicines' misuse is generally related to their consumption level (Rossow & Bramness, 2015; Roussin et al., 2016), and some EU studies have addressed the use, misuse and consequences of PMed in the general population (Chenaf et al., 2019; Driot et al., 2019; Haukka et al., 2018; Hedenmalm et al., 2019; Kalkman et al., 2019; Kostnapfel et al., 2022; Pierce et al., 2021; Ponté et al., 2018; Public Health England, 2019; Rossow & Bramness, 2015; Schjerning et al., 2016). However, to our knowledge no such studies exist at national level.

We therefore aimed with this study to characterise the use of 21 PMed prescribed in a densely populated region of Portugal (ARSLVT), and to assess their misuse using several methodologies, contributing to real-world evidence on this topic in our country, important not only at national, but also at EU level given the paucity of published research.

Material and methods

Design, data source and setting

In this descriptive cross-sectional study, reported following the RECORD-PE (REporting of studies Conducted using Observational Routinely collected

health Data statement for pharmacoepidemiology) guidelines (Langan et al., 2018), data were extracted from the information system database of ARSLVT (SIARS). This regional administrative branch of the Portuguese National Health Service covers 3.65 million inhabitants, 37.3% of the total population of Portugal mainland. All reimbursed drugs prescribed in ARSLVT and dispensed in community pharmacies, irrespective of prescription type (public or private) and dispensing location, are registered in SIARS, where information on patients' diagnoses, as well as demographic and administrative data regarding patients and prescribers, is collected.

Inclusion criteria

All patients who were prescribed at least one reimbursed package of any of the 21 medications considered of interest to the study in ARSLVT in 2017, which were dispensed between 1st January 2017 and 30th June 2018, were included. The additional 6-month period in 2018 was added to cover dispensing of renewable prescriptions (validity: 6 months), issued in 2017 but dispensed only in 2018.

Medications studied

All analgesic opioids with sales data in Portugal were included in the analysis. The other PMed studied were defined based on a preliminary analysis of 5-year (2014–2018) nationwide sales data from Health Market Research Portugal on prescription-only reimbursed PMed, together with morbimortality data from the Portuguese Poison Control Centre (CIAV) and from the National Institute of Legal Medicine and Forensic Sciences (INMLCF, I.P.) on reports of poisonings and deaths involving PMed with sales data in Portugal. The PMed with higher sales data and most frequently involved in CIAV and INMLCF reports, were selected for the present study.

All PMed of interest, identified by their International Non-proprietary Name (INN), were classified in therapeutic groups according to the WHO ATC/DDD classification system,[1] version 2022 (WHO Collaborating Centre for Drugs Statistics and Methodology, 2022a). The 21 medications and their therapeutic group are displayed in Table 1.

Variables extracted

For each medicine, the following variables were extracted according to the study protocol submitted to ARSLVT and approved by ARSLVT Ethics Committee: anonymised ID, age, gender and the following International Classification

[1]WHO ATC/DDD Index – Anatomical, Therapeutical and Chemical classification of the WHO Collaborating Centre for Drug Statistics Methodology.

Table 1. Studied PMed and their therapeutic groups.

Therapeutic group	Therapeutic subgroup	ATC code (2022)	Medicine (INN)
Opioid for OUD treatment[a]	–	N07BC01	Buprenorphine
Opioid analgesics (OA)	Strong opioid analgesics[b]	N02AE01	Buprenorphine
		N02AB03	Fentanyl
		N02AA03	Hydromorphone
		N02AA01	Morphine
		N02AA05	Oxycodone
		N02AA55	Oxycodone + naloxone
		N02AX06	Tapentadol
	Weak opioid analgesics[b]	N02AX02	Tramadol
		N02AJ13	Tramadol + Paracetamol
		N02AJ06	Paracetamol + Codeine
Benzodiazepines and related z-drugs (BZDR)	Anxiolytic benzodiazepines (BZD)	N05BA12	Alprazolam
		N05BA08	Bromazepam
		N05BA01	Diazepam
		N05BA18	Ethyl loflazepate
		N05BA06	Lorazepam
	Hypnotics and sedatives – BZD-like or z-drugs	N05CF02	Zolpidem
Anticonvulsants (AC)	–	N03AE01	Clonazepam
		N03AX16	Pregabalin
Antidepressants (AD)	–	N06AB06	Sertraline
		N06AX05	Trazodone

[a]OUD: opioid use disorder. Methadone was excluded because, in Portugal, it is dispensed only in addiction treatment centres and not sold in community pharmacies.
[a]The WHO cancer pain relief guidelines, published in 1986, classify OA in strong (e.g. morphine, buprenorphine, pethidine, methadone, hydromorphone) and weak (e.g. tramadol, codeine).

of Primary Care diagnosis codes (ICPC-2) (World Health Organization, n.d.); all ICPC-2 cancer codes and psychiatric codes P01 and P74 (anxiety), P03 and P76 (depression), P06 (sleep disturbance), P18 (medication abuse) and P19 (illegal drug abuse). Data were cleaned and validated to eliminate possible inconsistencies and to check for missing information. Prescribers' anonymised ID and medical specialty were also collected, along with PMed dispensing dates and quantities – number of packages and defined daily doses (DDD[2]) (WHO Collaboration Centre for Drug Statistics Methodology, 2022b). Considering the analyses to be performed, new variables were created by grouping extracted data: for example, patients were divided in age groups, INN were gathered in therapeutic classes, similar diagnosis codes were grouped (P01 + P74 for anxiety, P03 + P76 for depression), and related prescriber specialties were assembled (e.g. orthopaedics and rheumatology, psychiatry and neurology, surgical specialties).

Data were validated by comparing the global number of packages and DDD dispensed by INN extracted from SIARS, with the corresponding data

[2]DDD – technical unit of measurement of medicine use, defined as the assumed average maintenance dose per day for a medicine used for its main indication in adults. It is assigned by the WHO Collaborating Centre for Drug Statistics Methodology, according to the DDD-ATC methodology.

for the LVT region contained in the national reimbursement database, managed by the National Authority of Medicines and Health Products (INFARMED).

All personal data obtained were anonymised at source, both for patients and prescribers.

Classification of users

Users of each medicine were classified as chronic if they were dispensed at least 180 DDD of the medicine during the study period (T. Kurko et al., 2018; Luijendijk et al., 2008; Lunghi et al., 2020; Mellbye et al., 2016; Schonmann et al., 2018). With the aim of estimating the magnitude of long-term concomitant (LTC) use of OA with other CNS-acting medicines, known to carry increased risk of serious adverse consequences, chronic OA users were further classified, in terms of concomitant use with other therapeutic groups of the study, in non-concomitant users (no overlap in the days using the different medications), short-term concomitant (STC) users (from 1 to 29 consecutive days), and LTC users (for $\geq$30 consecutive days) (Wei et al., 2018). Treatment periods were defined as the interval between the dispensing date and the last day of supply covered by the prescription, assuming a daily dose of one DDD. Users that have multiple episodes of concomitant use were counted as many times in each combination as the number of episodes.

Data analysis

Analysis of consumption

Utilisation was assessed by estimating the prevalence of use of each PMed/therapeutic group based on population data from Statistics Portugal (INE), as well as the number and type of users, number of DDD consumed (DDD/1000 population/day and DDD/user/year, surrogates for point prevalence – therapeutic intensity), both at PMed and therapeutic group levels. Users of more than one of the studied PMed were counted as many times as the number of categories they belong to (e.g. a patient using a BZD and an antidepressant was counted in both groups – BZD and AD).

Analysis of misuse

We assessed misuse by investigating the pattern of use of the PMed included in the study. Concomitant use of several PMed, even if clinically recommended, increases their associated risks. Therefore, concomitant use, defined in our study as the overlapping of at least one day in the prescription periods of two or more PMed, was used as a proxy of misuse.

Chronic use of PMed, that should be avoided in PMed mostly recommended for short-term treatments, such as BZDR, was also considered indicative of misuse.

Another misuse indicator defined in our study was long-term concomitant OA use with other PMed, considering the known harms associated with OA chronic treatment and their potential increase if OA are taken together with other PMed, which is common (Khan et al., 2021).

Estimation of doctor shopping parameters was also used as a proxy for medicines' misuse, assessing the extent and risk of abuse of the studied PMed. Doctor shopping is a practice where patients obtain overlapping prescriptions from different prescribers, ultimately resulting in the access to a daily dose of medication that is higher than intended by each prescriber. The doctor shopping indicator is therefore a measure of the risk of abuse (i.e. excessive use) of a given medicine. Doctor shopping parameters were calculated and analysed according to the methodology described by several authors (Frauger et al., 2011, 2016; Micallef et al., 2015; Ponté et al., 2018; Pradel et al., 2004, 2009, 2010; Soeiro et al., 2023), both at INN and at therapeutic group level. A detailed description of the method, that considers the number of overlaps of prescriptions of a given medicine or therapeutic group issued by different prescribers, is provided in Supplemental Material 1.

For each dispensing of a given medicine/therapeutic group to a given patient, two variables were computed: the Quantity dispensed (Q) and the Doctor Shopping Quantity (DSQ): these were estimated considering the number of prescription periods overlapping at the date of dispensing and removing the proportion of medication obtained by overlapping prescriptions from repeated visits to different prescribers that is considered medically legitimate. Summing up these quantities for all users, the total dispensed Quantity (Q_{tot}) and the total DSQ (DSQ_{tot}) for each PMed and each group were calculated, forming the basis of the Doctor Shopping Indicator (DSI), the proportion of the quantity doctor shopped among the total quantity dispensed of each PMed/therapeutic group, expressed as a percentage ($DSQ_{tot}/Q_{tot}*100$). The DSI, standardising the quantity doctor-shopped according to the use level of the drug, reflects the risk of abuse, while the DSQ_{tot} indicates the extent of the abuse. For the medications and therapeutic groups for which a DSI higher than 1% (empiric threshold derived from previous published studies [Nordmann et al., 2013; Ponté et al., 2018; Rouby et al., 2012]) was found, a correction was performed in order to minimise the background noise of overlapping prescriptions common to all medicines irrespective of their abuse potential. As such, for PMed and therapeutic groups with DSI > 1%, the corrected DSI (DSI_c: DSI minus 1%) and the corrected DSQ ($DSQ_c = Qto_t*DSI_c$) were estimated. Because the quantities

involved in this study are low, results were expressed in DDD/100,000 inhabitants/day, instead of DDD/1000 inhabitants/day (Ponté et al., 2018; Soeiro et al., 2023).

Statistical analysis

Data were analysed using descriptive statistics, summarising discrete variables as absolute and relative frequencies. We analysed continuous variables using measures of central tendency and dispersion. Results were presented for all patients and stratified by INN, therapeutic group and OA subgroup (strong/weak).

Comparisons were made using Chi-square tests for discrete variables or Wilcoxon/Kruskal–Wallis tests for continuous data. We used multivariate logistic regression to assess the chance of STC and LTC use vs. non-concomitant use, and to explore potential factors affecting long-term concomitant treatment of chronic OA users with other PMed, more susceptible to have adverse consequences. OR were computed, adjusted for age, gender, prescription by general practitioner (GP), psychiatrist or neurologist, or presence of a diagnosis of cancer, anxiety, depression, sleep disturbance, medication abuse or drug abuse.

In the doctor shopping method, we used an interruption threshold (IT) of 30 + 7 days (30 days – the validity of most prescriptions in 2017, plus 7 days to account for delayed prescription fills).

All analyses adopted a confidence level $\alpha = 0.05$ and were performed using SAS Enterprise Guide v7.15 (SAS Institute, Cary NC, USA) and R Statistical Software.

Ethics approval

Ethical approval was granted by the Ethics Committee of ARSLVT I (Opinion 9981/CES/2018), following assessment of the study protocol (Proc.100/CES/INV/2017).

Results

Prescribing and dispensing

More than 4.5 million packages of PMed were dispensed in ARSLVT in 2017, of which 49.4% concerned BZDR, and 23.6% OA. An important part of PMed prescribing in ARSLVT is performed in primary care (PC), especially BZDR (lorazepam and zolpidem standing out, both with almost half of dispensed packages prescribed in PC) and the three weak opioids (also approximately half of dispensed packages prescribed in PC), contrasting with strong opioids, mostly prescribed in the hospital outpatient setting (except tapentadol, essentially PC prescribing).

Prevalence of PMed use in ARSLVT was 21.7%, corresponding to 29.0% of female and 13.4% of the ARSLVT male populations. Female predominance – 70.8% of the total 778,772 ARSLVT PMed users – was observed for all PMed included in the study, except for OUD buprenorphine and BZD in young boys (≤14 years). Prevalence of strong OA use was 1.0%, and 6.0% for weak OA, and there were 2.9 times more women using strong OA than men (21,564 vs. 7483 users). Prevalence of any OA use was 6.6% (236,314 users, 71.3% females and 47.3% older than 65 years), 68.9% of the combination tramadol + paracetamol, with 17.4% of all ARSLVT older females (≥65 years) having been dispensed at least one package of this tramadol combination. Almost half (49.3%) of the users of this combination were elderly. Prevalence of BZD use was 12.7%, while AD were used by 5.3% of the ARSLVT population. About 11.5% and 8.0% of ARSLVT older females were alprazolam and sertraline users, respectively.

Looking at consumption expressed in DDD/1000 population/year, the highest PMed consumption in 2017 was of BZD (51.9), especially alprazolam (17.6) and lorazepam (10.3), and of antidepressants (26.6), particularly sertraline (21.2).

Nearly 13.6% of OA users had a neoplastic diagnosis, 25.1% for strong and 13.4% for weak OA users, with a cancer diagnosis present for 38.1% of morphine, 33.3% of fentanyl and 15.2% of tapentadol users. Only 19.0% of patients treated with BZD had been diagnosed with anxiety, and a scarce 15.3% of zolpidem users had a sleeping disorder diagnosis (the only approved therapeutic indication for zolpidem in Portugal), while 37.7% of patients treated with AD had a diagnosis of depression (Tables 2a, 2b, and 2c).

In 2017, 17.6% of PMed prescribers were GP. These were the main prescribers of OUD buprenorphine (41.0% of total OUD buprenorphine prescribers), as well as of OA (20.5% of total OA prescribers) and BZD (17.0% of total BZD prescribers). About 94.3% of oncologists prescribing OA prescribed strong OA, contrasting with dentists for which this proportion was much lower – 5.7%. Only 7.0% of AD prescribers were psychiatrists or neurologists.

Misuse

Chronic PMed use

About 24.5% of users of at least one PMed were chronic, summing up a total of 8455 chronic users of OA (78% of which females), 111,176 of BZD (73% females), 15,978 of the z-drug zolpidem (75% females), 6981 of AC (67% females), and 69,518 of AD (75% females), corresponding to 3.6%, 24.4%, 20.5%, 7.0% and 36.7%, respectively, of total users of each therapeutic group (Table 3).

About 13.1% of strong OA users were chronic, contrasting with only 2.9% of weak opioid users. With the highest proportion of chronic users were AD

Table 2a. Characteristics of psychoactive medicine users, consumption and prescription, by therapeutic group.

Characteristic	Any psychoactive medicine	Analgesic opioids (N02A)			Anxiolytic benzodiazepines (N05B)	Hypnotics and sedatives Z – drugs (N05C)	Anticonvulsants (N03A)	Antidepressants (N06A)	Opioid for OUD treatment (N07B)
		Analgesic opioids	Strong analgesic opioids	Weak analgesic opioids					
Users									
Total number of users	778,772	236,314	34,305	216,022	456,493	78,079	99,583	189,555	2588
Prevalence of use in ARSLVT	21.7%	6.6%	1.0%	6.0%	12.7%	2.2%	2.8%	5.3%	0.1%
Gender									
Male (%)	227 411 (29.2)	67 729 (28.7)	7 483 (21.8)	63 321 (29.3)	125 695 (27.5)	20 528 (26.3)	28 485 (28.6)	47 425 (25.0)	1 786 (69.0)
Female (%)	551 361 (70.8)	168 585 (71.3)	21 564 (62.9)	138 703 (64.2)	330 798 (72.5)	57 551 (73.7)	71 098 (71.4)	142 130 (75.0)	802 (31.0)
Age									
Patient's age, mean (SD), y	61.3 (17.5)	62.6 (17.3)	68.0 (14.8)	62.2 (17.4)	61.7 (17.4)	62.2 (15.9)	61.8 (16.4)	61.7 (17.4)	47.7 (10.5)
0–14	3345	296	21	278	2403	28	202	602	0
15–24	17,254	4716	11	4641	9225	860	1414	4366	16
25–44	112,735	32,408	2297	31,022	62,922	9998	13,398	26,597	929
45–64	243,898	70,943	9522	65,321	143,302	27,132	32,858	59,822	1150
65–84	285,415	93,304	15,899	84,463	171,966	29,190	37,727	70,519	132
≥85	54,410	18,576	3793	16,299	32,791	5098	5907	14,032	17
Patient's age, median (Q1–Q3)	63.0 (49.0–75.0)	65.0 (51.0–76.0)	70.0 (58.0–79.0)	64.0 (50.0–76.0)	64.0 (50.0–75.0)	63.0 (51.0–74.0)	63.0 (50.0–74.0)	64.0 (49.0–75.0)	46.0 (41.0–52.0)
Proportion ≥65 years	43.6%	47.3%	57.4%	46.6%	44.9%	43.9%	43.8%	44.6%	5.8%
Consumption									
Number of packages dispensed	4,559,953	1,077,565	254,184	823,381	1,806,158	446,314	503,339	644,028	82,549
DDD/1,000 population/day	89.2	6.0	1.7	4.3	45.7	6.2	4.3	26.6	0.4
Cancer diagnosis									
Yes (%)	103 683 (13.3)	32 009 (13.5)	8 602 (25.1)	28 980 (13.4)	54 223 (11.9)	9 393 (12.0)	11 446 (11.5)	21 796 (11.5)	125 (4.8)
No	675,089	204,305	25,703	187,042	402,270	68,686	88,107	167,759	2463
Anxiety diagnosis									
Yes (%)	129 322 (16.6)	31 449 (13.3)	4 433 (12.9)	29 008 (13.4)	86 814 (19.0)	14 046 (18.0)	17 622 (17.7)	40 847 (21.5)	302 (11.7)
No	649,450	204,865	29,872	187,014	369,679	64,033	81,961	148,708	2286
Depression diagnosis									

Yes (%)	179 181 (23.0)	45 862 (19.4)	7 443 (21.7)	41 764 (19.3)	110 975 (24.3)	20 950 (26.8)	28 577 (28.7)	71 549 (37.7)	399 (15.4)
No	599,591	190,452	26,862	174,258	345,518	57,129	71,006	118,006	2189
Sleep disturbance diagnosis									
Yes (%)	62573 (8.0)	17503 (7.4)	2780 (8.1)	15 940 (7.4)	35 241 (7.7)	11 941 (15.3)	8 834 (8.9)	21 327 (11.3)	102 (3.9)
No	716,199	218,811	31,525	200,082	421,252	66,138	90,749	168,228	2486
Medication abuse diagnosis									
Yes (%)	1 770 (0.2)	490 (0.2)	93 (0.3)	446 (0.2)	1336 (0.3)	222 (0.3)	273 (0.3)	555 (0.3)	32 (1.2)
No	777,002	235,824	34,212	215,576	455,157	77,857	99,310	189,000	2556
Illicit drug abuse diagnosis									
Yes (%)	4 940 (0.6)	1 096 (0.5)	113 (0.3)	1 035 (0.5)	2 768 (0.6)	383 (0.5)	852 (0.9)	1 291 (0.7)	731 (28.2)
No	773,832	235,218	34,192	214,987	453,725	77,696	98,731	188,264	1857
Prescription									
Total number of prescribers	18,359	13,719	7155	13,400	18,472	11,297	7724	12,070	909
Prescriber's specialty									
Anesthesiology	526	241	107	229	422	160	140	177	21
Surgical specialties	1144	855	361	832	1037	549	502	547	21
Dental medicine, stomatology, orthodontics	1985	1003	57	984	1468	347	296	413	4
General practice	3240	2819	2313	2804	3149	2751	2696	2814	373
Internal medicine	1241	1066	761	1033	1191	887	900	992	57
Non-specialists	3043	2320	1406	2270	2852	1846	1864	1993	174
Oncology	150	140	132	139	147	132	122	123	20
Orthopaedics and rheumatology	605	548	337	545	548	344	406	295	16
Psychiatry and neurology	934	550	262	535	897	701	746	842	103
Other	5381	3095	1174	2987	4976	2804	2342	2943	90
Origin of prescription (number of packages)									
Primary care	2,157,793	535,155	85,711	449,444	894,895	226,347	191,164	301,762	8470
Public hospitals	578,054	278,985	110,584	168,401	3943	48,069	131,691	111,423	3943
Private hospitals	178,326	77,154	16,018	61,136	253	25,315	37,459	37,892	253
Private outpatient care	532,109	138,140	31,773	106,367	8438	115,158	107,309	154,626	8438

Note: OUD – opioid use disorder.

Table 2b. Characteristics of users of opioid psychoactive medicines, consumption and prescription, by INN.

Characteristic	Opioid for OUD treatment	Analgesic opioids									
	Buprenophine (OUD)	Buprenorphine (analgesic)	Fentanyl	Hydromorphone	Morphine	Oxycodone + Naloxone	Oxycodone	Tapentadol	Paracetamol + Codeine	Tramadol	Tramadol + Paracetamol
Users											
Total number of users	2588	4315	7397	2201	4160	1987	185	23,069	30,080	38,678	162,768
Prevalence of use in ARSLVT	0.1%	0.1%	0.2%	0.1%	0.1%	0.1%	0.0%	0.6%	0.8%	1.1%	4.5%
Gender											
Male (%)	1 786 (69.0)	920 (21.3)	1805 (24.4)	510 (23.2)	1 123 (27.0)	477 (24.0)	45 (24.2)	4 834 (21.0)	8 188 (27.2)	12 303 (31.8)	46 624 (28.6)
Female (%)	802 (31.0)	3 395 (78.7)	5 592 (76.6)	1 691 (76.8)	3 037 (73.0)	1 510 (76.0)	140 (75.8)	18 235 (79.0)	21892 (72.8)	26 375 (68.2)	116 144 (71.4)
Age											
Patient's age, mean (SD), y	47.7 (10.5)	72.6 (14.3)	70.1 (14.9)	66.8 (14.4)	66.3 (15.3)	66.7 (14.9)	64.6 (13.3)	66.8 (14.5)	59.3 (18.7)	61.2 (17.5)	63.2 (16.9)
0–14	0	1	10	0	12	1	0	1	51	135	95
15–24	16	13	14	3	13	10	0	62	1191	688	2879
25–44	929	162	274	146	193	146	14	1665	5509	5860	21,219
45–64	1150	698	1310	629	884	554	67	6755	8778	11939	49,081
65–84	132	1840	2551	931	1197	938	76	10,640	10,474	13,919	67,223
≥85	17	719	833	202	282	159	7	2010	1982	2609	12,968
Patient's age, median (Q1–Q3)	46.0 (41.0–52.0)	76.0 (64.0–83.0)	72.0 (60.0–82.0)	68.0 (57.0–78.0)	68.0 (56.0–78.0)	69.0 (57.0–78.0)	65.0 (54.5–76.0)	69.0 (57.0–78.0)	61.0 (45.0–74.0)	63.0 (49.0–75.0)	66.0 (52.0–77.0)
Proportion ≥65 years	5.8%	59.3%	45.7%	51.5%	35.6%	55.2%	44.9%	54.8%	41.4%	42.7%	49.3%
Consumption											
Number of packages dispensed	82,549	17,732	69,396	13,216	25,168	7725	955	119,992	75,108	141,447	606,826
DDD/1,000 population/day	0.4	0.4	0.5	0.1	0.1	0.0	0.0	0.6	0.5	0.9	2.9
		#REF!	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!			
Cancer diagnosis											
Yes (%)	125 (4.8)	1 009 (23.4)	2 462 (33.3)	507 (23.0)	1 583 (38.0)	313 (15.7)	44 (23.7)	3 504 (15.2)	3 109 (10.3)	5 411 (14.0)	20 460 (12.6)
No	2463	3306	4935	1694	2577	1674	141	19,565	26,971	33,267	142,308
Anxiety diagnosis											
Yes (%)	302 (11.7)	485 (11.2)	689 (9.3)	202 (9.2)	368 (8.8)	173 (8.7)	26 (14.1)	3 373 (14.6)	4 001 (13.3)	4 983 (12.9)	22 410 (13,8)
No	2286	3830	6708	1999	3792	1814	159	19,696	26,079	33,695	140,358

Depression diagnosis											
Yes (%)	399 (15.4)	873 (20.2)	1 181 (16.0)	381 (17.3)	639 (15.4)	264 (13.3)	43 (23.2)	5 560 (24.1)	5 811 (19.3)	7 601 (19.7)	32 162 (19.8)
No	2189	3442	6216	1820	3521	1723	142	17,509	24,269	31,077	130,606
Sleep disturbance diagnosis											
Yes (%)	102 (3.9)	333 (7.7)	454 (6.1)	124 (5.6)	239 (5.7)	121 (6.1)	14 (7.6)	2 073 (9.0)	2 035 (6.8)	2 872 (7.4)	12 405 (7.6)
No	2486	3982	6943	2077	3921	1866	171	20,996	28,045	35,806	150,363
Medication abuse diagnosis											
Yes (%)	32 (1.2)	15 (0.3)	22 (0.3)	7 (0.3)	14 (0.3)	3 (0.2)	0 (0.0)	58 (0.3)	55 (0.2)	126 (0.3)	312 (0.2)
No	2556	4300	7375	2194	4146	1984	185	23,011	30,025	38,552	162,456
Illicit drug abuse diagnosis											
Yes (%)	731 (28.2)	15 (0.3)	34 (0.5)	5 (0.2)	18 (0.4)	0 (0.0)	3 (1.6)	65 (0.3)	126 (0.4)	322 (0.8)	662 (0.4)
No	1857	4300	7363	2196	4142	1987	182	23,004	29,954	38,356	162,106
Prescription											
Total number of prescribers	909	2293	3670	1057	1822	809	121	5458	5946	8781	11,271
Prescriber's specialty											
Anesthesiology	21	57	74	56	54	52	24	89	78	130	177
Surgical specialties	21	77	209	21	78	19	1	190	211	576	676
Dental medicine, stomatology, orthodontics	4	6	20	4	7	3	0	37	531	227	492
General practice	373	951	1185	464	609	357	38	2106	2094	2434	2716
Internal medicine	57	271	484	75	268	51	11	505	309	791	940
Non-specialists	174	401	703	187	330	134	14	1017	932	1646	2009
Oncology	20	82	125	52	121	40	3	108	54	126	128
Orthopaedics and rheumatology	16	64	79	29	22	39	11	311	302	399	526
Psychiatry and neurology	103	46	108	18	44	20	0	204	194	316	437
Other	90	290	567	126	234	73	10	719	839	1672	2455
Origin of prescription (number of packages)											
Primary care	8470	5580	13,018	3695	4246	2630	136	56,406	34,950	68,530	345,964
Public hospitals	3943	7913	39,793	7626	17,238	3372	639	34,003	15,543	40,592	112,266
Private hospitals	253	1132	4305	503	1408	694	45	7931	6231	9735	45,170
Private outpatient care	8438	2023	9105	1034	1848	771	92	16,900	15,409	16,208	74,750

Note: OUD – opioid use disorder.

Table 2c. Characteristics of users of non-opioid psychoactive medicines, consumption and prescription, by INN.

	Hypnotics and sedatives Z-drugs (N05C)	Anxiolytic benzodiazepines					Anticonvulsants		Antidepressants	
Characteristic	Zolpidem	Alprazolam	Bromazepam	Diazepam	Ethyl loflazepate	Lorazepam	Clonazepam	Pregabaline	Sertraline	Trazodone
Users										
Total number of users	78,079	163,161	80,296	121,223	78,988	72,002	39,964	63,252	108,320	97,568
Prevalence of use in ARSLVT	2.2%	4.5%	2.2%	3.4%	2.2%	2.0%	1.1%	1.8%	3.0%	2.7%
Gender										
Male (%)	20 528 (26.3)	57 551 (35.3)	20 240 (25.2)	36 942 (30.5)	20 123 (25.5)	19 424 (27.0)	12 272 (30.7)	17 140 (27.1)	26 762 (24.7)	24 374 (25.0)
Female (%)	57 551 (73.7)	120 341 (73.8)	60 056 (74.8)	84 281 (69.5)	58 865 (74.5)	52 578 (73.0)	27 692 (69.3)	46 112 (72.9)	81 558 (75.3)	73 194 (75.0)
Age										
Patient's age, mean (SD), y	62.2 (15.9)	62.2 (16.4)	67.1 (15.1)	57.5 (18.3)	55.0 (16.9)	69.1 (15.4)	60.4 (17.3)	62.6 (15.7)	61.6 (18.6)	61.8 (15.9)
0-14	28	128	36	2,079	140	57	168	35	551	63
15-24	860	2,586	681	3,165	3,272	575	782	677	3,471	1,161
25-44	9,998	21,200	6,078	21,966	17,561	4,404	6,174	7,705	16,160	12,771
45-64	27,132	53,853	21,353	41,503	29,792	16,796	12,706	21,484	30,038	35,043
65-84	29,190	62,347	38,634	38,507	21,458	33,509	13,895	25,171	41,354	35,505
≥85	5,098	11,046	7,779	5,606	2,197	10,063	2,377	3,726	8,844	6,310
Patient's age, median (Q1–Q3)	63.0 (51.0-74.0)	64.0 (51.0-75.0)	69.0 (58.0-78.0)	59.0 (45.0-71.0)	55.0 (43.0-68.0)	72.0 (60.0-81.0)	62.0 (48.0-74.0)	64.0 (52.0-75.0)	64.0 (48.0-77.0)	63.0 (51.0-74.0)
Proportion ≥65 years	43.9%	45.0%	57.8%	36.4%	29.9%	60.5%	40.7%	45.7%	46.3%	42.9%
Consumption										
Number of packages dispensed	446,314	634,890	314,859	327,298	151,592	377,519	228,065	275,274	370,431	273,597
DDD/1,000 population/day	6.2	17.6	3.5	8.1	6.3	10.3	0.9	3.4	21.2	5.4
Cancer diagnosis										
Yes (%)	9 393 (12.0)	19 608 (12.0)	10 219 (12.7)	11 810 (9.7)	7 026 (8.9)	9 619 (13.4)	4 015 (10.0)	7 727 (12.2)	11 975 (11.1)	10 849 (11.1)
No	68,686	143,553	70,077	109,413	71,962	62,383	35,949	55,525	96,345	86,719

Anxiety diagnosis										
Yes (%)	14 046 (18.0)	35 339 (21.7)	14 059 (17.5)	21 368 (17.6)	19 312 (24.4)	11 717 (16.3)	7 512 (18.8)	10 944 (17.3)	23 945 (22.1)	21 045 (21.6)
No	64,033	127,822	66,237	99,855	59,676	60,285	32,452	52,308	84,375	76,523
Depression diagnosis										
Yes (%)	20 950 (26.8)	44 579 (27.3)	18 469 (23.0)	28 089 (23.2)	21 965 (27.8)	17 483 (24.3)	12 619 (31.6)	17 457 (27.6)	41 824 (38.6)	37 353 (38.3)
No	57,129	118,582	61,827	93,134	57,023	54,519	27,345	45,795	66,496	60,215
Sleep disturbance diagnosis										
Yes (%)	11 941 (15.3)	12 945 (7.9)	5 917 (7.4)	8 548 (7.1)	5 825 (7.4)	7 637 (10.6)	3 938 (9.9)	5 308 (8.4)	9 067 (8.4)	14 467 (14.8)
No	66,138	150,216	74,379	112,675	73,163	64,365	36,026	57,944	99,253	83,101
Medication abuse diagnosis										
Yes (%)	222 (0.3)	453 (0.3)	293 (0.4)	346 (0.3)	162 (0.2)	387 (0.5)	123 (0.3)	164 (0.3)	301 (0.3)	318 (0.3)
No	77,857	162,708	80,003	120,877	78,826	71,615	39,841	63,088	108,019	97,250
Illicit drug abuse diagnosis										
Yes (%)	383 (0.5)	889 (0.5)	304 (0.4)	1 119 (0.9)	427 (0.5)	473 (0.7)	471 (1.2)	412 (0.7)	701 (0.6)	730 (0.7)
No	77,696	162,272	79,992	120,104	78,561	71,529	39,493	62,840	107,619	96,838
Prescription										
Total number of prescribers	11,297	13,983	11,622	13,135	9,872	11,637	7,724	9,125	10,399	9,504
Prescriber's specialty										
Anesthesiology	160	251	164	186	110	164	63	125	132	101
Surgical specialties	549	702	583	679	378	635	259	410	425	347
Dental medicine, stomatology, orthodontics	347	776	436	594	346	376	171	164	276	200
General practice	2,751	2,925	2,761	2,814	2,702	2,747	2,490	2,589	2,727	2,679
Internal medicine	887	1,055	876	988	755	959	629	808	915	826
Non-specialists	1,846	2,193	1,770	2,243	1,583	1,905	1,318	1,652	1,768	1,596
Oncology	132	138	127	119	102	134	77	110	106	99
Orthopaedics and rheumatology	344	400	336	431	232	383	179	372	228	221
Psychiatry and neurology	701	805	687	761	719	737	684	675	805	771
Other	2,804	3,568	2,982	3,296	2,163	2,889	1,483	1,778	2,362	2,047

(*Continued*)

Table 2c. Continued.

Characteristic	Hypnotics and sedatives Z-drugs (N05C)	Anxiolytic benzodiazepines					Anticonvulsants		Antidepressants	
	Zolpidem	Alprazolam	Bromazepam	Diazepam	Ethyl loflazepate	Lorazepam	Clonazepam	Pregabaline	Sertraline	Trazodone
Origin of prescription (number of packages)										
Primary care	226,347	329,749	157,080	144,690	70,029	193,347	76,294	114,870	172,924	128,838
Public hospitals	48,069	70,929	30,629	64,432	16,875	51,061	61,962	69,729	65,860	45,563
Private hospitals	25,315	32,445	18,975	19,879	12,253	15,914	17,197	20,262	21,872	16,020
Private outpatient care	115,158	163,631	87,462	76,781	44,276	90,408	54,529	52,780	88,140	66,486

Table 3. High-dose PMed use and demographics of chronic users.

Characteristic	Any psychoactive medicine	Analgesic opioids (N02A)			Anxiolytic benzodiazepines (N05B)	Hypnotics and sedatives – Z drugs (N05C)	Anticonvulsants (N03A)	Antidepressants (N06A)	Opioid for OUD treatment
		Analgesic opioids	Strong analgesic opioids	Weak analgesic opioids		Zolpidem			Buprenophine (OUD)
Chronic users	190,455	8455	4503	6316	111,176	15,978	6981	69,518	925
Total users	778,772	236,314	34,305	216,022	456,493	78,079	99,583	189,555	2588
% of users that are chronic	24.5%	3.6%	13.1%	2.9%	24.4%	20.5%	7.0%	36.7%	35.7%
Prevalence of chronic users	5.3%	0.2%	0.1%	0.2%	3.1%	0.4%	0.2%	1.9%	0.0%
Gender									
Male chronic users	50,802	1855	1065	1333	29,657	3937	2280	17,320	755
Female chronic users	139,653	6600	3438	4983	81,519	12,041	4701	52,198	170
% of female chronic users	73%	78%	76%	79%	73%	75%	67%	75%	18%
Age									
Chronic users' age, mean (SD), y	65.1 (15.7)	69.7 (13.9)	69.2 (14.1)	69.8 (13.7)	65.4 (14.7)	67.7 (14.0)	61.9 (14.9)	64.1 (17.3)	46.0 (8.0)
0–14 (n)	215	1	1	1	30	0	3	186	0
15–24 (n)	1992	7	2	6	519	32	54	1495	4
25–44 (n)	18,386	396	213	308	9510	950	891	8274	395
45–64 (n)	59,651	2208	1231	1617	37,091	4980	2648	19,969	467
65–84 (n)	85,086	4212	2062	3304	50,345	7860	2856	29,888	16
≥85 (n)	17,101	1102	565	810	9302	1707	314	6556	0
Patient's age, median (IQR)	67 (55.0–77.0)	72.0 (60.0–80.0)	71.0 (59.0–80.0)	72.0 (61.0–80.0)	67.0 (55.0–76.0)	69.0 (58.0–78.0)	63.0 (51.0–73.0)	67.0 (53.0–78.0)	45.0 (41.0–51.0)

(*Continued*)

Analgesic opioids (N02A)									
Buprenorphine (analgesic)	Fentanyl	Hydromorphone	Morphine	Oxycodone + Naloxone	Oxycodone	Tapentadol	Paracetamol + Codeine	Tramadol	Tramadol + Paracetamol
807	1096	251	128	13	5	794	519	1498	2350
4315	7397	2201	4160	1987	185	23,069	30,080	38,678	162,768
18.7%	14.8%	11.4%	3.1%	0.7%	2.7%	3.4%	1.7%	3.9%	1.4%
0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
167	335	56	57	5	3	158	93	333	445
640	761	195	71	8	2	636	426	1165	1905
79%	69%	78%	55%	62%	40%	80%	82%	78%	81%
73.6 (13.4)	68.6 (14.9)	61.3 (17.5)	61.2 (13.7)	61.3 (17.5)	64.0 (16.1)	67.1 (13.3)	69.3 (14.6)	67.9 (13.6)	71.5 (13.6)
1	0	0	0	0	0	0	0	0	0
0	1	0	0	0	0	0	0	1	4
24	59	0	9	0	0	38	40	91	99
159	284	0	55	0	2	281	117	466	525
405	425	0	37	0	2	375	283	762	1278
157	138	0	5	0	0	74	61	144	383
77.0 (65.0–83.0)	70.0 (57.0–81.0)	66.0 (56.0–76.0)	61.0 (51.0–71.0)	61.0 (53.0–73.0)	62.5 (51.5–76.5)	68.0 (57.0–77.0)	73.0 (60.0–80.0)	70.0 (58.0–78.0)	74.0 (63.0–82.0)

Notes: PMed – psychoactive medicine; OUD – opioid use disorder.

(36.7%), followed by OUD buprenorphine (35.7%) and by anxiolytics (24.4%). At medicine level, 56.2% of sertraline, 38.8% of lorazepam (67.4% of which older than 65y), 35.7% of OUD buprenorphine and 27.5% of alprazolam (52.4% of which elderly) users were chronic. Significant differences were found between age of chronic and non-chronic users for all PMed, except for diazepam, morphine, oxycodone and oxycodone + naloxone, with the highest differences observed for OUD buprenorphine (mean age chronic users 46.0y, SD = 8.0; non-chronic users 61.3, SD = 17.5) and clonazepam (mean age chronic users 49.8y, SD = 13.2; non-chronic users 61.3, SD = 17.5). The oldest PMed chronic users were pain buprenorphine (mean 73.6y, SD = 13.4), tramadol + paracetamol (71.5y, SD = 13.6) and lorazepam (70.6y, SD = 13.7) users.

Concomitant use of two or more PMed

About 34.6% of ARSLVT PMed users were concomitant users of two or more PMed (Table 4). BZDR were frequently consumed in association with other therapeutic groups: in a rate of 2558 users/100,000 ARSLVT inhabitants combined with AD, and in 2310 users/100,000 ARSLVT inhabitants, the concomitant use was with OA (in both cases, other PMed therapeutic groups could also be present). Almost half (48.5%, N = 91,939) of AD users concomitantly used BZDR and 35.1% of OA users were additionally being treated with BZDR. At substance level, the most frequent combinations found were alprazolam with sertraline (8430 patients – 7.8% of sertraline users and 5.2% of alprazolam users), diazepam with tramadol +

Table 4. Concomitant psychoactive medicine use.

	Number of users	Rate (*100,000 inhabitants)
Total PMed users	778,772	21,669
No combination	509,690	14,182
Combination of PMed (%)	269 082 (34.6)	7487
Total BZDR users	502,137	13,972
Total AD users	189,555	5274
Total OA users	236,314	6575
Total AC users	99,583	2771
Combination of therapeutic groups		
BZDR + AD	91,939	2558
BZDR + OA	83,028	2310
BZDR + AC	39,502	1099
AD + OA	31,715	882
AD + AC	23,217	646
OA + AC	28,703	799
Combination of PMed		
Alprazolam with sertraline	8430	235
Diazepam with tramadol + paracetamol	7573	211
Alprazolam with trazodone	6999	195
Alprazolam with tramadol + paracetamol	6900	192

Notes: OA – opioid analgesics; BZDR – benzodiazepines and z-drugs; AD – antidepressants; AC – anticonvulsants; PMed – psychoactive medicine.

paracetamol (7573 patients – 6.2% of diazepam users and 4.7% of tramadol + paracetamol users), alprazolam with trazodone (6999 patients – 7.2% of trazodone users and 4.3% of alprazolam users), and alprazolam with tramadol + paracetamol (6900 patients – 4.2% of both tramadol + paracetamol and alprazolam users).

Long-term concomitant treatment of chronic OA users with other PMed

About 24.2% of OA chronic users had a diagnosis of cancer, 27.6% of depression, 14.3% of anxiety and 9.7% of sleeping disorders. More than half (N = 4403; 52.1%) of total OA chronic users were LTC users with at least another PMed of the study. About 72.6% (N = 3196) of total LTC chronic OA users were long-term concomitant users with BZDR, 81.7% of which females and 61.0% aged ≥65y. Nearly three quarters (74.1%) of these LTC OA-BZDR users received at least one prescription from a GP. LTC chronic OA use with AD is less common (N = 1427; 32.4% of total OA chronic users), with a slightly higher female (83.3%) and older age (63.8% aged ≥65y) predominance. Less than a quarter of LTC OA-BZDR, OA-AD and OA-AE users (22.8%, 22.4% and 22.1%, respectively) had a cancer diagnosis (Table 5).

The results of the multivariate logistic regression used to explore potential factors affecting long-term concomitant treatment of chronic OA users with other PMed have shown that age (aOR = 0.996, $p = 0.0210$), and gender (aOR = 1.388, $p < 0.0001$), influence the risk of LTC OA-BZDR use, with female OA chronic users having higher odds of LTC use with BZDR – Table 6. The existence of a depression or anxiety diagnosis in OA chronic users was also identified as a risk factor for LTC OA-BZDR use (aOR = 1.563 and aOR = 1.432, $p < 0.0001$) and LTC OA-AD use (aOR = 2.593, $p < 0.0001$ and aOR = 1.200, $p = 0.0267$, respectively). In addition, OA chronic users that had a prescription from a psychiatrist or neurologist had a higher odds of LTC use with BZDR, AD or AC (aOR = 1.556, 1.627 and 1.832, $p < 0.0001$). Having a medication abuse diagnosis was identified as a risk factor for LTC OA-AD use (aOR = 1.940, $p = 0.0383$). Younger age and a depression diagnosis were also identified as risk factors for LTC OA-AC use (aOR = 0.975 and aOR = 1.411, respectively, $p < 0.0001$).

Doctor shopping of PMed

The detailed results, included in Figure 1 and Table 7, show that several strong opioids had DSI higher than 1%, therefore possessing a relevant risk of abuse: fentanyl (4.2%), OUD buprenorphine (3.7%) – the only opioid for OUD sold in community pharmacies in Portugal – morphine (3.0%) and hydromorphone (1.4%). For weak opioids, widely used in ARSLVT, the risk of abuse was not meaningful (DSI = 0.8%), with the three studied medicines

Table 5. Characteristics of long-term concomitant chronic OA use with BZDR, AD, AC, BZDR + AD, BZDR + AC, AD + AC, BZDR + AD + AC.

	OA chronic users	Long-term concomitant OA chronic users						
		OA + BZDR	OA + AD	OA + AC	OA + BZDR + AD	OA + BZDR + AC	OA + AD + AC	OA + BZDR + AD + AC
Total	8455	3196	1427	1035	628	357	192	87
Male users (%)	1855	586 (18.3)	239 (16.7)	239 (23.1)	91 (14.5)	78 (21.8)	32 (16.7)	16 (18.4)
Female users (%)	6600	2 610 (81.7)	1 188 (83.3)	796 (76.9)	537 (85.5)	279 (78.2)	160 (83.3)	71 (81.6)
Mean age (SD)	69.7 (13.9)	68.9 (13.6)	69.7 (13.8)	64.5 (13.5)	67.9 (13.4)	62.5 (13.1)	63.3 (14.0)	60.7 (12.9)
Users ≥ 65 years (%)	5 314 (62.9)	1 951 (61.0)	911 (63.8)	520 (50.2)	372 (59.2)	160 (44.8)	92 (47.9)	32 (36.8)
Users with a cancer diagnosis (%)	2 044 (24.2)	728 (22.8)	320 (22.4)	229 (22.1)	129 (20.5)	71 (19.9)	38 (19.8)	15 (17.2)
Users with a diagnosis of anxiety (%)	1 210 (14.3)	578 (18.1)	276 (19.3)	161 (15.6)	137 (21.8)	60 (16.8)	36 (18.8)	20 (23.0)
Users with a diagnosis of depression (%)	2 337 (27.6)	1 112 (34.8)	643 (45.0)	368 (35,6)	290 (45.2)	149 (41.8)	100 (52.1)	45 (51.7)
Users with a diagnosis of sleeping disorders (%)	816 (9.7)	375 (11.7)	169 (11.8)	97 (9.4)	73 (11.6)	38 (10.6)	22 (11.5)	10 (11.5)
Users with a GP prescription (%)	6 151 (72.7)	2 367 (74.1)	1 060 (74.3)	698 (67.4)	467 (74.4)	255 (71.4)	141 (73.4)	65 (74.7)

Notes: OA – opioid analgesics; BZDR – benzodiazepines and z-drugs; AD – antidepressants; AC – anticonvulsants; SD – standard deviation; GP – general practitioner.

Table 6. Factors influencing LTC OA use with other PMed.

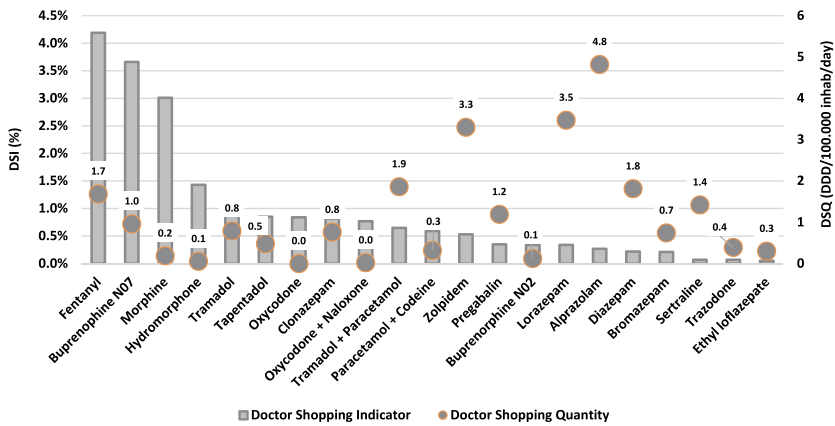
	Long-term use vs. non-concomitant use			Short-term use vs. non-concomitant use		
Variable	Multivariate aOR	Confidence Interval	*p*-value	Multivariate aOR	Confidence Interval	*p*-value
Concomitant use OA-BZDR						
Age	0.996	0.992–0.999	0.0210	1.001	0.996–1.006	0.6460
Female gender (ref: male gender)	1.388	1.227–1.571	<0.0001	1.177	0.995–1.392	0.0575
Prescription by GP	1.108	0.982–1.250	0.0957	1.197	1.012–1.417	0.0362
Prescription by psychiatrist or neurologist	1.556	1.252–1.933	<0.0001	0.947	0.669–1.340	0.7581
Cancer diagnosis	0.939	0.833–1.058	0.2989	1.099	0.935–1.291	0.2531
Anxiety diagnosis	1.432	1.244–1.649	<0.0001	1.309	1.068–1.604	0.0095
Depression diagnosis	1.563	1.397–1.748	<0.0001	1.077	0.912–1.271	0.3828
Sleep disturbance diagnosis	1.361	1.156–1.601	0.0002	1.147	0.905–1.453	0.2570
Medication abuse diagnosis	1.276	0.686–2.374	0.4420	1.287	0.534–3.103	0.5736
Drug abuse diagnosis	1.184	0.644–2.175	0.5868	0.606	0.207–1.778	0.3618
Concomitant use OA-AD						
Age	1.005	1.000–1.009	0.0449	1.005	0.997–1.012	0.2489
Female gender (ref: male gender)	1.230	1.047–1.445	0.0116	1.059	0.813–1.381	0.6693
Prescription by GP	0.961	0.827–1.116	0.5987	1.057	0.818–1.365	0.6718
Prescription by psychiatrist or neurologist	1.627	1.277–2.071	<0.0001	1.569	1.050–2.347	0.0281
Cancer diagnosis	0.988	0.853–1.146	0.8772	0.934	0.725–1.204	0.6002
Anxiety diagnosis	1.200	1.021–1.410	0.0267	1.253	0.957–1.639	0.1005
Depression diagnosis	2.593	2.276–2.954	<0.0001	2.030	1.625–2.537	<0.0001
Sleep disturbance diagnosis	1.178	0.973–1.426	0.0940	1.477	1.096–1.991	0.0105
Medication abuse diagnosis	1.940	1.036–3.632	0.0383	0.828	0.195–3.514	0.7985
Drug abuse diagnosis	1.122	0.524–2.399	0.7675	0.457	0.062–3.388	0.4439
Concomitant use OA-AC						
Age	0.975	0.970–0.980	<0.0001	0.995	0.991–1.000	0.0374
Female gender (ref: male gender)	0.900	0.756–1.071	0.2363	1.128	0.970–1.311	0.1181
Prescription by GP	1.081	0.915–1.276	0.361	1.017	0.882–1.173	0.8175

(*Continued*)

Table 6. Continued.

Variable	Long-term use vs. non-concomitant use			Short-term use vs. non-concomitant use		
	Multivariate aOR	Confidence Interval	*p*-value	Multivariate aOR	Confidence Interval	*p*-value
Prescription by psychiatrist or neurologist	1.832	1.393–2.410	<0.0001	1.590	1.237–2.044	0.0003
Cancer diagnosis	0.838	0.702–0.999	0.0489	0.973	0.843–1.122	0.7054
Anxiety diagnosis	0.981	0.803–1.199	0.8527	0.946	0.795–1.127	0.5367
Depression diagnosis	1.411	1.205–1.653	<0.0001	1.179	1.028–1.352	0.0186
Sleep disturbance diagnosis	0.993	0.782–1.262	0.957	1.056	0.866–1.288	0.5892
Medication abuse diagnosis	1.724	0.795–3.739	0.1677	1.221	0.583–2.556	0.5964
Drug abuse diagnosis	0.721	0.268–1.944	0.5186	1.766	0.896–3.481	0.1005

Notes: OA – opioid analgesics; BZDR – benzodiazepines and z-drugs; AD – antidepressants; AC – anticonvulsants; aOR – adjusted odds ratio; GP – general practitioner.



DSI - doctor shopping indicator
DSQ - doctor shopping quantity, corrected if DSI>1%

Figure. 1. Doctor shopping parameters, by INN.

showing a DSI below 1% (tramadol: 0.9%; tramadol + paracetamol: 0.7%; paracetamol + codeine: 0.6%).

OA as a whole had a DSI of 1.6%. AD, BZD and z-drug zolpidem seem to pose no risk of significant abuse, with DSI of 0.1%, 0.3% and 0.5%, respectively (Table 7).

Regarding DSQ, that provides an estimate of the extent of medicine abuse, data have shown that, although the DSQ for BZD is almost double than for OA

Table 7. Doctor shopping parameters, by therapeutic group and opioid analgesic subgroup.

Therapeutic group / subgroup	Qtot (100,000 inhab/day)	DSQt (100,000 inhab/day)	DSI (%)	DSQc (100,000 inhab/day)
Opioid analgesics (N02A)	602	9.2	1.5%	8.6
Strong opioid analgesics	168	4.3	2.5%	2.8
Weak opioid analgesics	434	3.6	0.8%	NA
Anticonvulsants (N03A)	430	2.4	0.6%	NA
Anxiolytic benzodiazepines (N05B)	4575	14.0	0.3%	NA
Z-drug (N05C)	621	3.3	0.5%	NA
Antidepressants (N06A)	2656	3.3	0.1%	NA
Opioid for OUD treatment	36	1.3	3.7%	1.0

Notes: OUD – opioid use disorder; Qtot – Total quantity dispensed; DSQt – Total doctor shopping quantity; DSI – doctor shopping indicator; DSQc – corrected doctor shopping quantity, if DSI > 1%.

(14.0 vs. 9.2 DDD/100,000 inhabitants/day), their doctor shopping indicator is one fifth that of OA (0.3% vs 1.6%).

Discussion

Main findings and implications

Our study results have shown that psychoactive medicine users are more likely to be females, confirming previously published data (Carmona Araújo et al., 2023; Conselho Nacional de Saúde, 2019; Coordenação Nacional da Estratégia do Medicamento e dos Produtos de Saúde, 2017; INFARMED, 2017, 2020; Faria Vaz et al., 2017a). Existing evidence points to a higher prevalence of pain (Campbell et al., 2010; United Nations Office on Drug and Crime, 2017a), depression (European Medicines Agency, 2023) and anxiety in females (Conselho Nacional de Saúde, 2019), which combined with a greater general medicine consumption in the female gender (Boyd et al., 2015; Campbell et al., 2010; Carmona Araújo et al., 2023; Cartagena et al., 2017; Delaš Aždajić et al., 2019; Hedenmalm et al., 2019; Hockenhull et al., 2021; Madeira et al., 2023; Muller et al., 2019; Schjerning et al., 2016), contributes to the clear female predominance in psychoactive medicine consumption. This gender gap in Portugal is reported to be the widest across the EU in what concerns depression (OECD European Observatory on Health Systems and Policies, 2023). In our study, this was reflected in the striking difference in AD consumption (triple in women compared to men), in line with previous research (Madeira et al., 2023). It is also acknowledged that women, as well as the elderly, have an increased risk of misusing medicines (Araújo et al., 2023; Casati et al., 2012), resulting in a higher probability of adverse consequences in older females. A recent OECD report (OECD European Observatory on Health Systems and Policies, 2023) emphasises the high prevalence

of mental health problems in Portugal (22.0% of the population, higher than the EU average of 16.7%), driven mainly by anxiety and depressive disorders (9% and 6% of the population in 2019, respectively).

Relevant proportions of chronic users of BZDR, a therapeutic class whose included PMed are recommended to be administered for short periods, were observed in our study: 38.8% of lorazepam, 27.5% of alprazolam and 20.5% of zolpidem users were chronic. Lorazepam, mainly prescribed in primary care, is an intermediate-acting, high potency BZD reported to be a significant predictor of long-term BZD use, dose escalation or heavy use (Kurko et al., 2015). Considering that lorazepam is included in the EU(7)-PIM list adapted to Portugal, and also in the most recent updates of both Beers and STOPP and START criteria (2023 American Geriatrics Society Beers Criteria® Update Expert Panel, 2023; O'Mahony et al., 2023), identifying potentially inappropriate medicines in older patients (Rodrigues et al., 2020) who are more susceptible to suffer from BZDR adverse effects (Gomes et al., 2023; Madeira et al., 2023; Prazeres, 2023), and that most ARSLVT lorazepam users are older patients – 53.7% of our chronic lorazepam users were aged 65 or more – the lorazepam chronic use found in our study is a cause for concern. Besides lorazepam, our results have also shown that analgesic buprenorphine and tramadol + paracetamol users are the oldest PMed users (mean 73.6 and 71.5 years, respectively). Considering that opioids are included in the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP3S)-tool (Ghent University – Faculty of Pharmaceutical Sciences, 2023) as potentially inappropriate medication for older people, according to which tramadol should be especially avoided because of increased risk of hypoglycaemia, hyponatremia and serotonin syndrome due to drug–drug interactions with other serotonergic medicines, our findings on chronic PMed use in the elderly deserve special attention.

Female gender predominance in PMed use (70.8% of PMed ARSLVT users), together with its identification as a risk factor for both LTC OA-BZDR and LTC OA-AD use in our study, reinforces the need of intervention programmes to increase awareness of the risks of PMed utilisation with a particular focus on the most vulnerable groups. Medication abuse diagnosis was also identified as a risk factor for LTC OA-AD use, and females have an increased risk of misusing medicines (Araújo et al., 2023; Casati et al., 2012). Therefore, such intervention programmes should aim at reducing PMed consumption, especially BZDR, and minimising their misuse, targeting most frequent users – especially older females (Lombardi et al., 2020) – and the healthcare workforce that has a role in prescribing and dispensing – clinicians and pharmacists.

Off-label use, defined as the use of a medicine outside its approved therapeutic indications, is a relatively common practice worldwide, and Portugal is no exception (Conselho Nacional de Ética para as Ciências da Vida, 2023). In our study, we assumed diagnoses as a proxy for the drug's main therapeutic

indication. Therefore, the use of a medicine in a patient not having the diagnosis of its main indication was considered off-label use. It is true that the use of a medicine in a secondary indication is not off-label use, and that missing diagnoses in the database may not necessarily mean that patients do not have those conditions, but only that records are incomplete, both leading to an overestimation of off-label use. Nevertheless, it was evident in our results that this phenomenon has a relevant expression in ARSLVT: a scarce 15.3% of zolpidem users had a sleeping disorder diagnosis, the only therapeutic indication for zolpidem approved in Portugal; only 37.7% of antidepressant users had a depression diagnosis, and only 28.2% of OUD buprenorphine users had a diagnosis of illicit drug use included in SIARS.

Most OA are not exclusively intended to treat cancer pain, but controversy currently exists on the effectiveness of OA in non-cancer pain treatment. Only about 13.5% of OA users had a neoplastic diagnosis, reaching 25.1% for strong OA users and 13.4% for weak OA users, with a cancer diagnosis present for 38.1% of morphine, 33.3% of fentanyl and 15.2% of tapentadol users. OA are only used in pain treatment; not having data on pain diagnoses, we assumed that all OA use with no neoplastic diagnosis was for the treatment of acute or chronic non-cancer pain (CNCP). Given the low proportions of neoplastic diagnoses in ARSLVT OA users (13.5% any OA, 21.5% strong and 13.4% weak OA) and that for chronic use only 24.2% of OA chronic users had a cancer diagnosis, it is reasonable to assume that most OA use in ARSLVT is in CNCP treatment, which is line with several other studies (Bedson et al., 2016; Hider-Mlynarz et al., 2018; Kalkman et al., 2019; Zin et al., 2014).

OA, used in chronic cancer and non-cancer pain, should be prescribed with caution, not only because they can pose serious health risks, that appear to be dose-dependent (Chou et al., 2015), but also due to limited evidence of long-term benefit (Campbell et al., 2010; Chou et al., 2015; Keto et al., 2022). Our study has shown that the prevalence of OA use in ARSLVT is low – 6.6% – when compared with data from other countries, with the exception of Germany (long-term opioid therapy – 1.3%) (Marschall et al., 2016) and the Netherlands (6.0%) (Bedene et al., 2019). In fact, in France the prevalence of OA use was 14% in one study (Ponté et al., 2018) and 17.5% in another study (Chenaf et al., 2019), in Italy 12.2% (OsMed, n.d.), in Slovenia 12.6% (Kostnapfel et al., 2022), in Finland 7% (Keto et al., 2022), in Spain 6.7% (Regueras & López Guzmán, 2021) and 4.9% in young adults (Carrasco-Garrido et al., 2022), and in the UK 13% (Public Health England, 2019). In Norway, Denmark and Sweden, higher prevalences in women compared to men, have been observed (12.1%, 8.9% and 8.4% vs 9.2%, 6.6% and 6.3%, respectively) (Muller et al., 2019). In addition, our data has shown that, except for tapentadol, most strong OA are prescribed in hospitals, thereby ensuring closer monitoring of opioid therapy, probably in the context of pain management consultations.

However, the scenario regarding BZD use is quite different, and our results, pointing to chronic BZDR use, especially by the elderly, are in line with OECD data: in 2017, Portugal ranked third regarding chronic BZD use in people aged 65 and over, with 65.5 DDD/1000 inhabitants/day (OECD, 2020). Recognising this problem, in the last years several interventions have been implemented in our country, both at national and regional level, to encourage BZD discontinuation in all age groups (Faria Vaz et al., 2017a; Fernandes et al., 2022; Gomes et al., 2023; Oliveira et al., 2019; Vaz, et al., 2017b). However, although some improvement has been observed in the use of anxiolytics (ATC code N05B) (Fernandes et al., 2022; Gomes et al., 2023; Oliveira et al., 2019), decreasing consumption from 93.9 DDD/1000 inhabitants/day in 2017, to 85.0 DDD/1000 inhabitants/day in 2022, a decrease has been observed also in other OECD countries. This implies that despite the decrease in absolute figures, our country is still on the top of the BZD use ranking in relative terms (OECD, 2023).

Concomitant use of several PMed, reported in other studies (Torrance et al., 2018), and especially long-term concomitant use of OA with BZDR or other CNS depressants bears serious health risks (Araújo et al., 2023), including fall-related injury, hospitalisations and emergency department visits, fatal and non-fatal opioid overdoses that can ultimately result in respiratory depression, coma and death (FDA, 2016). Despite the relatively low OA prevalence of use in ARSLVT, more than half (52.1%) of OA chronic users were LTC users with other PMed, especially with BZDR, reinforcing the need to raise awareness, both of prescribers and patients, on the possible harms of LTC use of OA concomitantly with other PMed.

The doctor shopping analysis performed in our study has shown that this does not seem to be a cause for concern in ARSLVT. In France the scenario is different, with several studies (Ponté et al., 2018; Pradel et al., 2010; Soeiro et al., 2023) pointing to higher DSI, and for more PMed, than in ARSLVT. In our results, although the DSQ for BZD (14.0 DDD/100,000 inhabitants/day) was almost 2-fold higher than for OA (corrected DSQ = 8.6 DDD/100,000 inhabitants/day), their doctor shopping indicator (0.3%) was one fifth that of OA (1.5%). This apparent contradiction of a higher DSQ for BZD and a lower DSI compared to OA, highlights the fact that the extent of psychoactive medicine abuse is a combination of its abuse potential (generally lower for BZD) and the availability of the medicine (higher for BZD). In fact, in Portugal BZD are widely prescribed, whereas physicians refrain from prescribing opioids, especially strong, which are all controlled substances in our country, in line with the United Nations Single Convention on Narcotic Drugs (Transnational Institute, 2015). Nevertheless, the first four positions of the ARSLVT DSI ranking are occupied by strong opioids, all shown to possess a meaningful risk of abuse, as opposed to BZD and AD, which are in the bottom of the DSI ranking. Fentanyl is the PMed with the highest

DSI – 4.2% – which together with its relevant DSQ (1.7 DDD/100,000 inhabitants/day, sixth position in the DSQ ranking) found in our study, points to the need to closely monitor the use of this opioid. Due to its high lipophilicity, fentanyl has a fast transition through the blood – brain barrier and consequently a rapid onset of action, thereby possessing a high abuse liability. Transdermal formulations are expected to have lower abuse liability, nonetheless fentanyl is also available in Portugal in immediate release transmucosal formulations that, bypassing first-pass metabolism, provide fast analgesia and are for that reason indicated for breakthrough cancer pain. These transmucosal formulations, being undeniably important in the management of intense pain in cancer patients, are also more prone to be misused. As such, it would be important to further develop the doctor shopping analysis stratifying by formulation (transdermal vs. transmucosal), in order to distinguish their specific abuse risk. Yet it should be emphasised that, given the above mentioned relatively low prevalence of OA use in ARSLVT, and in particular the reduced number of fentanyl users (3% of total OA users) when compared to other opioids, the possibly higher risk of transmucosal fentanyl is not expected to have a strong impact from a public health protection perspective.

An important next step of our work would be to study, at national level, the use and misuse of PMed, especially the PMed highlighted in our research as requiring particular attention, namely by analysing the morbimortality consequences (e.g. hospitalisations, poisonings and deaths) associated with their use, allowing a detailed assessment of the risks associated with PMed use and misuse in Portugal.

Strengths and limitations

This study is, to our knowledge, the first in Portugal combining the analysis of consumption of PMed with information on their potential misuse. Using patient-level data, we describe PMed consumption patterns in the ARSLVT region of Portugal while also analysing their possible misuse, based on the type of use (chronic use of the studied medicines that are recommended for short-term treatments, as well as long-term concomitant use of opioids with other PMed and their risk factors) and estimation of doctor shopping indicators. The main strength of the study is the use of a large population-based cohort containing detailed prescription and dispensing data that also includes patient diagnoses (used as proxies for indications of use), as well as information on prescribers and prescription setting. Further, the use of data on prescriptions actually dispensed, instead of issued prescriptions, ensures that the analysis is closer to actual medicine consumption.

However, our study also has several limitations, the first of which is related to the potential limited representativeness of the population-based cohort

studied, which cannot be ascertained, hampering generalisability (external validity) of results to the whole Portuguese population. In addition, the use of DDD as a consumption measure has several limitations. In fact, in the situations where the actual daily dose is significantly different from the DDD, such as when evaluating drug use in older adults (in whom lower doses are frequently used), in indications other than the main therapeutic indication (indications are not included in SIARS), or when studying prescription opioid use (where doses are often titrated according to the patient's response to obtain sufficient pain relief), the use of DDD leads to less precise consumption estimates (Nielsen et al., 2017). Consequently, classifying users as chronic based on the number of DDD consumed may not be totally accurate. Likewise, the calculation of the number of days of supply assumes the use of 1 DDD/day, leading to over or underestimation of this number when the dose actually used is significantly different from the DDD.

Another limitation is the fact that SIARS only contains information on reimbursed medicines; as such, medicines not reimbursed or dispensed without a medical prescription, or obtained through illicit sources, as well as consumption by hospitalised patients, are not covered by our data. Besides, we acknowledge that our off-label estimates may be overestimated due to missing diagnosis codes in SIARS. We also assumed that diagnoses were present at the time the medicine was dispensed, which may not be the case as we had no information on the date the patient was diagnosed with the medical condition.

In the concomitant use analysis and in the doctor shopping method, we considered patients to be continuously exposed to the medicines based on dispensing dates and days' supply, not being able to ascertain whether patients actually consumed these medications continuously over the study period. In addition, our measure on treatment interruption was based on the validity of most prescriptions in 2017 (30 days), not taking into consideration the higher validity (180 days) of renewable prescriptions. However, considering that most studied medicines are intended for short-term treatments, this limitation is expected to have low impact on the results. We also assumed that overlapping dispensing periods of two or more medicines meant their concomitant use, which we cannot be certain as we are not sure if they both were actually consumed during the same treatment period. Finally, the different PMed dosages available in the Portuguese market, which have not been taken into account in our study, could influence the doctor shopping results, as higher dosages are expected to have higher DSI (Pradel et al., 2010).

Conclusions

The PMed with higher prevalence of use are BZD, followed by OA and AD. Moreover, there is a high proportion of chronic users of BZDR, especially of

lorazepam and alprazolam. OA are mainly used for conditions other than chronic cancer pain, and long-term concomitant use of OA with other PMed is frequent, particularly with BZDR. The female gender is a risk factor for long-term concomitant use of OA with AD and with BZDR. This female predominance in PMed consumption resulting in a higher probability of adverse consequences in females, especially older, prompts the need to develop specific policies to more effectively address excessive PMed consumption, especially chronic. BZDR have smaller doctor shopping indicators but more expressive doctor shopping quantities than OA, reflecting their lower risk of abuse but higher accessibility, also suggesting that availability is an issue that needs further analysis.

A comprehensive and real-world-based characterisation of PMed use and misuse at national level, including of their morbimortality consequences, should be performed, ideally resorting to data linkage between national databases, a common practice in Northern European countries.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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