Universidade de Lisboa

Faculdade de Farmácia


# USE AND MISUSE OF MEDICINES WITH PSYCHOACTIVE EFFECTS IN PORTUGAL

Rita João Martins Casal

Dissertation supervised by Professor Ana Paula Mecheiro de Almeida Martins Silvestre Correia and co-supervised by Filipa Alves da Costa

Master in Regulation and Evaluation of Medicines and Health Products

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## Resumo

Introdução

O mau uso de medicamentos psicoativos (MUMP) é um problema de saúde pública, sendo mais significativo nos Estados Unidos da América. Na União Europeia (UE), a evidência é limitada e quase ausente em Portugal. O objetivo desta dissertação é adquirir conhecimento sobre as consequências do MUMP a nível europeu e nacional, e identificar indicadores de morbilidade associada a este fenómeno em Portugal (2014-2018).

Metodologia

De forma a avaliar as consequências do MUMP na UE foi realizada uma *scoping review*. A PubMed, Scopus e a Web of Science foram as bases de dados (BD) utilizadas para a realização da pesquisa entre 2011 e 2020. Adicionalmente, artigos de outras fontes foram incluídos na pesquisa. Uma análise preliminar foi realizada à BD de hospitalizações.

Resultados

Com a *scoping review*, foram identificados 1.339 artigos, dos quais 110 artigos foram incluídos. Os mesmos reportaram dados sobre o consumo, fatores de risco, mau uso e suas consequências e características da população. A análise preliminar da base de dados realça um total de 13.813 admissões hospitalares (AH) registadas num período de 5 anos, com uma tendência de crescimento observada (aumento de 2,2 vezes). A maioria das AH associadas ao mau uso de MP foram em mulheres e as principais classes terapêuticas foram ansiolíticos (65%) e antidepressivos (16%).

Conclusão

A evidência disponível na UE sobre o MUMP, foca-se nos opioides, benzodiazepinas/z-hipnóticos e gabapentinoides. Foi observada uma diferença entre mulheres e homens, com estudos a reportar o mau uso de benzodiazepinas/z-hipnóticos em mulheres e o mau uso de opioides nos

homens. Em Portugal, as AH envolveram mais mulheres, com ansiolíticos e sedativos como a causa principal de admissões hospitalares.

**Palavras-chave:** mau uso de medicamentos, medicamentos psicoativos, uso não médico, abuso, consequências do mau uso

## Abstract

Introduction

Misuse of psychoactive medicines is a worldwide public health concern, with a more significant problem in USA. European Union (EU) evidence is scarce, with an apparent increase in prescription drug abuse and misuse, and almost absent in Portugal. This dissertation aims to acquire knowledge on the consequences of misuse of psychoactive medicines at European and national levels and to study morbidity indicators associated with the identified problem of misuse in Portugal, between 2014 and 2018.

Methodology

To assess the health outcomes of PPD misuse in the EU, a scoping review on the misuse of PPDs was conducted using the PubMed, Scopus, and Web of Science databases between 2011 and 2020. In addition, articles from other sources were included in the search. Furthermore, a preliminary analysis was performed to the hospital morbidity database.

Results

In the scoping review, 1,339 articles were identified, of which 110 were included, reporting data on consumption, risk factors, misuse and its consequences, and demographic characteristics. The preliminary analysis of the Portuguese hospital morbidity database highlighted a total of 13,813 hospital admissions registered over this 5-year period, with an increasing trend observed (2.2-fold increase). Most hospital admissions associated with psychoactive substances misuse were in females and the top therapeutic classes identified were anxiolytics (65%) and antidepressants (16%).

Conclusion

Current evidence on the misuse of PPD focuses on opioids, benzodiazepines/z-drugs, and gabapentinoids around the EU. A clear difference between females and males is identified, with females being more likely to misuse BZD/z-drugs and males more likely to misuse opioids.

Specifically, in Portugal, hospital admissions were more observed in females, with anxiolytics and sedatives being the main therapeutic classes causing emergency visits.

**Keywords:** prescription drug misuse, psychoactive medicines, non-medical use, abuse, consequences of misuse

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I would like to acknowledge INFARMED, I.P and *Administração Central do Sistema de Saúde, I.P.*, for sharing the relevant data to perform this project.

At last, but with the same importance, I would like to thank my family, particularly my mother, for all the unconditional support during these very intense academic years.

## List of published papers

1. Scoping Review Protocol – Araújo AC, Casal RJ, Goulão J, et al Protocol for a scoping review on misuse of psychoactive medicines and its consequences BMJ Open 2022;12:e060519. doi: 10.1136/bmjopen-2021-060519

2. Araújo, A., Casal, R., Goulão, J., Martins, A. (2022). Morbidity consequences of misuse of psychoactive prescription drugs in Portugal: The misumedpt project. Pharmacoepidemiol Drug Saf, 31(S2), 38–39. https://doi.org/https://doi.org/10.1002/pds.5518

## List of planned papers

1. Misuse of psychoactive medicines and its consequences: Scoping Review – Currently, the draft is being prepared. Hopefully, will be submitted in December to the Journal of Substance Use.

2. Morbimortality consequences of misuse of psychoactive medicines in Portugal – To be prepared and submitted for publication in 2023.

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**Abbreviations**

**AB** – Aberrant behaviour

**ADHD** – Attention deficit hyperactivity disorder

**ADR** – Adverse drug reaction

**AOC** – Adequacy of opioid consumption

**ARSW** – Adjective rating scale for withdrawal

**ATM** – Addiction to medicines

**ATC** – WHO Anatomical Therapeutic Chemical Classification

**BZD** – Benzodiazepine

**CNCP** – Chronic non-cancer pain

**CNS** – Central Nervous System

**DDD** – Defined daily dose

**DFM** – Dependence-forming medicines

**DRAMES** – Death related to the abuse of medicines

**DRD** – Drug Reimbursement Database

**DSI** – Doctor-shopping indicator

**DSQc** – Corrected doctor-shopping quantity

**DSM** – Diagnostic and statistical manual of mental health disorders

**DUS** – Drug utilization studies

**ED** – Emergency Department

**EU** – European Union

**ICD** – International Classification of Diseases

**HAM-A** – Hamilton anxiety rating scale

**HAM-D** – Hamilton depression rating scale

**MedDRa** – Medical Dictionary for Regulatory Activities

**NMU** – Non-medical use

**NMPDU** – Non-medical prescription drug use

**NPPSSP** – Non-prescribed prescription sedatives and sleeping pills

**OMT** – Opioid maintenance treatment

**OPPIDUM** – Observation of illegal products and misuse of psychotropic medications

**OST** – Opioid substitution treatment

**OUD** – Opioid use disorder

**PC** – Poison centres

**PO** – Prescription opioids

**PPD** – Psychoactive Prescription Drugs

**PRR** – Proportional reporting ratio

**PTSD** – Post-traumatic stress disorder

**SICAD** – General Directorate for Intervention on Addictive Behaviours and Dependencies

**SMQ** – Standardised MedDRA Query

**SR** – Sustained release

**TSSp** – Tranquillizers, sedatives and sleeping pills

**USA** – United States of America

# 1. Introduction

## 1.1. Psychoactive Substances

A psychoactive substance is any substance that affects the mental process, such as perception and consciousness, when taken in or administered into one's the system(1). This definition includes psychoactive prescription drugs, as they have the potential to be non-medically used due to their positive psychoactive effects produced in the Central Nervous System(2).

## 1.2. Misuse of Psychoactive Prescription Drugs

Non-medical use of Psychoactive Prescription Drugs (PPD) is a worldwide public health problem and a growing concern(3). The psychoactive medicines most likely to be non-medically use are prescription opioids, opioid maintenance therapy medicines, sedatives/hypnotics, antidepressants, and benzodiazepines(3).

The misuse of PPD is a problem that affects several countries. However, the problem in USA is more significant, as their prescription opioid abuse is almost at the same level as the use of cannabis(3–5). The most evidence of the misuse of prescription drugs currently available comes from the USA(6,7). Apparent differences between the USA and Europe, such as healthcare system and prescribing practices, make it challenging to generalise data beyond USA(8).

Furthermore, the terminology to describe the phenomenon of medicines misuse is diverse and ambiguous(9), which is a critical factor in assessing data on this topic(9). The term "misuse" has been defined in the literature according to the prescription status (e.g., any prescription-only medicine use that occurs without a prescription) and reasons for use (e.g., any intentional uses for intensification of effects of other psychoactive medicines or illegal drugs)(9,10). This approach shows similarities with the definition of abuse – "*persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful or psychological effects*"(11). The term "misuse" has also been defined as non-medical use of medicinal products, which refers to the consumption of a medication that is not prescribed to a user or that is consumed in a manner not intended by the prescriber (e.g., taking higher doses than prescribed, using non-approved routes of administration)(9), differing from intentional non-adherence to

treatment, which is related to the patient's decision to take the prescription drug at different times, or different doses, or not all due to feeling better, to high co-payment, to impact of treatment on daily life, and lack of information given to the patient, for example(12,13). For this dissertation, the misuse of medicinal products will be considered any situation where a medicinal product is intentionally and inappropriately used, not in accordance with the terms of the marketing authorisation(11), including non-medical use and abuse.

### 1.2.1. The United States: Overview

The USA represents the world's largest drug market; until the 1990s, most drug problems were focused on illegal drugs(14). Since the 1990s, the opioid crisis has emerged with the increase in opioid prescribing(14) leading to the misuse of psychoactive medicines, in particular prescription opioids reaching epidemic proportions(15). The moral duty for physicians to treat pain, the over-prescription of opioids for all kinds of diseases, the massive production and distribution of prescription opioids by pharmaceutical companies, and the acceptance attitude toward the use of prescription opioids by healthcare professionals are some of the factors that contributed for the current epidemic in the USA(16,17).

Over the last two decades, the growth of prescription drugs misuse was reflected in the increase of overdose deaths(18–21) and emergency department (ED) visits(20,21), where opioid pain relievers and benzodiazepines were the PPD most frequently associated with both events(21,22). In particular, an increase in overdose deaths associated with benzodiazepines in combination with other medicines, namely opioid analgesics(23), has been observed. Young adults are the population where the non-medical use of prescription drugs is more prevalent(24). The worsening of the opioid crisis(19,23) led the U.S. Department of Health and Human Services to declare a health crisis emergency in 2017(25,26). In parallel with the opioid crisis, the USA registered an increase in the prescription rates of benzodiazepines among the older population (≥ 65 years old)(27). Additionally, an increase in the prescription rates of sedatives and hypnotics, and tranquillizers/anxiolytics has also been reported in the USA(28).

Data from the 2015 National Survey on Drug Use and Health (NSDUH) showed that around 119 million Americans were PPD users in the past year, with 97.5 million people pain reliever users, 39.3 million tranquillizer users, and 18.6 million sedative users. Of all therapeutic classes, pain relievers were the most used, with a predominance in the adult population (38.3%) within

the 97.5 million pain reliever past year users, with females more likely to have used prescription pain relievers than males (38.8% and 33.9%, respectively)(29). Table 1 reflects the percentage of all therapeutic classes' users, separated by age group.

**Table 1: Percentage (%) of PPD users**

| Therapeutic Classes / Age Group | Pain Relievers | Tranquillizers | Sedatives |
|---|---|---|---|
| **Youths (12-17 years) (%)** | 22.7 | 4.3 | 2.4 |
| **Young Adults (18-25 years) (%)** | 34.8 | 12.1 | 3.8 |
| **Adults (26 years or older) (%)** | 38.3 | 16.4 | 8.0 |

Additionally, around 18.9 million Americans misused PPD in the past year, with an estimated 12.5 million prescription pain reliever misusers, 6.1 million prescription tranquillizer misusers, and 1.5 million prescription sedative misusers. Of all therapeutic classes, pain relievers were the most misused, with a predominance in the young adults' population (8.5%) within the 12.5 million prescription pain reliever past year misusers, and males were more likely to misuse prescription pain relievers than females (5.3% and 4.0%, respectively)(29). Table 2 reflects the percentage of all therapeutic classes' misusers, separated by age group.

**Table 2: Percentage (%) of PPD misusers**

| Therapeutic Classes / Age Group | Pain Relievers | Tranquillizers | Sedatives |
|---|---|---|---|
| **Youths (12-17 years) (%)** | 3.9 | 1.6 | 0.4 |
| **Young Adults (18-25 years) (%)** | 8.5 | 5.4 | 0.8 |
| **Adults (26 years or older) (%)** | 4.1 | 1.8 | 0.5 |

More recent data, presented in the 2020 NSDUH, reported that around 9.3 million people misused prescription pain relievers in the past year, where young adults (4.1%) continued to be more likely to misuse pain relievers than youths (1.6%) and adults (3.4%). Around 6.2 million people misused tranquillizers or sedatives in the past year, *where young adults (3.7%) continued to be more likely to* misuse tranquillizers or sedatives than youths (0.9%) and adults (2.2%). In addition, the 2020 NSDUH reported that 4.8 million people misused prescription benzodiazepines in the past year, with higher rates among young adults (3.3%), followed by adults (1.6) and youths (0.6%)(30). In both reports, the most commonly misused pain relievers were hydrocodone (2.7% misusers in 2015 vs 1.7% misusers in 2020), followed by oxycodone (1.6% misusers in 2015 vs 1.1% misusers in 2020)(29,30). In 2015 the most commonly misused tranquillizers were benzodiazepines, in particular alprazolam, with a record of 4.1 million alprazolam misusers. For sedatives, the most frequently misused were zolpidem (1.1 million people)(29). Studies have reported that friends or relatives are the most common source of prescription opioids, sedatives and hypnotics, tranquillizers, and anxiolytics, including benzodiazepines, followed by a healthcare professional, such as a physician(26,28–33).

### 1.2.2. European Union: Overview

In some EU countries an increase in prescription drug abuse and misuse has been observed(6,34). For example, in France, the consumption of gabapentinoids (pregabalin and gabapentin) increased between 2010 and 2019, with 70.9% of abuse reports observed in 2018 and 2019(35). Another study in France reported that 49.7% of the survey subjects (average age of 48 years and mainly women) were dependent on at least one benzodiazepine or z-drug, where the most prescribed benzodiazepines/z-drugs were alprazolam (24.2%), followed by bromazepam (18.7%) and zolpidem (13.9%)(36). In Germany, a study reported that in the 400 study subjects (elderly inpatients admitted to hospital), 10.8% (n=43) presented a dependence on opioid analgesics, whose addiction severity was mild in 65.1% of cases and severe in 11.6%(37). A Swedish study on the general population between 2008 and 2009 reported a total prevalence of 5.0% for non-medical use of prescription analgesics, sedatives and combined non-medical prescription drug use (NMPDU) for the Swedish population aged 15-64(38). Additionally, in the same study, the patterns of NMPDU were associated with the female gender, hazardous alcohol use, habitual smoking, and cannabis use(38).

Although many studies pointed to an increasing trend of prescription drug abuse across European countries(39), overall, the misuse of PPD in the EU is poorly understood as published evidence is non-uniform between countries and the terminology use being ambiguous.

#### 1.2.2.1. Portugal: Overview

In Portugal, the information on use and misuse of psychoactive medicinal products is almost absent. One of the primary sources is the General Directorate for Intervention on Addictive Behaviours and Dependencies (SICAD), who has published some information on the topic. One example is the "IV National Survey on the Consumption of psychoactive substances in the general population 2016/17", and the "Statistical Bulletin 2020 – Medicines". Both publications focus on the consumption of sedatives, tranquillizers, and hypnotics. Women were the main population to consume medicines, the consumption having increased with age, except for the age range 15-24, where men had a higher prevalence of consumption than women(40). Among those who consumed medicinal products 12 months before the questionnaire, 94.3% purchased them with a medical prescription, 4.3% in the pharmacy without a medical prescription, and 1.1% from family and known people(40). Compared to 2012, the sedatives, tranquillizers, or hypnotics' prevalence, used with or without prescription, decreased between the age ranges 15-74, 15-24, and 25-34 years (13.7% vs 9.4%, 3.9% vs 2.7%, and 6.8% vs 4.8%, respectively) in 2016/17(41). Additionally, lifetime prevalence of non-prescribed use of tranquillizers or sedatives in 18 years-old people increased between 2015 (7.3%) and 2016 (7.9%). In 2017 a decrease was observed (6.1%), the prevalence of use having increased once more until 2019 (7.4%)(41). Between 2011 and 2020, deaths by overdose in the presence of benzodiazepines in association with illicit substances, as well as deaths by overdose in the presence of methadone peaked in 2019, with a total of 63 overdoses, 29 involving benzodiazepines, and 14 involving methadone(41). Despite the importance of SICAD's published information, the same is limited since it mainly approaches medicinal products identified as "sedatives", "tranquillizers", "hypnotics", not being specifically known which active substances are included. In addition, SICAD's questionnaire focus on the patterns of consumption, reporting limited information on the misuse.

Pharmacovigilance is essential in monitoring the safety of the medicinal products available in the market, namely spontaneous adverse drug reaction reports (ADRs). Underreporting of ADRs is a problem common to all pharmacovigilance systems, and Portugal is no exception: in 2020, the National Pharmacovigilance System received 8,801 ADR notifications from

patients, healthcare professionals, and the industry(42)), representing a reporting date of 898 per million inhabitants.

Overall, the information gathered until now in Portugal on the use and misuse of psychoactive medicinal products is scarce and limited. Additionally, underreporting to the National Pharmacovigilance Units and the lack of published information, at national level, on the hospitalisations and deaths with psychoactive medicinal products involvement, intensifies the known gap on this topic.

## 2. Objectives

MisuMedPT – *"Uso e mau uso de medicamentos psicoativos"* – is a PhD project conceived to fulfil a national gap on what is known about how psychoactive medicinal products are used in Portugal, and to what extent they are being misused, using medicine-related hospitalisations, poisonings, and deaths as proxies for this assessment. Incorporated in the MisuMedPT project, focusing on the misuse of psychoactive medications and its morbi-mortality consequences in Portugal, this dissertation aims to:

a) Identify and explore consequences of the misuse of psychoactive prescription drugs at European and national levels.

b) Study morbidity indicators associated with the misuse of psychoactive medicinal products in Portugal during a defined period.

In order to answer to the following research questions:

1) What is known about the misuse of psychoactive medicines at European level and in Portugal?

2) What is the epidemiological pattern of ADRs reported involving the misuse of psychoactive medicines in a defined period in Portugal?

3) What are the characteristics and evolution of hospitalizations associated with the use and misuse of psychoactive medicinal products in a defined period in Portugal?

Both aims focused on the following therapeutic classes (per ATC code)/INN:

- Opioid analgesics (N02A) – tramadol/paracetamol, tramadol, tapentadol, paracetamol/codeine, fentanyl, morphine, buprenorphine, hydromorphone, oxycodone and oxycodone/naloxone;
- Medicines for the treatment of addiction disorders (N07B) – buprenorphine;
- Antiepileptics (N03A) – pregabalin and clonazepam;

- Anxiolytic benzodiazepines (N05BA) – alprazolam, lorazepam, diazepam, bromazepam and ethyl loflazepate;
- Hypnotics and sedatives (Z-hypnotic or benzodiazepine-like hypnotic) (N05C) – zolpidem;
- Antidepressants (N06A) – sertraline and trazodone.

# 3. Methodology

## 3.1. Scoping review

Since misuse of psychoactive substances is a vast topic and the existing knowledge presents heterogenicity, namely in the definitions of misuse, a scoping review was performed according to the framework created by Arksey and O'Malley(43), further developed by Levac et al.(44) and the Joanna Briggs Institute(45), and the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) checklist(46). The latter was used as guidance to organize the presentation of results.

### 3.1.1. Identifying the research question

Based on the first goal described in Chapter 2 and together with the research team of the MisuMedPT project, the following main research question was defined:

1) What is known from the existing literature about the misuse of psychoactive medicines in the EU?

### 3.1.2. Identifying relevant studies

The search strategy (Annex I) was developed to meet the most suitable Medical Subject Headings terms and other terms used to describe medicines' misuse to identify all relevant studies in an accurate and robust way.

PubMed, Scopus, and Web of Science were the literature databases where the search strategy was applied, considering the search criteria of each database. The searches were limited to studies published between 1st January 2011 and 31st December 2020 in English, French, Portuguese, or Spanish. Additionally, articles and reports from non-systematic searches or included in alerts originating from PubMed alerts and from the Scientific and Technical Documentation Centre of the National Authority of Medicines and Health Products (NFARMED), which came to the authors' knowledge during the conception phase of the MisuMedPT project and were considered relevant, were also analysed.

All results retrieved were exported to Mendeley Reference Manager Application, which was also used to exclude all existing duplicates.

### 3.1.3. Study selection

To perform an effective study selection, two reviewers of the research team defined inclusion and exclusion criteria (Table 3) based on the Population, Concept, Context, and Type of Evidence framework(45):

1. **Population:** individuals of all genders older than 15 years old
2. **Concept:** misuse of psychoactive medicinal products and its possible consequences
3. **Context:** studies published between 1st of January 2011 and 31st of December 2020 in English, French, Portuguese, or Spanish in any country of the European Union
4. **Types of evidence:** observational studies, research letters, letters to the editors, editorials, surveys, reports, all types of reviews and conference proceedings. Articles where an abstract was expected but was not available, were excluded.

The study selection involved two phases, where both reviewers applied the pre-defined eligibility criteria: an abstract inclusion/exclusion phase, and a full-text article inclusion/exclusion phase. In order to guarantee the consistency of eligibility criteria application, ensuring the robustness of the study selection process, a pilot-test was performed in both phases. Disagreements about study eligibility of articles in both phases were discussed between the two reviewers until consensus was reached or by arbitration of a third reviewer, if necessary.

**Table 3: Eligibility Criteria**

| PCCToE Framework | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| **Population** | ✓ Individuals older than 15 years old<br>✓ Individuals of all genders<br>✓ Individuals who have misused prescription drugs | |

| | | |
|---|---|---|
| | ✓ Individuals with substance use disorder | |
| **Concept** | ✓ Studies focusing on the prevalence of psychoactive medicines' misuse<br>✓ Studies reporting morbi-mortality consequences of misuse (namely adverse drug reactions, poisonings, hospitalisations, or deaths)<br>✓ Studies reporting different forms of medicines' misuse<br>✓ Studies reporting data of any of the following therapeutic groups of interest: opioid analgesics, antidepressants, benzodiazepines, antiepileptics, sedatives/hypnotics or medicines used in opioid agonist treatment | × Studies focusing mainly on non-pharmaceutical therapies or drugs<br>× Studies focusing on treatment of psychoactive substance misuse<br>× Studies conducted on specific patient or population groups not expected to have a higher risk of misuse of psychoactive medicines (patients with neurodegenerative diseases, pregnant women)<br>× Studies focusing on how drug use disorders increase the risk of other diseases or how other diseases influence the risk of drug use disorders<br>× Studies focusing on reasons for medicines misuse<br>× Studies focusing on economic, ethical, social, or psychological aspects of substance misuse |
| **Context** | ✓ Studies reporting data from any country of the European Union, including the United Kingdom<br>✓ Evidence published between 2011 and 2020, covering a | |

| | | |
|---|---|---|
| | period of data ending during or after 2011 | |
| **Types of Evidence** | ✓ Observational studies<br>✓ Surveys<br>✓ Research letters<br>✓ Letter to the editors/Editorials<br>✓ All types of reviews<br>✓ Reports<br>✓ Conference proceedings<br>✓ Evidence published in English, French, Portuguese, or Spanish | × Qualitative studies<br>× Evidence from social media<br>× Books<br>× Commentaries/Viewpoints<br>× News<br>× Case studies/reports<br>× Clinical trials<br>× Preclinical/animal studies<br>× Study protocols<br>× Studies for which the abstract is not available, where an abstract would be expected to exist<br>× Articles for which the full text is not available |

## 3.2. Hospital Morbidity Database

The second aim of this dissertation was not fulfilled, having only be possible to carry out a preliminary analysis of the Hospital Morbidity Database (Source: ACSS - *Administração Central do Sistema de Saúde, I.P.*).

The preliminary analysis was conducted to analyse the admissions to emergency departments of public hospitals of Portugal mainland of patients presenting at least one diagnosis of abuse, dependence, and poisoning, involving one of the medicinal products selected in the MisuMedPT project, from 2014 to 2018.

The information was collected from ACSS (*Administração Central do Sistema de Saúde, I.P.*) database, following a formal request, by e-mail, to this institution on:

- Data admissions on the patients admitted to public hospitals between 2014 and 2018 for suspected intoxication involving at least one of the medicinal products of interest.

No opinion from an Ethic Commission was needed since all patient's data were made available anonymised.

The variables studied in the preliminary analysis were:

- Gender
- Age
- Length of hospital stay
- Type of diagnosis (abuse, poisoning, dependence)
- Severity

# 4. Results

## 4.1. Scoping Review

After the duplicates detection and removal, a total of 1,399 articles were retrieved from the databases and other sources.

In the abstract selection phase, a total of 1,245 articles were excluded due to population (n=1, Individuals under 15 years old), concept (n=62, not reporting data of any therapeutic class of interest = 9; specific patients/populations = 10; how drug use disorders increase the risk of other diseases = 3; focus on treatment of psychoactive substance misuse = 17; focus on non-pharmaceutical therapies or drugs = 8; focus on economic, ethical, social, or psychological aspects of substance misuse = 10; focus on reasons for medicines misuse = 5), context (n= 1070, country = 995; evidence not published between 2011 and 2020, nor covering a period of data ending during or after 2011 = 75), and type of evidence (n=112; no abstract available = 8; book = 12; commentaries/viewpoints/news = 34; clinical trials =18; case reports/studies = 26; qualitative studies = 3; social media = 11).

In full-text phase, a total of 154 articles were analysed, of which 44 were excluded due to concept (n=6, focus on illegal drugs = 1; focus on economic, ethical, social, or psychological aspects of substance misuse = 2; focus on treatment = 2; not reporting data of any therapeutic class of interest = 1), context (n=25, country = 17; evidence not published between 2011 and 2020, nor covering a period of data ending during or after 2011 = 8), and type of evidence (n=13, no full-text available = 2; case reports/studies = 2; commentaries/viewpoints = 5; letter = 2; protocol = 1; social media = 1). After both phases concluded, a total of 110 articles were included. The results are presented above (Table 4).

**Table 4: Scoping Review Results**

| Reference | Country | Type of Study | Results/Key findings |
|---|---|---|---|
| **Reimer et al., 2016(47)** | Australia, UK, Israel, Singapore, and the USA | Systematic Review | The misuse and diversion of OST impact the individual poor adherence to treatment, mortality increase and quality of life, and impact society's unsupervised use, unintended exposures to children, drug-related criminal behaviour, and economic costs. Deaths where methadone was present on the death certificate increased from 201 to 249 between 2003 and 2013 in England and Wales. Between 2004 and 2014, 17 deaths were reported, most related to methadone and buprenorphine. The expert opinion agreed on the increase in individual mortality rates, the increase in accidental ingestion of OST medicines in children, and the increase in crime rates. |
| **Koechl et al., 2012(48)** | Austria | Review | Licit and illicit substance abuse by the elderly is associated with a wide range of health risks, social exclusion, and isolation. Ageing is often characterised by social, psychological and health problems, which are also risk factors for substance misuse and dependence. Addiction can be mistaken for depression and dementia in elderly patients, which explains the underestimated prevalence of addiction in this population. Incorporating gender mainstreaming into the public health policy is essential as gender and age are important factors in the treatment of dependence. |

| | | | |
|---|---|---|---|
| **Silbernagl et al., 2019(49)** | Austria | Retrospective observational study | Inmates with ADHD symptom status were significantly younger at first substance abuse, reported more drug overdoses, longer duration of cocaine and prescribed medication abuse and more in- and outpatient treatments. For all inmates in OMT, a high rate of psychiatric comorbidities was observed (78.9%). |
| **Lyphout et al., 2019(50)** | Belgium | Retrospective observational study | There were 2119 presentations to the ED of the Euro-DEN project sentinel centres associated with recreation use of 25 different BZD and/or z-drugs, of which 77.3% were prescription drugs. Clonazepam (29.5% of presentations), diazepam (19.9%), alprazolam (11.7%), and zopiclone (9.4%) were the most commonly used BZD/z-drugs, having the proportion of types of BZD/Z-drugs related to ED-presentation varied between countries. There was a moderate (Spain, UK, Switzerland) to high (France, Ireland, Norway) positive correlation between ED presentations and sales data, with a higher correlation in countries with higher ED presentation rates. |
| **Lehne et al., 2018(51)** | Belgium, Denmark, Germany, the Slovak Republic, Spain, Turkey, and the UK | Retrospective observational study | In all countries, students reported having used NPPSSP at least once in their lifetime, having the prevalence rate varied from 4.0% of females and 2.3% of males in Belgium to 12.5% of females and 18.2% of males in the UK. 51.0% of students perceived their peers' NPPSSP use to be higher than their personal use, 62.9% perceived that the peer approval towards NPPSSP was identical to their personal approval, and 29.7% higher than their personal approval. |

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| **Kuzman & Posavec, 2016(52)** | Croatia | Retrospective observational Study | 9.64% of students answered positively about using tranquillizers or sedatives prescribed by a doctor in 2011. A higher probability of tranquillizers/sedatives use was associated with students who used marijuana in the last 12 months, who had lower school performance, who missed school days, who had a risk behaviour, who had low satisfaction with parents, family financial status and with themselves. Students who drank six times or more in the last 12 months had twice the probability of using tranquillizers/sedatives, and those who had symptoms of depression had a twice or three times higher probability of prescription drug use. Students who non-medically use tranquillizers/sedatives had six to ten higher probabilities of using prescription drugs, having the risk increase from 2003 to 2011. |
| **Delaš Aždajić et al., 2019(53)** | Croatia | Retrospective observational study | An increase of 4.1% in BZDs prescriptions was observed between 2015 and 2016. The number of patients who used BZD increased from 860,664 (8.67%) in 2015 to 876,046 (8.76%) in 2016. Diazepam was the most prescribed BZD, followed by alprazolam. BZD consumption was higher among female patients in all age groups, with the number of used BZD prescriptions per patient being highest in the oldest age group (80 +), comprising seven prescriptions per patient in 12 months. |
| **Schjerning et al., 2016(54)** | Denmark | Retrospective observational study | 9.6% of individuals were prescribed more than 600 mg/day of pregabalin during six months and 6.5% during 12 months. Doses above 1200 mg/day of pregabalin were prescribed in 0.65% |

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| | | | of individuals during six months and 0.33% during 12 months. Male gender, age between 20 and 40 years, and prescription of antipsychotics and BZD were associated with an increased risk of being prescribed pregabalin in the above-recommended doses. |
| **Eriksen & Bjerrum, 2015(55)** | Denmark | Retrospective observational study | Prescriptions of long-acting and short-acting BZD registered a decrease of 66% and 37% between 2003 and 2013, respectively (from 25.8 DDD/1000 inhabitants/day in 2003 vs 8.8 DDD/1000 inhabitants/day in 2013 for long-acting BZD; from 26.1 DDD/1000 inhabitants/day in 2003 vs 16.4 DDD/1000 inhabitants/day in 2013 for short-acting BZD). The variation of prescriptions went from a reduction of 92% for flunitrazepam and no reduction for clobazam, and a higher reduction of 71% for triazolam to a lower reduction of 28% for zolpidem. |
| **Lindestrand et al., 2015(56)** | Denmark | Retrospective observational study | There was no relationship between opioid administration to opioid-naive patients during hospitalisation for hip fracture and continued use of opioids 3 and 6 months after discharge. Trends suggesting opioid abuse were not seen. Opioid use before admission and a pre-existing diagnosis of osteoporosis upon admission were predictors of continued opioid analgesics use. The results demonstrated no general reason to hold back from prescribing opioids based on a fear of potential abuse or increased mortality. |
| **Scholten et al., 2019(57)** | Denmark | Retrospective observational study | In 2015, Germany, Canada, and Austria had the highest adequacy of opioid consumption, while Nigeria, Myanmar, and Madagascar had the |

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| | | | lowest adequacy of opioid consumption. Findings showed that the inequality in the sufficiency of access to opioid analgesics continues to be massive worldwide. Only 840 million people (11.5%) lived in countries with a moderate or adequate consumption level. The AOC Index developed was a quick indicator, useful for policy purposes and showed the magnitude of opioid adequacy. |
| **Simonsen et al., 2020(58)** | Denmark | Retrospective observational study | Fatal poisonings in Nordic countries in 2017 occurred mainly in men, involving women in 7-23% of fatal poisoning. The age range was 14-70 years, having the median age of 41 years being higher in Denmark and Norway. Opioids, including buprenorphine, registered the highest cause of death. The median number of drug use per case varied between 4 and 6. 73.5% to 88% of the cases involved BZDs in all countries, being the most frequently detected in fatal poisonings. |
| **Jacqui Wise, 2016(59)** | Denmark, Germany, the UK, Spain, and Sweden | Retrospective observational study | Non-medical prescription drug use was reported to be lower in Germany and higher in the UK, Spain, and Sweden. Regarding opioids, higher levels of non-medical use were reported in Spain (18.3% in a lifetime) and the UK (14.6% in a lifetime). Spain and Sweden reported higher levels of non-medical use for sedatives, followed by the UK and Denmark. Male, unemployed, and non-white people were the main characteristics of non-medical prescription drug use. Family and friends were the primary sources of prescription drugs for non-medical use (44% for opioids and 62% for |

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| | | | sedatives), followed by taking drugs from other people without their knowledge. |
| **Taylor et al., 2019(60)** | UK (England) | Review | Between 2017-2018, 11.5 million adults in England received and had dispensed at least one prescription of antidepressants (17% of the adult population), opioid pain medicines (13%), gabapentinoids (3%), and z-drugs (2%). The rate of antidepressants prescription increased from 15.8% of the adult population to 16.6%, and for gabapentinoids from 2.9% to 3.3%, between 2015-2016 and 2017-2018, respectively. The annual number of opioid pain medicines prescriptions slightly decreased from 2016. The most combined prescription drugs were antidepressants and opioids, with 14% receiving a combination which included both these classes and up to 3 other classes. The most common combination of 3 classes was antidepressants, opioids and gabapentinoids. Women represented the higher rates of prescription (alone and concomitantly), and generally, the rates increased with age. BZDs, z-drugs, opioid pain medicines and gabapentinoids were associated with dependence and withdrawal, whereas antidepressants were only associated with withdrawal. |
| **Farias et al., 2017(61)** | UK (England) | Retrospective observational study | Primary care was where DFM was potentially most prescribed, having in 2015 opioids been twice as likely to be prescribed (5%) than BZDs, z-drugs, and GABAergic (2%). DFM prescription increased from 6% in 2000 to 9% in 2015, except for BZDs, which decreased from 3.5% to 2.5%. People living in deprived |

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| | | | neighbourhoods, older people and people with cancer or epilepsy tended to be prescribed BZDs, z-drugs, and opioids for longer. DFM was more likely to be prescribed to women; the average age was around 60 years for both women and men, except for BZDs prescriptions from 2000 and 2004, where women were older than men. |
| **Sehmi et al., 2019(62)** | UK (England) | Descriptive analysis | For individual prescriptions to exceed 30 days, BZDs decreased in 2014, and since 2004 the same has happened for GABAergic. For the length of continuous prescribing periods, a decrease in periods exceeding 30 days was observed for BZDs. For z-drugs, 37% of continuous prescribing periods exceeded 30 days, 13% exceeded six months, and 6% exceeded 12 months. For opioids, the proportion of continuous prescribing periods exceeding 30 days decreased from 2001 (38%) to 2014 (34%), with no reduction observed for longer periods. From 2010 to 2014, continuous gabapentin prescribing periods exceeding 30 days decreased (76% to 60%). Older people were more likely to be prescribed BZDs, z-drugs and GABAergic for more than six months, contrary to opioids that were more likely to be prescribed to younger people. |
| **Layton et al., 2014(63)** | UK (England) | Retrospective observational study | Among the included patients with prescribed products, most risk factors reported for dependence were smoking, psychiatric disorders and a history of substance misuse. Among patients with aberrant behaviour, the most common was escalating drug use. The patients' |

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| | | | characteristics were younger, receiving higher tests, effective/maintenance doses, and having longer treatments and indications other than cancer pain. Additionally, patients with aberrant behaviour presented a history of alcohol abuse/substance misuse and psychiatric disorders as risk factors for dependence. The prevalence of at least one pre-existing risk factor for dependence was 26%. |
| **Osborn, 2018(64)** | UK (England and Wales) | Retrospective observational study | In 2017, 3,756 deaths related to drug poisoning were reported. The number of male fatalities decreased (91.4 deaths per 1 million population in 2016 to 89.6 in 2017), and female fatalities increased for eight consecutive years to 42.9 deaths per 1 million in 2017. Drug misuse was the main cause of deaths, involving a higher rate of males (71%) than females (57%), and reporting an increase between people between 50 and 69 years and those aged 70 years or older. Deaths involving fentanyl increased by 29% and were mixed with heroin, and codeine deaths increased by 20%, contrary to deaths involving buprenorphine, methadone and oxycodone that decreased. The number of deaths involving antidepressants increased (8.6 deaths per 1 million population). Deaths related to zopiclone, and zolpidem also increased in 2017 (126 vs 94 in 2016); the same happened with pregabalin (4 in 2009 to 136 in 2017). |
| **Lyndon et al., 2017(65)** | UK (England and Wales) | Retrospective observational study | An increase of 24% per year was registered for pregabalin and gabapentin prescriptions from 2004 to 2015, having the number of deaths involving gabapentinoids from fewer than one |

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| | | and Interview | per year between 2009 and 2015 (79% involved opioids). Among heroin users, pregabalin was reported to be easier to obtain; some mentioned that a doctor prescribed it, and others obtained it in the streets. Between 30 heroin users interviewed, pregabalin was used orally in a tablet form, and doses ranged from 300 and 1,500 mg. |
| **Häkkinen et al., 2014(66)** | Finland | Retrospective observational study | All cases found positive for Finland's most prescribed opioids: buprenorphine, codeine, fentanyl, methadone, oxycodone, or tramadol. Of all fatal cases, at least 0.5% of the deaths in Finland during 2010-2011 involved prescription opioid abuse, a proportion higher than the estimated 0.1%-0.2% reported in 2005. Buprenorphine was the most abused prescription opioid. Tramadol was, by its figures, the second most abused prescription opioid, with an abuse percentage of 29.4% of all tramadol-related deaths. |
| **Kurko et al., 2015(67)** | Finland | Systematic review | Despite the decrease in BZD use during the last decade in most countries, long-term use appears to remain common. Treatment over six months or longer during a year was the most common definition for long-term BZD use. The prevalence of long-term BZD use in the general population was estimated to be about 3%. Long-term use typically involved treatment with low, steady dosages of BZD continuously. In elderly patients, long-term BZD uses and exceeding recommended doses was relatively common. |

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| **Haukka et al., 2018(68)** | Finland | Retrospective observational study | In 50.4% of the studied cases, at least one medicine was detected without a prescription. Clonazepam, alprazolam, and tramadol were the most prevalent non-medical findings. The risk of non-medical use of prescription drugs was especially high in cases with a history of drug abuse (88.5%) and fatal poisonings (71.0%). A valid prescription for one or more of any psychoactive drugs was associated with lower odds for non-medical use of the studied substances. Additionally, the higher the proportion of psychoactive drugs prescribed by a psychiatrist, the lower the probability of non-medical use. Non-prescribed psychoactive drugs were commonly found at post-mortem in drug poisoning deaths in Finland, with a history of drug abuse as a significant contributing factor. |
| **Touchard et al., 2020(69)** | France | Retrospective observational study | Of the 81,174 individuals with at least one hypnotic drug reimbursement, 39.1% were men, and the mean age was 59.8 years. Among 2143 individuals had at least one reimbursement of zolpidem. Before the decree, 26% had at least one reimbursement of zolpidem, whereas it dropped to18.4% after the decree. Among the 545 long-term users, the reimbursement of zolpidem was discontinued after the decree for 60.4%, and 24.2% retained zolpidem as a treatment, having zopiclone as the primary drug replacing zolpidem (6.4%). Among the 1598 excessive users, the reimbursement of zolpidem was discontinued after the decree for 16.5%, and 56.3% retained zolpidem as a treatment, |

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| | | | having zopiclone as the primary drug replacing zolpidem (12.2%). |
| **Driot et al., 2019(70)** | France | Retrospective observational study | Misuse concerned 1112 subjects in the pregabalin group, 130 in the gabapentin group and 313 in the duloxetine group. Most events occurred within the first two years of prescribing, with one-third of treatment sequences with misuse followed by at least one other sequence with misuse. 11.3% of pregabalin users, 5.9% of gabapentin users and 8.3% of duloxetine users experienced a first sequence of misuse, which included 839 women, and the mean age was 54.2 years. After the first episode of drug misuse, 11.6% of gabapentin and 10.7% of pregabalin and 7.3% of duloxetine misusers developed a primary addiction. The risk factors of misuse were associated with pregabalin, age, number of different prescribers, presence of cancer, multiple sclerosis, neuropathy, depressive disorders, and methadone. |
| **Balayssac et al., 2018(71)** | France | Retrospective observational study | Among all pharmacy students, 6.1% used only psychotropic medications, 18.2% only illegal drugs, and 3.3% used both. Between psychotropic medications users, 43,1% of BZD and z-drugs were self-medicated and 40.3% received a medical prescription, and 23.8% used them non-medically; whereas 36.6% of opioid users were self-medicated, 33.8% received a medical prescription, and 42.3% used them non- |

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| | | | medically. The mean age of psychotropic medication users receiving a medical prescription was 22.8 years, and for the ones self-medicated was 23.3 years. The proportion of females for students receiving a medical prescription was 62.2%, and 64.3% for self-medicated students. The most common psychotropic medications used were alprazolam, bromazepam, zolpidem, codeine, and tramadol. |
| **Eiden et al., 2016(72)** | France | Retrospective observational study | Between 2002 and 2012, buprenorphine ADRs ranged from 1.5% and 1.8% of the annual total cases notified, being the misuse with other drugs connected mainly with BZD. The ADRs reported were associated primarily with men, with a mean age of 34 years, and the most common route of administration notified was intravenous (68%). The OPPIDUM survey reported that buprenorphine misuse characteristics decreased significantly. The DRD reported a population constituted mainly of men (73.2%), with a median age of 40 years and a median daily dose of 7.6 mg. |
| **Peyriere et al., 2013(73)** | France | Retrospective observational study | Between 1996 and 2011, morphine sulphate consumers and abusers were predominantly men, young (mean age: 34 years), with a history of abuse. BZD, cannabis, cocaine, and heroin were the most common substances combined with morphine sulfate. The street and medical prescriptions were the most sources of morphine sulfate in spontaneous notifications, and the OPPIDUM survey reported an increase in the acquisition by dealers and doctor shopping. Falsified or forged prescriptions of |

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| | | | morphine sulfate involved more men than women, with a mean age of 35.4 years, where false prescriptions and prescriptions written on a stolen form were the main criteria for suspicion of falsification. |
| **Binder et al., 2016(74)** | France | Retrospective observational Study | Of patients under OST, 22.9% were women, mean age of 38.3 years and presented a distribution of different forms of 66% brand names and 31% generic. The mean dose for brand-name products was 8.4 mg, and for the non-brand-name product, 6.3 mg. Co-prescription of BZD was 20.6%, and prescriptions from an institutional physician represented 13.6%. Those who preferred the brand name had higher addiction severity index scores, excessive alcohol consumption and daily psychotropic co-medication more frequently. Additionally, those having adopted OST with brand-name products after using generic forms more frequently presented an elevated addiction severity index score and a dosage higher than 8 mg than brand-name users with no generic forms experience. |
| **Eiden et al., 2019(75)** | France | Retrospective observational Study | Participants were mainly women with a mean age of 50 (46.2% had symptoms of anxiety or depression) and younger than 65 (50.0% had symptoms of anxiety or depression). The percentage for "Desire to stop", "Craving", "The drug has been repeatedly used in situations where it was physically dangerous", and "Withdrawal symptoms" was significantly higher for opioids in the MME ≥100 category. |

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| | | | The assessment of opioid misuse revealed that it was present in 76.9% of the patients and was severe in 51.9%. |
| **Nordmann et al., 2011(76)** | France | Review | Spontaneous reports and risk management plans, drug-related deaths, population surveys, drug-related emergency visits, data from poison control centres, prescription/reimbursement databases and electronic prescription monitoring programmes are several sources of misuse monitoring systems. Some countries, like France, perform triangulation between several sources to better understand the phenomenon. France is the only EU country with a formal system for assessing potential abuse of psychoactive substances. |
| **Lapeyre-Mestre, 2013(77)** | France | Review | Addictovigilance is the monitoring of abuse, misuse and dependence cases involving any psychoactive substance, except for tobacco and alcohol. The French Addictovigilance Network aims to assess the potential for abuse and dependence on psychoactive medicines by combining data from several sources, namely spontaneous reports from healthcare professionals, information from healthcare databases, surveys, and forensic and hospitalisation data on the consequences of medicines misuse. |
| **Faure et al., 2013 (78)** | France | Retrospective observational study | Fifty-three patients (64% women), with a median age of 52 years, were included in the study, with the main pain reported as back and neck pain. Morphine (43%) and fentanyl (42%) were the most used opioids. At admission, 62% of patients presented a depressive state. A significant misuse of strong opioids by |

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| | | | inappropriate use of different strong opioids was reported in more than half of the cases. |
| **Cadet-Taïrou, 2015(79)** | France | Retrospective observational Study | The break-up of BZD users among harm reduction facilities clients in different use profiles, cross-checked with the prevalence of psychoactive medicine misuse, confirms that the latter is primarily related to the intensity of addictive practices and risks taken. Misuse is more frequent among users with high consumption of opiates and substances circulating in festive techno events. |
| **Lapeyre-Mestre & Dupui, 2015(6)** | France | Review | France set up its Addictovigilance system in the early 90s, aiming to assess the potential for abuse of psychoactive substances (licit or illicit) using the combination of several sources. In other European countries, despite several pharmacoepidemiological sources of information, such as pharmacovigilance and toxicology databases, none is systematically available in all European countries. It becomes difficult to assess the prevalence of use, abuse, and dependence, identify risk factors and estimate the impact in terms of mortality and morbidity. |
| **Guerlais et al., 2015(36)** | France | Retrospective observational Study | 75.7% of patients used at least two psychotropic drugs, and 12.9% used four or more. An antidepressant from the SSRI family was found to be combined for 45.7% of patients, 22.2% of patients using an antidepressant of another family combined, and 5.2% presented combined drug use with other anxiolytic other than |

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| | | | a BZD/z-drug. 77.4% of BZD or related drug users take at least three medications. 23.6% of included patients have a prescription for at least 2 BZD or related drugs, prescribed mainly by a general practitioner (46.0%). The most consumed drugs were alprazolam (24.2%), bromazepam (18.7%) and zolpidem (13.9%). The risk of developing BZD/z-drugs dependence is significantly associated with psychiatric history and the quantity of BZD/z-drugs taken. |
| **Roussin et al., 2015(81)** | France | Review | Between 2012 and 2013, the rate number of cases of tramadol abuse and dependence increased by 2.9%, not having exceeded the increase in pharmaceuticals containing tramadol, alone or combined with paracetamol, sales. Addiction monitoring for tramadol in France did not conclude a significant public health problem of abuse and dependence, not invalidating the importance of awareness of its abuse and dependence to healthcare professionals. Implementing repeated observational programs on abuse and dependence on psychoactive drugs is an essential aid to health authorities. |
| **Deschenau et al., 2016(82)** | France | Review | For opioids (illegal and prescription opioids), the time between regular to problematic use is similar between men and women; however, analysing illicit opioids and prescription opioids separately, men progress to problematic use slower than women (3.10 vs 0.14 years). It is essential to focus on specific subgroups of polydrug users, considering socioeconomic and medical factors, drug use and administration |

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| | | | route to perform successful prevention and treatment. |
| **Airagnes et al., 2016(83)** | France | Review | The study reported that the use of BZD becomes more prevalent with ageing, reaching a nine-fold risk of using more than 189 daily doses/year for subjects aged 85 or older compared to younger adults. Two-thirds of the cases reported inappropriate use of BZD, having the most common situations been excessive duration and/or dosage of a medical prescription. Female gender, multiple prescribers and polypharmacy, chronic pain, physical disabilities or reduced mobility, cognitive impairment, social withdrawal, and suicidal ideation were the individual factors associated with the BZD and BZD-related hypnotic misuse reported in the elderly population. |
| **Frauger et al., 2017(84)** | France | Retrospective observational study | OPPIDUM data are very valuable for monitoring psychoactive substances for which the potential for abuse and dependence is known (such as morphine) or for early identification of emerging abuse phenomena, supplementing the few data resulting from spontaneous reports. Morphine was the primary prescription opioid used, and diazepam and oxazepam were the BZD most consumed. OPPIDUM data can be used alone or with other surveillance systems, spontaneous notifications, and data from health insurance databases. This multisource approach helps address the complex and |

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| | | | multidimensional abuse phenomenon, overcoming each method's methodological limits. |
| **Rolland et al., 2017(85)** | France | Review | Most recommendations offered to clinicians regarding managing prescription opioid misuse associated with pharmacological dependence on the same prescription opioid are based on expert opinion, reflecting a lack of information on how to address these patients. The main areas to focus on are the treatment of addictive behaviour, the adapted treatment of any residual pain, and the treatment of comorbidities and management of associated social problems. Initiatives to inform prescribing physicians, political decision-makers, and the public will allow a growing awareness of this problem. Hopefully, the investment will be made in research to address France's still insufficiently studied problem. |
| **Ponté et al., 2018(87)** | France | Retrospective observational study | Strong opioid analgesics had the highest DSI (2.79%), and the BZD anxiolytics had the highest DSQc (24,43 DID/100 000). Although the DSQc of anxiolytics and hypnotics was 10-fold higher than opioids, the DSI of opioids for moderately severe to severe pain were mostly higher than hypnotics (2.06%) and anxiolytics (1.81%). Opioid analgesics were used by 1200 000 patients (14% had a prescription during a year). The same proportion was found with |

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| | | | BZD (14.6%), while its use remains high in France. |
| **Dupui et al., 2019(88)** | France | Review | The literature search of articles published since 2004 on the interest of health insurance databases in the field of addictovigilance and drug safety monitoring focusing on drugs with abuse potential retrieved 34 articles corresponding to DUS, ten articles focused on complications of drug abuse and misuse, and nine studies deal with different methodological issues. The DUS focused on the characteristics of the use of different drugs with a suspected or well-known abuse potential, some investigating patterns of psychoactive medication use in specific populations. Opioids were the most widely cited in 9 specific studies, followed by BZDs in 8 specific studies and psychostimulants in 5 particular studies. Regarding studies focusing on complications of drug abuse and misuse, some were based on hospital databases to identify and describe serious complications in the field of addictovigilance, and others were observational studies aiming to identify factors associated with some specific outcomes. |
| **Chenaf et al., 2019(89)** | France | Retrospective observational study | The annual prevalence of PO analgesic use from 2004 to 2017 has decreased by 8.9%, from 19.2% to 17.5%. Strong opioid use increased from 0.54% to 1.1%, while weak opioid use dropped from 19.1% to 17.1%. Among |

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| | | | PO analgesic users, the proportion of strong opioid users doubled, from 2.8% in 2004 to 6.0% in 2017, while the proportion of weak opioid users decreased from 97.2% to 94.0%. From 2004–2017, the DDD/1000 inhabitants/day for weak opioid analgesics decreased by 6.8%, contrary to strong opioids, which increased by 59%. Irrespective of the year, PO analgesics were typically used for noncancer pain. Shopping behaviour increased by 34%, from 0.50% in 2004 to 0.67% in 2017, for all PO analgesics. |
| **Vodovar et al., 2019(90)** | France | Review | France, like the rest of the world, faces a serious public health problem linked to the use of opioids. Although on a smaller scale than the USA, this worrying situation could worsen in the years to come. Even though safe and effective treatment for opioid poisonous patients is widely available, prevention is the best response to reduce the prevalence of overdose. Prevention needs to take place at multiple levels and be based on sound opioid use, patient education and screening for opioid use disorders |
| **Micallef et al., 2019(91)** | France | Review | The tools of pharmacosurveillance developed by the French Addictovigilance Network are multidimensional, including spontaneous reporting, DRAMES, OPPIDUM, and heterogenous data sources (such as data from hospitals or claims databases). The French addictovigilance system provides updated knowledge each year on the methods of use and exposure to psychoactive medicines and |

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| | | | identifies evolving trends, exploring their potential for abuse and dependence. These programs, unique in France and without equivalent outside France, are renewed yearly. |
| **Baumevieille et al., 2019(92)** | France | Review | Addictovigilance refers to a monitoring system developed in France since 1990. The French medicines agency, created in 1993, was involved in this monitoring system; pharmacodependence evaluation was added by law to the missions of the agencies AFSSAPS (1998) and ANSM (2011). Although pharmacodependence centres and AFSSAPS have used it since 2007, the term ‘‘Addictovigilance’’ first appeared in French Law in 2017. It is defined as the monitoring of the use of psychoactive substances (medicines, illegal drugs, or plants) and their side effects (apart from alcohol and tobacco). |
| **Hedenmalm et al., 2019(93)** | France and Germany | Retrospective observational study | Despite tramadol prescribing being higher in females and increasing with age, in both France and Germany, the prevalence of tramadol prescription decreased during the study period. In France, in combination with paracetamol, tramadol was the most commonly prescribed tramadol type (59.7%), while in Germany was plain tramadol SR formulations (56.1%). In both countries, higher doses were associated with males and those in the middle age groups, and plain tramadol SR formulations had higher doses and duration. The mean daily doses of tramadol increase with the increase of prescriptions by patients during the study period. An increasing age, history of abuse or misuse and |

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| | | | treatment with plain tramadol SR formulations were the risk factors of long-treatment reported. |
| **Hider-Mlynarz et al., 2018(94)** | France, Germany, UK, Italy, Spain, Denmark, and Sweden | Retrospective observational study | From 2006 to 2015, paracetamol was the most consumed analgesic in France, and the use of oxycodone has increased significantly (a 7-fold increase). Despite sharing common regulations for medications, different patterns of consumption were observed across Europe in 2015. France ranked first for paracetamol consumption, but its use of strong opioids was among the lowest. Oxycodone may, together with fentanyl, have replaced part of the market share of morphine. The difference in analgesic preferences observed between European countries in this study may reflect the role of national guidelines, prescription policies and the marketing strategies of pharmaceutical companies, which can differ between these countries. Still, it can also be explained by cultural backgrounds and local traditions in managing chronic pain. |
| **Marschall et al., 2016(95)** | Germany | Retrospective observational study | 1.3% of all insured persons in Germany received long-term opioid prescriptions for CNCP, of which 15.5% received high-dose prescriptions (≥100 mg morphine equivalent/day). Only 0.56% of patients with CNCP had a 1-year prevalence of opioid abuse/dependence on prescribed opioids. Long-term opioid treatment was more associated with |

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| | | | women and older people, and male gender and mental health diagnosis were more related to high-dose opioid use. Co-prescriptions of anti-convulsants were more associated with opioid use in Germany. The negative association of high-dose prescription with older age and internal diseases may indicate the cautious use of opioids in elderlies with multiple comorbidities. |
| **Casati et al., 2012(96)** | Germany and Portugal | Systematic review | Opioid analgesics, methadone, buprenorphine, BZDs, and z-drugs were the main groups of misused medicinal products detected in the EU. Among opioid analgesics, fentanyl showed a significant misuse and dependence potential. Tramadol was found to be often misused. Women, the elderly, subjects with a history of substance dependence, and individuals with a history of alcohol and sedative/hypnotic dependence are the population identified as having a higher risk. |
| **Iwanicki et al., 2020(97)** | Germany, Italy, Spain, and the UK | Descriptive study | Distribution, use, misuse, and abuse of tramadol and three conventional prescription opioids in Europe showed similar patterns across all countries. Codeine was used by the most significant number of adults in all countries, and oxycodone was used by the fewest. Similarly, codeine was misused by the largest number in all countries and abused by the largest number in 3 of 4 countries except for Italy. In Germany, Italy, Spain, and the UK, data from harmonized national surveys on prescription drug use showed that tramadol misuse and abuse were uncommon in an absolute number |

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| | | | of cases and in comparison to conventional prescription opioids. Despite high availability, tramadol had a low rate of misuse and abuse in all countries. |
| **Papazisis et al., 2018(98)** | Greece | Retrospective observational study | Among medical students, the prevalence of lifetime use was 19.3% for opioid painkillers, 7.3% for tranquillizers, 14.7% for sleeping drugs, and 1.4% for stimulants. Self-treatment was most prevalent in all non-medically used classes (18.4% for opioids, 5.4% for tranquillizers, 10.3% for sleeping drugs and 1.4% for stimulants). Lifetime and past-year use did not show significant differences between men and women compared to the association between the clinical level of students and the use of tranquillizers, indicating that senior students were more likely to misuse tranquillizers than junior students. Self-treatment with tranquillizers tended to be more prevalent among women, contrary to recreational use, which was more prevalent among men. |
| **Kennedy et al., 2019(99)** | Ireland | Retrospective observational study | The mean age of the case subjects was 23 years; of those with age recorded, 38% were less than 18 years, and 3% were 65 or older; of those with a gender recorded, the majority were female (63%). 30% of the poisoning cases reported contained paracetamol and codeine (500 mg/8 mg), and 55% of the poisoning cases were most frequently associated with intentional overdose. Overall, reported codeine-related poisonings decreased by 53% from 2005 to 2016, mainly because of the 62% decrease in cases involving non-prescription codeine |

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| | | | products in the same period. There was no increase in the rate of pharmacy claims for the two prescription-only medications containing paracetamol and higher doses (30 mg) of codeine. |
| **Murphy et al., 2018(100)** | Ireland | Retrospective observational Study | Participants described starting BZD use with small doses, building up to higher doses, having dependence and hence compulsion to continue BZD use being observed after six weeks of use. Many participants said their limit for BZD misuse was the inability to purchase it. The study involved people between 118-25 years old and reported that dependence might occur sooner if young people used the maximum dose. |
| **Wells et al., 2018(101)** | Ireland, South Africa, and UK (England) | Retrospective observational Study | The consumption of codeine-containing products did not present a significant difference between males and females in Ireland and England. 94% of English respondents stated they consumed combination codeine-containing analgesics. 65% of Irish and 45% of English respondents said they purchased codeine-containing medicines from local pharmacies. In both Ireland and England, more females tended to agree that codeine-containing medications were harmful and addictive, as well as people with a higher level of education. |
| **Chiappini & Schifano, 2016(102)** | Italy | Retrospective observational study | Pregabalin and gabapentin spontaneous reports increased consistently year after year. Pregabalin and gabapentin ADRs involved "intentional product misuse" (32.2% and 28.3%, respectively), "drug dependence" (31.9% and |

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| | | | 31.8%, respectively), and "drug abuse" (22.3% and 24.8%, respectively). For both products, spontaneous reports involved mainly female adults. The drugs most concurrently misused in combination with pregabalin, and gabapentin included opioids (10.35% and 12.9%, respectively, of ADRs), antidepressants and BZD. In the pregabalin group, 27 fatalities were identified, mainly in female adults, and 86 were identified in the gabapentin group, mainly female adults. |
| **van Amsterdam et al., 2015(103)** | USA and UK | Systematic review | A shared market was observed for opioid painkillers and heroin in the USA and the UK. Still, the price of heroin in the USA is 7-8 times higher than in the UK, which may have prevented or retarded the development of an illegal drug market and misuse of opioid analgesics. Street heroin was ranked the most harmful opioid in the UK, followed by the non-medical use of prescription opioids. Compared to oxycodone abuse in the USA (maybe due to its high promotion and commercialization), its use was moderately harmful in the UK. This illustrates the correlation between drug harm and the prevalence of use. |
| **Kalkman et al., 2019(104)** | The Netherlands | Retrospective observational study | Between 2008 and 2017, the overall number of prescription opioid users nearly double, mainly due to oxycodone users having quadruped from 574 to 2568 per 100 000 inhabitants. Additionally, the number of opioid-related hospital admission tripled, and between 2008 and 2015, the number of patients in addiction care for OUD other than heroin increased from 3.1 to |

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| | | | 5.6 per 100 000 inhabitants. Opioid-related mortality was stable between 2008-2014 with 0.21 per 100 000 inhabitants, but after 2014 suffered an increase to 0.65 per 100 000 inhabitants in 2017. |
| **Bedene et al., 2019(105)** | The Netherlands | Retrospective observational study | In 2017, 6.0% of the total population received at least one opioid prescription (mean age, 59.3 years; 59.7% women). The rate of hospital admissions for opioid overdose was 9.2 per 100000 inhabitants in 2013 and 13.1 per 100000 inhabitants in 2017. Similarly, an increased risk of opioid overdose death was observed, from 0.83 per 100000 inhabitants in 2013 to 1.2 per 100000 inhabitants in 2017. Risk factors associated with opioid prescription included being older than 65 years and reporting feeling symptoms of depression, among others. Unemployment was not associated with an opioid prescription, and alcohol use disorder was negatively associated with an opioid prescription. |
| **Holloway et al., 2014(106)** | UK (North Wales) | Retrospective observational Study | In the study population (university students), pain relievers, in particular co-comadol, tramadol, and dihydrocodeine, were the most common prescription drugs misused, followed by tranquillizers (diazepam and temazepam), and sedatives (zopiclone, temazepam, and diazepam). One-third of the students who used prescription drugs not prescribed to them reported using antidepressants daily during the last period of misuse. Changes in the frequency of use or the quantity of medication were the most common form of misuse among students |

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| | | | using their prescribed medicines inappropriately (48%). |
| **Bates et al., 2017(107)** | UK (Northwest England) | Retrospective observational Study | 66% of the healthcare professionals that completed the study reported suspecting ATM in one or more patients weekly or more frequently, and 12% reported admitting ATM with the same frequency. ATM was suspected for anxiolytics and hypnotics (53%), weak (47%) and strong (39%) opioid analgesics, and antiepileptics and neuropathic analgesics (26%). Addiction to anxiolytics and hypnotics, opioid analgesics, and antiepileptic and neuropathic analgesics was most frequently associated with middle-aged or older patients with a history of chronic pain, depression and anxiety, and addiction to anxiolytics and hypnotics, opioid analgesics and stimulants were linked to younger patients who concomitantly used illicit substances or engaged in pleasure-seeking behaviour. |
| **Bramness et al., 2013(7)** | Norway | Bibliometric study | The USA presented higher publish evidence than any European country, than Europe as a whole. Europe had an average increase of 113.8 million papers per year. Norway, Denmark, the Netherlands, and Sweden reported a more significant increase in the number of published articles. In the field of illicit drugs, medicinal drug abuse and steroids, Norway had the highest relative number of publications, |

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| | | | followed by the USA. The Netherlands had the highest citation rate, followed by the USA and Denmark. |
| **Piskorska et al., 2013(108)** | Poland | Review | Most population with epilepsy decreased (91%) their doses or stopped the treatment with no consent from their doctor instead of abusing it (9%). The most reported forms of misuse were interrupted drug consumption, long-lasting discontinuation, single dose omissions, self-dependent reduced or increased drug doses and drug abuse. Gabapentin (53%), followed by tiagabine (45%), topiramate (44%), valproate (42%), phenobarbital (39%), and oxacarbazepine (38%), were the most misused antiepileptic drugs. |
| **Biernikiewicz et al., 2019(109)** | Poland | Systematic review | Definitions of doctor-shopping were heterogeneous. About 40% of studies examined the use of opioids, antidepressants, or other psychoactive drugs. The prevalence of doctor-shopping ranged from 0.5% among opioid users in the USA to 25% of patients registered at general practices in Japan. Comorbidities, especially mental disorders, history of alcohol and substance abuse, poor socioeconomic status, greater distance from the healthcare facility, younger age, longer disease, and poor patient satisfaction, were identified as risk factors for doctor-shopping. Factors such as a good patient-doctor relationship and a positive patient experience may reduce the rate of doctor-shopping. |

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| **Dinis-Oliveira, 2014(110)** | Portugal | Review | This review focused on the illicit potential of some xenobiotics, many of which are used firstly as medicines, like BZD, prescription opioids or antidepressants. When applicable, the addictive properties of those drugs were described. |
| **Alves et al., 2016(111)** | Portugal | Retrospective observational study | The total number of intoxication cases during the study period was 1269, with 73.8% males and 26.2% females, of which 22.85% had medicines involved. Prescription drugs were the most relevant substances involved in fatal intoxications, namely BZDs (79.96%), including their association with other substances. Antidepressants presented 38.11% of the cases and were mainly associated with suicide cases. Among all cases of suicide (347), 23.05% had toxicological tests positive for antidepressants, and 8.93% were considered suicide by poisoning with medicines, including antidepressants. Regarding opioids, of all cases where they were involved, 45.23% were positive for morphine. |
| **Faria Vaz et al., 2017(112)** | Portugal | Review | Portugal is one of the EU countries with the highest consumption rate of BZD (96 DDD/1000 inhabitants/day). Benefits of BZD treatment are limited in time, with longer treatments having a higher risk of falls and injury, withdrawal syndrome, memory impairment and dependence. BZD use should be limited to short treatments, at the lowest effective dose and in monotherapy. Concomitant use of other psychoactive substances, such as other CNS-acting medicines, illegal drugs, or alcohol, |

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| | | | potentiates the severity and extent of adverse reactions. BZD adverse reactions are dose-dependent, and their risk increases with treatment duration and BZD half-life (although BZD with shorter half-lives has greater addiction potential. |
| **Sobreutilização das Benzodiazepinas e Z-Hipnóticos na Ansiedade e na Insónia, 2017(113)** | Portugal | Review | BZDs should be discontinued gradually during 4-6 weeks to avoid withdrawal symptoms. Conversion to diazepam can be an option due to its long half-life. Non-pharmacologic measures should be used in parallel. BZD and Z-drugs should be used for insomnia only if the symptoms are serious and disabling. Antidepressants such as trazodone and mirtazapine can be used as part of the discontinuation strategy. BZD should only be used for short-term relief (8-12 weeks, including gradual discontinuation) of serious and disabling anxiety. Antidepressants (SSRIs) can be alternative treatments. |
| **Oliveira et al., 2019(114)** | Portugal | Review | BZD have six main properties and clinically relevant actions: anxiolytic, hypnotic, anticonvulsant, muscle relaxant, anterograde and retrograde amnesia, and alcohol withdrawal. More serious adverse effects can result from long-term regular use in therapeutic dosage and self-prescription or recreational use in excessive doses. Some loss of efficacy of BZD may be developed after repeated use. The rate of development of tolerance may vary for different drug effects, develop at different speeds, and can vary between individuals. |

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| **The misuse of benzodiazepines among high-risk opioid users in Europe, 2018(115)** | Portugal | Review | The misuse of BZDs was identified as a concern among large groups of the general population, such as women and older people. Among high-risk opioid users, BZDs have been connected with severe treatment challenges and are involved in many drug-related deaths. Despite being prescribed with a legitimate intention to high-risk drug users, BZD use may produce unintended health consequences, in particular, if used for more than 2-3 weeks, from part of poly-drug use (usually combined with alcohol or illicit drugs) and used not according to the prescribing guidelines. The widespread availability of BZDs increases the potential for the misuse of these drugs to pose a serious public health problem, particularly where opioid users take them. |
| **Giraudon et al., 2013(116)** | USA, and UK | Descriptive study | Although the number of deaths related to drug poisoning is not as high in England and Wales as in the USA, the overall trend is similar. Opioid deaths in which methadone has a role are becoming notable in the UK. Across Europe, the form and availability of prescription opioids vary, as do opioid substitution treatments, drug use patterns and quality of drug-related deaths data. |
| **Torrance et al., 2018(117)** | UK (Scotland) | Retrospective observational study | Rates of weak opioid prescribing increased significantly with increasing age and with sex, with higher rates of prescribing found among women. With strong opioids, prescribing rates increased significantly with age, but no significant difference was found for sex. In 2012, 938 674 individuals in Scotland were |

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| | | | prescribed an opioid (18% of the population), with codeine being the most prescribed drug, followed by tramadol. Morphine was the most prescribed strong opioid. There was a significant association between pain severity and receipt of at least one opioid prescription. Co-prescribing of BZDs was more common for women than for men. Almost 19% of women aged 30-45 who were prescribed a weak opioid were also prescribed a BZD, and 38% of women were co-prescribed a strong opioid and a BZD. |
| **Coloma-Carmona et al., 2019(118)** | Spain | Retrospective observational study | The mean total of the ARSW score showed no statistically significant differences between women (52.99) and men (54.08). Predictive validity showed a good capacity for identifying the severity of the prescription opioid-use disorder, using both DSM-IV-TR and DSM-5 criteria with the ARSW. The increase in ARSW scores could be used as an indicator of the potential risk of prescription opioid-use disorder during long-term treatments, regardless of gender. |
| **di Giannantonio et al., 2020(119)** | Spain | Retrospective observational study | 14% of the subjects reported lifetime use of depressors, 9.4% opioids, and 37 subjects reported a lifetime misuse of prescription drugs, having mentioned BZD (66%), antiepileptic drugs (8%), antidepressants (6%), opioids (6%), among others. The abuse of unprescribed pharmaceuticals was negatively associated with the use of psychodysleptics. Subjects who admitted prescription drug misuse tended to report higher scores in HAM-D and HAM-A |

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| | | | Somatic Anxiety, despite not reaching a statistical significance. |
| **Núñez Olarte et al., 2018(120)** | Spain | Retrospective observational study | The prevalence of aberrant opioid-induced behaviours was calculated at 19.2%, and opioid addiction at 7.7%. The most common characteristics were younger age, presence of known risk factors of AB, wide range of opioids use for basal pain (oral morphine extended release, oral oxycodone extended release, oral hydromorphone extended release, fentanyl transdermal, buprenorphine transdermal), a large dose of opioids use (morphine equivalent dose 259.5 mg), and long opioid treatment duration (2.75 years). |
| **Miramontes et al., 2019(121)** | Spain | Retrospective observational study | The prevalence of NMPDU was higher in drug users, females with risky alcohol consumption and who started to consume alcohol before 15 years old. Risky alcohol and cannabis consumption and high frequency of heavy drinking were identified as risk factors of NMPDU for females. NMPDU increased with age in both females and males. |
| **Carrasco-Garrido et al., 2018(123)** | Spain | Retrospective observational study | The prevalence of misuse of TSSp, among high-school students in Spain, was 2.86% (5,116, both sexes) during the study period. The prevalence of consumption increased significantly in both sexes, although the values for consumption were consistently greater in adolescent girls than boys throughout the study |

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| | | | (3.51% vs 2.18%). Alcohol, tobacco, and marijuana consumption were factors associated with using TSSp. |
| **Forsman et al., 2019(124)** | Sweden | Retrospective observational study | Of all suicide cases, 80% were males, and 73% were under 65. Ethanol and GABAergic hypnotics were detected in 26% of suicide cases and 18% of non-suicide cases, contrary to opioids and other addictive medications that were more commonly seen in non-suicide cases. The dispensation ratio increased for all psychotropic medicines in completed-suicide cases, contrary to non-suicide cases that decreased. |
| **Hägg et al., 2020(125)** | Sweden | Review | ADR sources reported a higher proportion of pregabalin abuse-related reports than gabapentin. However, reports with fatal outcomes were higher for gabapentin. Pregabalin misuse was more likely to occur in new and younger users. Use of doses above the maximum approved dose, history of substance abuse, sex, age, low income, epilepsy and taking high doses of drugs with abuse potential were risk factors with higher risk for misuse and abuse. |
| **Molero et al., 2019(126)** | Sweden | Retrospective observational study | Head/body injuries were the higher outcome in the study population (36.7%), followed by unintentional overdose (8.9%), road traffic incidence or offence (6.3%), suicidal behaviour or death from suicide (5.2%), and arrests for a violent crime (4.1%). Pregabalin users were younger and associated with a higher prevalence of all outcomes described before than gabapentin users. Pregabalin was associated with increased hazards of all outcomes, contrary to gabapentin which was related to |

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| | | | decreasing road traffic incidents or offences. People aged between 15 and 24 years presented higher hazards of suicidal behaviour. High doses were associated with increased hazard ratios for suicidal behaviours and unintentional overdoses. |
| **Abrahamsson et al., 2017(127)** | Sweden | Retrospective observational study | Z-drugs and pregabalin use was significantly associated with overdose deaths, contrary to BZDs prescriptions that were significantly related to non-overdose deaths. After controlling sex, age, previous psychiatric inpatient treatment, previous non-fatal overdose, previous suicide attempt and opioid maintenance treatment, Z-drug and pregabalin use remain significantly associated with overdose deaths. |
| **Forsman et al., 2018(128)** | Sweden | Retrospective observational study | Prescription-based design to estimate continuous drug use modelled-drug use matched toxicology in 45.9% of presumed prescribed medicines, having antidepressants presented the highest positive predicted value or predicted adherence rate (71.9%). Predicted recreational use was low for all drugs involved in the study, having the highest levels observed for sedatives alimemazine (1.4%) and propiomazine (1.1%). Agreement between prescription-based predictions and toxicology results depends on actual continuous drug use. |
| **Helmerhorst et al., 2017(129)** | The Netherlands | Review | The increase in prescriptions fuelled by reports suggesting that they are safe, aggressive marketing of opioids by pharmaceutical companies, healthcare reform in pain management and ignorance about pain relief were involved in the causes of the opioid epidemic in the USA |

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| | | | and Canada. The misuse of prescription opioids continues to increase in both countries. Hydrocodone, in combination with paracetamol, was the most prescribed drug in the USA. Primary care physicians, including those in internal medicine and family practice, account for about half of the prescriptions of opioids for pain. Regarding Europe, an increasing trend in the prescription of opioids and related mortality was verified in almost all European countries, especially in the UK. Although the general number of deaths related to prescription opioids in Europe is not known for sure, it is much lower than in the USA but rapidly increasing in several European countries. |
| **Schifano et al., 2018(130)** | UK | Systematic review | Web enthusiasts report the ingestion of gabapentinoids alone or in combination with other drugs, such as cannabis, alcohol, opioids, and other prescribed drugs, at a dosage range of 1000-4800 mg for gabapentin and 750-12,000 mg for pregabalin. PRR values demonstrated higher abuse/dependence issues for pregabalin than for gabapentin. Emergency visits increased due to intentional drug overdoses with high doses and polydrug abuse. Gabapentinoids mortality data usually involved other psychoactive drugs, namely opioids and other sedatives. Ingestion of antidepressants, such as bupropion and venlafaxine, in larger doses and the misuse-/abuse-/dependence-/ and withdrawal-related ADRs reported indicated higher recreational values for bupropion. |

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| **Schifano et al., 2019(131)** | UK | Retrospective observational study | Most ADRs reported for zaleplon, zolpidem, and zopiclone involved more female adults between 18 and 64. Zaleplon's most ADR report was "intentional overdose" (51.9%). For zolpidem, the most ADR reported was "drug use disorder" (40.0%), and for zopiclone was "intentional overdose" (29.9%). Antidepressants, BZDs, and ethanol/z-drug were the most common substances concomitantly used with zaleplon. Antidepressants, BZDs, and opiates/opioids were the most associated with zolpidem, and BZDs, antidepressants, antipsychotics, and opiates/opioids were the most associated with zopiclone. Fatalities related to poly-drug misuse were more associated with zolpidem and zopiclone. PRR values showed zolpidem more involved in misuse/abuse and withdrawal issues, while zopiclone was more associated with overdose reports. |
| **Winstock et al., 2014(132)** | UK | Retrospective observational Study | Tramadol users reported using at least one other prescription opioid in the previous year, mainly codeine-containing analgesics, followed by oxycodone and morphine. Most users were white, men, heterosexual, employed and around 30 years old. Of tramadol-only users, 20.3% reported mixing it with alcohol and/or other drugs to enhance its effect, and 10.6% reported using higher doses than the prescribed and tried to obtain extra tramadol. The most common tramadol source was a medical prescription written for the respondent (63.7%), followed by acquisition from a friend (33.6%). |

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| **Stannard, 2013(133)** | UK | Review | Data from 2011 showed an overall decrease in the number of deaths involving analgesics, despite a gradual increase in deaths involving tramadol and methadone being reported. The prevalence of analgesics dependence is probably higher than what is registered, as most people do not seek help. The UK is not under a prescription opioid epidemic of misuse and mortality as its databases do not cover all the information. However, the UK may be considered under a prescription opioid epidemic due to increased prescriptions for higher doses and longer. |
| **Hockenhull et al., 2019(134)** | UK | Retrospective observational Study | Lifetime prevalence was higher for non-medical diazepam use (1.30%) than for non-medical alprazolam use (0.32%). No endorsement of recent non-medical alprazolam use between those with > 45 years older, contrary to recent non-medical diazepam use where an endorsement was verified between those with > 45 years and < 65 years old. The most common source of both alprazolam and diazepam were family and friends (65.8% and 62.1%, respectively), followed by a prescription from a doctor or dentist (35.6% and 48.4%, respectively). |
| **Higgins et al., 2018(135)** | UK | Systematic review and meta-analysis | A random effects model calculated the incidence of opioid dependence or abuse in 4.7% of patients prescribed opioid analgesics. Longer-term opioid analgesic exposure (more than three months) and prescription of strong opioids were associated with a significantly lower incidence (2.3%, and 0.7%, respectively) of opioid dependence or abuse than a varied |

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| | | | time of opioid exposure (10.7%) and weaker opioids (5.5%). |
| **D. Weisberg & Stannard, 2013(136)** | UK | Review | Per capita consumption of opioids in the UK in 2013 was similar to the USA in 2003, having prescriptions increased consistently over the last decade. Methadone used for pain treatment in the USA was reported to be the major cause of opioid overdose deaths, contrary to the UK, where it is primarily used as an opioid agonist treatment for addiction, which, used under a supervised context, may decrease the risk of overdose. Both the lower price of heroin compared to prescription opioids (both share the market) and the wide availability of addiction treatment in the UK compared to the USA may contribute to the, apparently, minor illicit market of prescription opioids in the UK. |
| **Wright et al., 2016(137)** | UK | Review | Three groups of strategies to address misuse and diversion were defined, having the promotion of access to treatment and the use of product formulation less likely to be misused the preferred strategies. |
| **Quinlan et al., 2017(138)** | UK | Review | The authors proposed that every Clinical Commissioning Group area should identify a lead general practitioner with a named addiction psychiatrist and pain consultant to offer integrated care, develop support services for prescribed drug dependence in their area, and provide a point of contact for local clinicians, with recognised time to lead this development. A specialist pharmacist could highlight patients or practices with high opioid use and utilise |

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| | | | prescribing data to monitor the outcomes of interventions. |
| **Hayhoe & Lee-Davey, 2018(139)** | UK | Review | Higher prescription rates are related to the increase in misuse, and both BZD and z-drugs remain widely prescribed in UK's primary and secondary care. A slight decrease in the proportion of patients prescribed with BZD in primary care between 2000 (3.5%) and 2016 (2.6%) was mirrored by an increase in z-drugs and very long-term prescriptions. The increase of availability online, through unregulated pharmacies and the dark web, is a concern and usually involves alprazolam. The diversion of prescribed BZD may be facilitated by the proliferation of private online primary care services, as visiting multiple prescribers is a recognised strategy for obtaining multiple prescriptions for illicit use. |
| **Jani et al., 2020(140)** | UK | Retrospective observational study | Codeine was the most prescribed opioid during the study period. A 5-fold increase in codeine prescriptions, a 7-fold increase in tramadol prescriptions, and a 30-fold increase in oxycodone prescriptions for non-cancer pain were found. High dose/potency of opioid or concurrent gabapentinoid use, older age, higher socioeconomic deprivation score, and other medical conditions including fibromyalgia, rheumatological conditions, history of substance abuse, suicide/self-harm, alcohol abuse, and major surgery were the risk factors associated with long-term opioid use reported. Only 3.5% of |

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| | | | prescribers had significantly higher prescribing practices leading to long-term use after adjustment of patient factors. However, this 3.5% of prescribers had a higher proportion of patients with long-term use compared to the population average. |
| **Grant et al., 2020(141)** | UK | Retrospective observational Study | Prescription sedative/tranquillizer misuse was reported by 2% to 3% of university students and was associated with a variety of mental health and drug use problems. The students who reported misuse (ever misuse/past year misuse) of sedative/tranquillizers had significantly lower educational achievement scores from examinations, significantly higher levels of problematic alcohol and illicit substance use and a greater likelihood of using numerous substances, even if not problematic. Sedative/tranquillizer misuse was significantly associated with higher depression, PTSD, ADHD, and anxiety rates. |
| **Novak et al., 2016(34)** | UK | Retrospective observational Study | Germany had the lowest levels of non-medical prescription drug use, and Great Britain, Spain, and Sweden had the highest. Spain and Sweden had the most prevalent use of sedatives, followed by Great Britain and Denmark. Non-medical prescription drug use was most common in males, unemployed, and non-white respondents. Among past-year non-medical sedative users, 48% of past-year users in Great Britain also used illicit drugs, compared to 26 % in Germany, 22 % in Denmark and Sweden, and 20 % in Spain. Among past-year nonmedical prescription opioid users, 43 % of past- |

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| | | | year users in Great Britain also used illicit drugs, compared to 41 % in Sweden, 30 % in Germany, 24 % in Denmark, and 21 % in Spain. Females were about half as likely to engage in concomitant illicit drug use as males. |
| **Kapil et al., 2014(142)** | UK | Retrospective observational Study | Results suggested that there is appreciable misuse of BZDs and Z-drugs in the UK, with approximately 7.7% of respondents self-reporting misuse of any of these medications. Diazepam and zopiclone were the most frequently misused medicinal products. A prescription from a healthcare professional was the primary source of BZDs and z-drugs (55.2%), followed by friends and/or family (39.7%). |
| **Bi-Mohammed et al., 2017(143)** | UK | Review | The intranasal route of buprenorphine sublingual tablets was reported in UK studies, and some participants were unaware of this route of abuse before going to prison. The type of medication abused in prisons varies widely between countries and is not limited to opioids. The main drug of abuse changed rapidly according to availability in an individual prison. Crushing tablets, opening capsules, and mixing the content with jam are some strategies to attempt to reduce diversion. |
| **Schifano et al., 2019(144)** | UK | Descriptive study | Fentanyl-related misuse, abuse, dependence, and withdrawal cases reported during 2004-2018 showed an increasing trend over time. The most ADRs reported to EMA were "drug dependence", "intentional product misuse", and "drug abuse". Most cases involved men and the concomitant use of other |

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| | | | prescribing/illicit drugs. A significant number of cases required a prolonged hospitalization (34.35%) or resulted in death (33.09%). FAERS identified 19,145 misuse/abuse/dependence/withdrawal-related cases, being most ADRs "overdose", "withdrawal", and "drug use disorder/drug abuse/drug diversion". |
| **Hulme et al., 2018(145)** | USA, Australia, France, Sweden, Finland, Germany, Spain, Belgium, The Netherlands, Italy, Norway, Denmark, UK, and Canada | Systematic review and meta-analysis | Family and friends (57%) were the most prominent source of pharmaceutical drugs for NMU in all populations and therapeutic classes. In contrast, doctor-shopping was an uncommon way to obtain pharmaceutical drugs for NMU (7%). Dealers were also the source for obtaining pharmaceutical drugs illegally, particularly those who use drugs (47%). Patients with aberrant medication behaviours, substance use disorders and students in fraternities/sororities were more at risk of diversion of pharmaceutical drugs. |
| **Martins et al., 2015(146)** | USA, Canada, Australia, Ireland, UK, Sweden, Scotland, and Vietnam | Systematic review | Population-based overdose mortality rates ranged from 0.04 to 46.4 per 100,000 person-years, being the highest rates recorded in cities such as Barcelona. Both overdose deaths and overdose-related hospitalizations showed an increase in their trends. The most common overdose-associated substances were cocaine, non-opioid analgesics, and opioids (including prescription opioids - morphine, methadone, codeine, and oxycodone). Men were more likely to self-report non-medical prescription |

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| | | | drug use, and women were more likely to abuse prescription drugs. Worldwide, unintentional drug overdoses were more associated with cocaine, prescription opioids, and heroin. |
| **Worley, 2014(147)** | USA | Review | Signs of doctor-shopping and medication abuse comprise claims of stolen or lost medicinal products, requests for early refills, asks for a particular medicine, claims of allergies to less potent medication, and manipulation or threats. Some doctor-shoppers' strategies include using fake IDs, pretending not to have insurance to pay in cash, using other people's medical exams, and falsifying urine drug screenings. |
| **Peteet et al., 2019(148)** | USA, Canada, Thailand, Norway, India, Mexico, Nigeria, Sweden, Australia, Japan, Finland, and China | Systematic review | Between the selected studies, women abused prescription drugs at equal or higher rates than men, being sedatives and tranquillizers the most frequently abused. Twenty-one studies reported that white women misused prescription drugs more often, and 13 studies reported a higher rate of prescription drug misuse among young adults. Most studies identified the use of marijuana, sedatives and alcohol as the most common substances correlated with prescription drug misuse. Low education level, unmarried, uninsured, unemployment status, low income, and physical and mental health issues were predictor factors of prescription drug misuse among women. |
| **Kunnumpurath et al., 2018(149)** | USA, UK, Australia, France, Hungary, | Review | The higher availability of opioid analgesics led to their diversion into the illegal drug market in various ways. Globally, morphine-based opiated consumption increased in the last 20 years, |

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| | India, Spain, Turkey, China, Korea, Canada, Western Europe, and New Zealand | | being codeine and hydrocodone the most consumed. According to the International Narcotics Control Board, more than 90% of the legal morphine consumption is used by around 20% of the world's population. Despite heroin continuing to be the most used opioid that people seek treatment for in Europe, it was observed an increase in treatment related to prescription opioids, mainly methadone, buprenorphine, fentanyl, codeine, morphine, tramadol, and oxycodone. |
| **Fischer et al., 2017(150)** | USA, France, Germany, Italy, and the UK | Retrospective observational study | Italy reported median ages in the 30s and 40s. BZDs appear to be most misused across all countries except France. The distribution in age was significantly different between BZDs, stimulants, opioids, and anticonvulsants for all countries except the UK, keeping in mind the UK only receives calls from healthcare providers. |
| **Kotecha & Sites, 2013(151)** | the USA and Europe (mainly UK) | Review | Prescription drug abuse has been emerging as the reports on alarming incidents of prescription drug abuse have been described in European Countries. EMCDDA reported similar results as the United Nations report in 2011, with an increase in the world market of prescription opioids. |
| **D. F. Weisberg et al., 2014(152)** | USA and UK | Review | The UK reported morphine as the most commonly prescribed prescription opioid of class A (schedule II) and codeine with acetaminophen as the most prescribed in class B (Schedule III). Despite the lack of national surveys, the prevalence of prescription opioid misuse has a smaller proportion than illegal drug use. The |

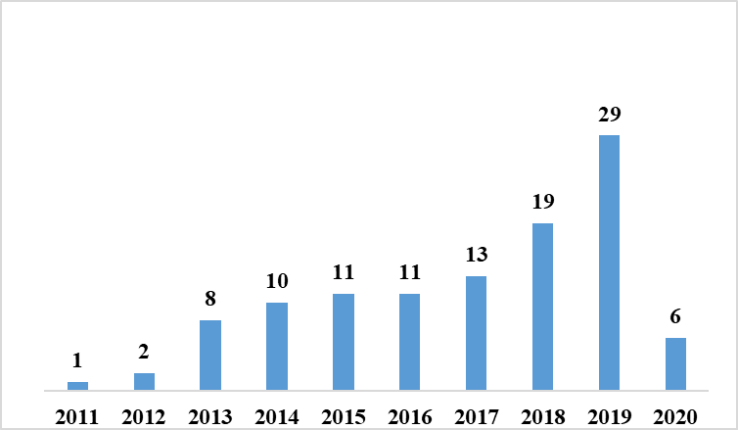
| | | | |
|---|---|---|---|
| | | | most common sources of prescription opioids were through general practitioners directly or friends and family. |
| **van Amsterdam & van den Brink, 2015(153)** | USA, Canada, Germany, Italy, Spain, UK, The Netherlands, Finland, and Scandinavia | Review | Italy, Spain, the UK, and The Netherlands were some European countries reporting an increase in the consumption of PO, having a total of 53.5 million DDDs of morphine, oxycodone, fentanyl, buprenorphine, and tramadol consumed in 2013 in The Netherlands. In England and Wales, tramadol-related deaths increase was observed between 2009 and 2012 and in methadone-related deaths in 2011. Overall, Europe is noticing an increase in PO consumption, although much smaller than the USA and Canada. |
| **Green et al., 2014(154)** | USA, Germany, Italy, The Netherlands, Switzerland, and the UK | Retrospective observational study | There was no difference in gender or age across countries. There was a significant difference across countries for exposure reason, route, and drug. The mean age for all PCs was 39.8 years, 58% male. In all countries, there were more calls for exposure in males, and the mean age was approximately 40. Case characteristics of exposures to oxycodone, buprenorphine and methadone as reported to poison centres in European countries are not different. However, the drug the patient was exposed to, the route, and the reason were statistically different by country. |

| | | | |
|---|---|---|---|
| **Cunliffe et al., 2019(155)** | USA, UK, Australia, Canada, India, Germany, Denmark, The Netherlands, Sweden, and China | Retrospective observational study | The UK represents 31% of the hypnotics and anxiolytics market, and Germany 11% of opioid dependency product sales. 8.5% of all cryptomarket sales were represented by hypnotics and anxiolytics at the beginning of the study in the UK, having the proportion increased by 1% per year. The UK well represents the dark net market, confirming the concern of high rates of non-medical prescription drug use. Denmark and Austria demonstrated a high and consistent level of sales for sedatives, and Sweden increased by close to 10% per year. |

Of the 110 articles included in the scoping review, most papers were retrospective observational studies (n=46), followed by reviews (including systematic reviews and systematic reviews with meta-analysis) (n=42).

Most articles included were from 2019 (n = 29). Overall, an increase was observed in the number of articles included per year, however in 2020 (n = 6), a decreased in published evidence was observed (Figure 1).

**Figure 1: Number of Articles included per year**




Regarding the geographic distribution of the articles, table 5 describes the number of articles included per country.

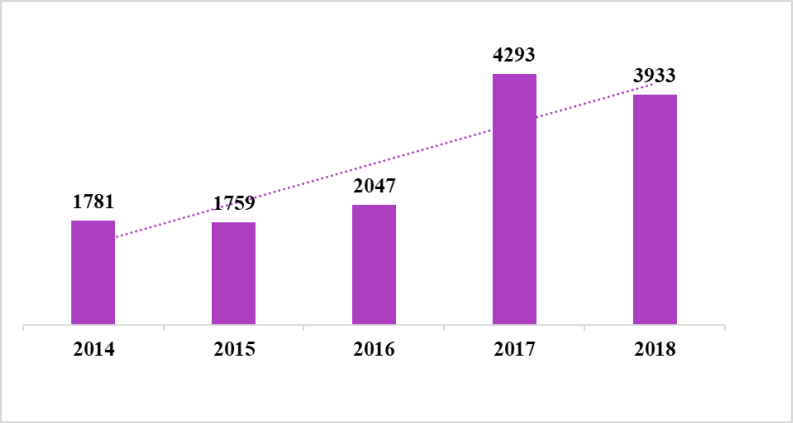
**Table 5: Number of articles per country**

| Country | Nº of Articles | Country | Nº of Articles |
|---|---|---|---|
| UK | 42 | Finland | 6 |
| France | 29 | Ireland | 4 |
| Spain | 12 | Belgium | 3 |
| Germany | 12 | Poland | 2 |
| Sweden | 11 | Austria | 2 |
| Denmark | 10 | Croatia | 2 |
| The Netherlands | 7 | Slovakia | 1 |
| Portugal | 7 | Hungary | 1 |
| Italy | 7 | Greece | 1 |

## 4.2. Hospital Morbidity Database

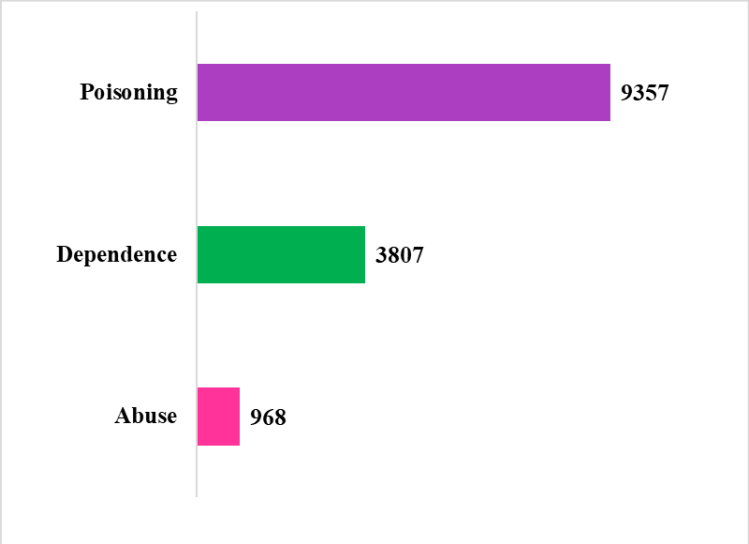
After the exclusion of admissions not involving at least one diagnosis of abuse, poisoning or dependence, a total number of 13,813 took place in Portuguese hospitals of patients presenting a diagnosis of abuse, poisoning or dependence of psychoactive medicine, increasing from 2014 (1,781 admissions) to 2018 (3,933 admissions) (Figure 2), 7,591 women (55%) and 6,222 men, with a mean age of 47.4 years ± 19.8 years.

**Figure 2: Annual distribution of Hospital Admissions**



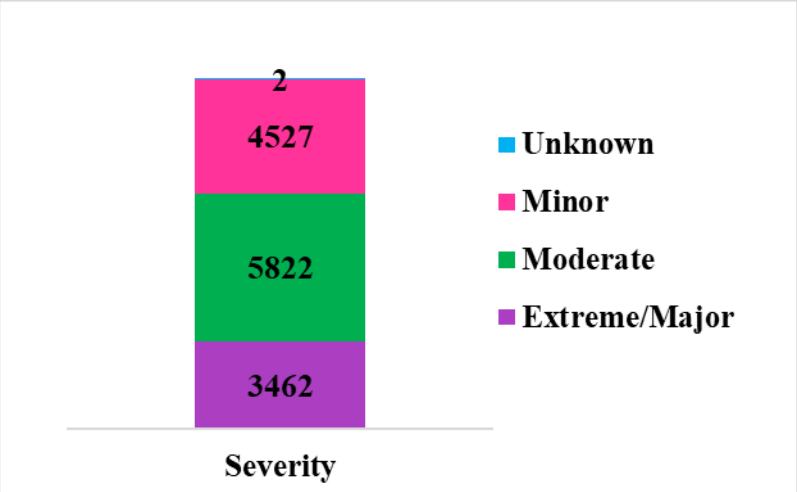

More than half of hospital admissions were for other reasons, the diagnosis of interest being secondary; 48% of ED visits were related to PPD misuse within the 5-year period. A total of 68% cases presented at least one poisoning diagnosis, 28% dependence and 7% an abuse diagnosis (Figure 3).

**Figure 3: Type of diagnosis at admissions**




Additionally, in 25% of admissions, severity was major or extreme (Figure 4), with effective hospitalisation occurring in 88% of ED visits (mean number of days: 11.3 ± 18.8).

**Figure 4: Severity of cases**




The top therapeutic classes (Figure 5) responsible for hospital admissions were anxiolytics (65%), followed by antidepressants (16%), both with a clear female dominance (73% and 75%, respectively (Figure 6)). In contrast, prescription and illegal opioids caused only 3,4% of ED visits, with a male predominance (65%).

**Figure 5: Top Therapeutic Classes**

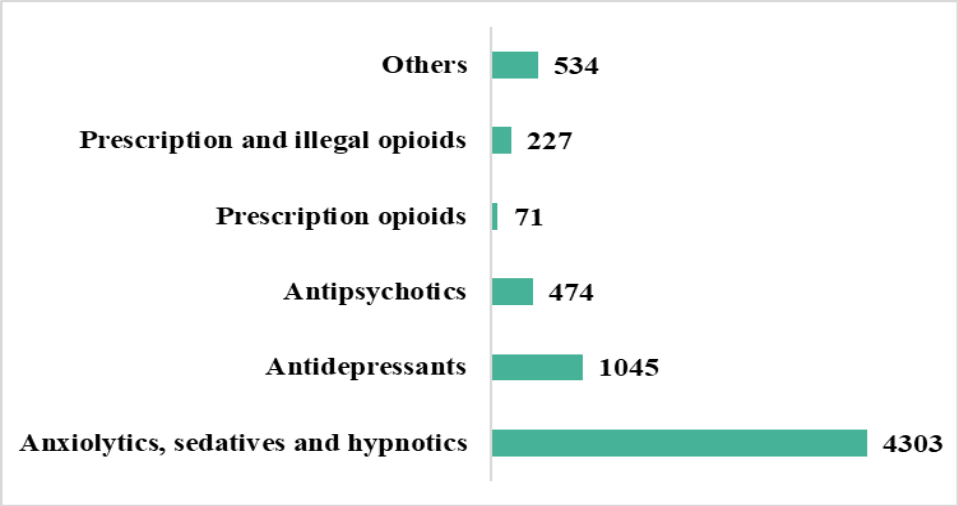
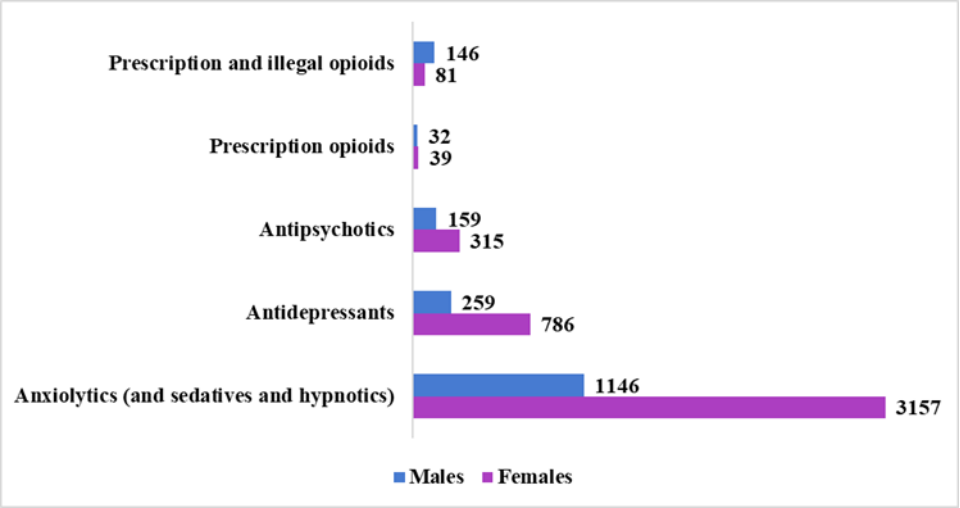


**Figure 6: Number of women**




The analysis of this database is an ongoing project, with an article to be prepared and submitted for publication in early 2023, along with other data from the MisuMedPT project (pharmacovigilance, forensic and poisoning data).

# 5. Discussion

The literature findings allowed to synthesise the knowledge on the consequences of the misuse of PPD around the EU. In addition, the preliminary analysis of hospital admission to Portuguese hospitals due to PPD intoxications allowed the characterisation of ED admissions related to these medicines, providing an overview of the situation regarding PPD misuse in Portugal.

Overall findings suggest an increase in awareness PPD use and misuse, as the number of papers published in the European Union showed an overall increase from 2011 and 2019, and in 2020 a decreased. The number of articles retrieved from the scoping review was higher than expected, since the decision to perform a scoping review was based on the perception of the lack of published information regarding the misuse of PPD in the EU in the beginning of the MisuMedPT project.

The UK (n = 42), France (n = 29), Spain (n = 12), Germany (n = 12), and Sweden (n = 11) with a greater number of articles. The higher number of scoping review findings in France may be attributed to the existence of the French Addictovigilance System. Set up in the early 1990s, this system allows to systematically assess and monitor the potential of abuse and dependence of psychoactive substances (including prescription drugs) by combining data from several sources, such as spontaneous ADR reports, forensic (DRAMES) and hospitalisation data, population surveys, and prescription/reimbursement data(6,76,77,91). Regarding the UK, the higher number of findings may be due to similarities with the USA regarding per capita consumption of opioids and number of deaths involving opioids(136). Both in the USA and in the UK opioid painkillers and heroin share a common market, but the price of heroin in the USA is significantly higher compared with the UK, preventing, or at least delaying the development of an illegal market of prescription opioids, whose availability in the UK is much more limited than in the USA. There are significant differences in the relative harms of the various non-medically used opioids, with street heroin whether injected or smoked ranking as the most harmful opioid in the UK followed by non-medically used prescription opioids like diamorphine or fentanyl(103).

In addition, a discrepancy between countries regarding the evidence published was found. The difference between the National Healthcare System (public vs private) within EU countries, the available tools to register and monitor the use of medicinal products and its consequences,

including the misuse and related implications (hospitalizations, deaths, and ADRs), the lack of standardized methods of classification of the outcomes of misuse, such as the criteria to classify the cause of death(152), and the different criteria/data considered important to register may be some of the reasons for the differences of evidence between the EU countries.

Non-medical prescription drug use was reported to be lower in Germany and higher in the UK, Spain, and Sweden(34,59). Some of the findings seem to be conflicting, with studies pointing to males, unemployed and non-white as the most common characteristics of non-medical prescription drug use(34,59), while in another study females were more likely to abuse prescription drugs, and males were more likely to self-report non-medical prescription drug use(146).

Prescription opioids were the PPD most consumed, with Italy, Spain, the UK, the Netherlands (all between 2010 and 2013), and France (in 2017) showing the greatest increase(89,153). Codeine was used by the most significant number of adults in Italy, the UK, Spain, and Germany(97), contrary to France, where morphine was the main prescription opioid used(84). In the UK, a 7-fold increase in tramadol prescriptions and a 30-fold increase in oxycodone prescriptions were observed between 2006 and 2017(140).
A rise of ADR reports related to fentanyl reported to EMA was observed, mainly "drug dependence", "intentional product misuse", and "drug abuse". Most involved men and the concomitant use of other prescribed/illicit drugs, and a significant number of prolonged hospitalisations or deaths(144), along with an increase of fentanyl-related deaths, mixed with heroin(64). In France, the impact of opioid use was reflected in an increase ranging from 1.5% to 18% during 2002-2012 in ADRs reported to buprenorphine, mainly in men, with a mean age of 34 years and intravenous as the primary route of administration(72). Also in France, the increase in prescription opioid use has resulted in the abuse of morphine sulphate among younger men, with a history of abuse(73), and in the increase of tramadol abuse and dependence, without an accompanying increase in tramadol sales(81). In the Netherlands, the increased in prescription opioid use led to a rise in hospital admissions for opioid overdoses and increased risk of opioid overdose deaths(105). These findings suggest a relation between prescription opioid consumption and misuse, with visible consequences in terms of misuse-related ADR reporting, morbidity, and mortality.

Benzodiazepines/z-drugs were the therapeutic class most commonly misused, especially in Italy, the UK and Germany, but not in France(150). In the UK, a slight decrease in patients

prescribed with benzodiazepines in primary care was observed(61,139), mirrored by an increase in z-drugs and longer-term prescriptions(139). Croatia reported an increase in BZD prescriptions between 2015 and 2016, with diazepam being the most prescribed and older females having higher consumption rates(53). Portugal was considered one of the EU countries with the highest consumption rate of BZDs(112). In the UK, an increase in BZD/z-drugs misuse due to the rise in prescription rates(139) has been observed, being diazepam and zopiclone the most frequently misused(142). Additionally, ADR reports involving zolpidem were found to be primarily associated with "drug use disorder" and involved the concomitant use of prescription benzodiazepines, opioids, and antidepressants(131). A moderate (Spain, the UK, Switzerland) to high (France, Ireland, Norway) positive correlation between ED visits and sales data has been observed for clonazepam, diazepam, alprazolam, and zopiclone, with different proportions in European countries(50). These findings suggest at least a moderate relation between the increase in benzodiazepines/z-drugs sales and an increase in their misuse and its consequences (ADR reporting and hospitalisations).

Gabapentinoids were also associated with misuse, the primary data coming from the UK, Sweden, and France. The UK was the only country reporting data on a slight increase in gabapentinoids (pregabalin and gabapentin) prescriptions between 2017 and 2018(60). Around the EU, pregabalin and gabapentin spontaneous reports increased over the years, mostly involving "intentional product misuse", "drug dependence", and "drug abuse" ADRs, female adults, and concomitant use with opioids, antidepressants, and BZD(102). Additionally, pregabalin was more frequently involved in ADR reports and fewer fatality outcomes than gabapentin(102). In France, the age, number of different prescribers, presence of cancer, multiple sclerosis, neuropathy, depressive disorder, and methadone use were risk factors associated with the subsequent pregabalin misuse after the first episode of misuse(70). In the UK, web enthusiasts reported the ingestion of gabapentinoids alone or in combination with other drugs, such as cannabis, alcohol, opioids, and other prescribed medications. In addition, intentional drug overdoses with high doses and polydrug use were associated with increased ED visits and mortality data (involving other psychoactive drugs, namely opioids and sedatives) among gabapentinoid users(130). A Swedish study reported a higher proportion of pregabalin abuse-related reports than gabapentin; however, fatal outcomes were higher in gabapentin cases(125). Another Swedish study reported pregabalin with a higher prevalence of head/body injuries, unintentional overdose, road traffic incidence or offence, suicidal behaviour or death from suicide, and arrests for a violent crime, and gabapentin was associated with decreasing road traffic incidents or offences(126). These

findings suggest a relation between gabapentinoids' misuse and its increased consequences (ADRs and mortality), with gabapentin misuse related to a higher number of deaths and pregabalin misuse with ADR reports.

The possible relation between the increase of the use of prescription opioids, benzodiazepines/z-drugs and gabapentinoids with the increase of their misuse and its consequences observed was expected due to the fact of the mechanism of action and addiction properties of these medicinal products.

The findings also reported females versus males' and population characteristics, risk factors, and sources. In the UK, people living in deprived neighbourhoods, older people, and people with cancer or epilepsy had a higher prescription of BZDs, z-drugs, and opioids, and for longer treatment of periods. Females were more likely to be prescribed all the types of PPD, with an average age of 60 years in both females and males(61). On the contrary, according to data reported in 2019, opioids tended to be prescribed for longer treatment periods in younger people, and BZDs, z-drugs and GABAergic in older people(62). Women, age, subjects with a history of substance dependence and abuse, with a history of alcohol and sedative/hypnotic dependence, low income, epilepsy, and people taking high doses of drugs with abuse potential were identified as risk factors for misuse and abuse(96,125). Young adult females with low education levels, unmarried, uninsured, unemployed, with low income, and physical and mental health issues were reported to misuse sedatives and tranquillizers more frequently(148). Tramadol users in the UK were mainly men, white, heterosexual, employed, and around 30 years old. They reported using at least one other prescription opioid in the previous year, primarily codeine-containing analgesics, followed by oxycodone and morphine(132). In 2017, the number of deaths related to drug misuse presented higher rates in males than females, with an increase between people aged 50-69 years and 70 years or older in the UK(64). These findings suggest a higher risk of misuse among females, mainly of BZDs/z-drugs and other sedatives/tranquillizers, possibly associated with the known higher stress factors during their lifetime, and males with the consequences of opioid misuse. Women were at higher risk for misuse, mainly women with low educational levels, low income, history of abuse, younger age, and comorbidities. However, men were related to a higher number of deaths.

The common sources of non-medical prescriptions were friends and family(59,145). Purchase through dealers was more common among people who use drugs(145). Taking drugs from other

people without their knowledge was also a common source reported(59). The most common tramadol source was a medical prescription written for the respondent, followed by an acquisition from a friend(132). The most common sources of zopiclone, diazepam and alprazolam in the UK were friends and family and a medical prescription form a healthcare professional(134,142). Visiting multiple prescribers is a recognised strategy for obtaining various prescriptions for illicit use(139). These findings suggest family and friends as the most common source of PPD. Source by a medical prescription was also commonly reported.

Papers describing data in Portugal were scarce, mainly reporting benzodiazepine consumption, misuse, intoxications, and adverse effects. The consumption of BZDs with the concomitant use of other psychoactive substances, such as other CNS-acting medicines, illegal drugs, or alcohol, enhanced the severity and extent of adverse reactions(112). BZDs (including their association with other substances), are the therapeutic class most commonly associated with fatal intoxications, followed by antidepressants, and opioids. Among all suicide cases, most involved antidepressants. In all cases of poisoning where opioids were involved, 45.23% were positive for morphine(111). BZD long-term use were associated with possible serious adverse effects in therapeutic dosage and self-prescription or recreational use in excessive doses(114). To complement the available published data for Portugal, the preliminary analysis of the Portuguese hospital morbidity database showed that the prevalence of ED admissions is higher among women, with 48% of hospital admissions directly due to PPD misuse. Of all admissions, the main type of diagnosis of misuse identified was poisoning, followed by dependence and abuse, with 25% of the cases presenting major or extreme severity. The top therapeutic classes responsible for hospital admissions were anxiolytics, followed by antidepressants, both with female predominance.

In contrast, prescription opioids and illegal opioids only caused 3.4% of ED visits, with a male predominance, probably attributable to illegal opioids, much less consumed than prescription opioids but more frequently used by men. These findings suggest a higher prevalence of anxiolytics and antidepressant use among the female Portuguese population and may point to a higher opioid use among males. However, in the hospital morbidity data available it is often not possible to distinguish, in opioid-related admissions, which refer to illegal opioid use and which refer to prescription opioid consumption, as some ICD codes include both (e.g., ICD-10-CM T40.2 - Poisoning by, adverse effect of and underdosing of other opioids is used to code opioid overdose, including heroin and prescription opioids like morphine or tramadol).

It would have been interested to study the main therapeutic classics associated with the different type of diagnosis in this dissertation. However, a more detailed analysis will be made for the article to be submitted as stated in Chapter 4.2.

It is known that the prison population is a high-risk subgroup on the misuse of PPD and illegal drug use(156). One study from Austria reported that younger inmates with ADHD symptoms are more likely to experience drug overdose, longer duration of cocaine and prescribed medications, and more in inmates in inpatient and outpatient treatment(49). In another study from the UK, focusing on opioids, specifically buprenorphine, intranasal use of buprenorphine sublingual tablets was reported, as most inmate participants were unaware of this route of abuse before being imprisoned. The same study reported crushing tablets, opening capsules, and mixing the content with jam as some strategies to attempt to reduce diversion(143). Due to the low number of articles identified (n=2), the misuse of PPD among inmates cannot be clearly discussed. Therefore, a clear gap in the EU is identified in what concerns studying the risks of misuse in the prison population.

Another gap identified is the prevalence of PPD misuse in the elderly population. Despite some findings reporting data on this subpopulation, only one paper focused only on this age group. This is even more relevant because, frequently, addiction in this population may be mistaken for depression and dementia, and a wide range of comorbidities, social exclusion, and isolation are risk factors for abuse of licit and illicit substances by the elderly(48).

More gaps may be identified during the writing of the article on morbi-mortality consequences of PPD misuse that is being prepared for publication in the MisuMedPT project.

The protocol of the scoping review of the MisuMedPT project has been prepared and submitted to BMJ open for publication, having been accepted on 29$^{th}$ June 2022, and published on 13th October 2022. Further dissemination activities for the report of the misuse and its morbi-mortality consequences were made. A scoping review article is being prepared and expected to be submitted before the end of 2022. Data on PPD-related hospital admissions were shared with the scientific community at ICPE 2022 Advancing Pharmacoepidemiology and Real-World Evidence for the Global Community that took place last August in Copenhagen, Denmark.

# 6. Limits and Strengths

One of the objectives of this dissertation was to synthesize, in a systematic, rigorous, and comprehensive manner, the available evidence on the consequences of misuse of medicines in the EU, providing the grounds for policymakers to take evidence-based decisions in order to ensure that patients benefit from the use of medicines at the lowest possible risk. A limitation of this work was the conservative approach to include the most frequently used definitions of misuse to address the variability in terminology and the absence of a universally accepted definition of misuse of medicines, which led to an excessive amount of data, posing challenges for feasibility within the project timelines. Another possible limitation is the fact that, although three electronic databases were used and targeted refined search strings to increase the probability of retrieving as many relevant publications as possible, database selection may not have been sufficiently comprehensive (i.e., searching other databases could have identified additional pertinent studies). The exclusion of grey literature from the search, or the fact that only articles from scientific journals and conference proceedings published in English, French, Spanish or Portuguese were considered eligible for inclusion, are also possible limitations of this study. Another limitation of this dissertation was the lack of time due to the pandemic context we have been facing since March 2020 and the conciliation between professional and academic life to better to assess the misuse of psychoactive medicinal products in Portugal.

In addition, given the pandemic context we have been facing since March 2020 and the often-difficult conciliation between professional and academic life, it was not possible to perform a more detailed characterisation of the Hospital Morbidity Database. Consequently, the lack of statistical measures, such as statistical association measures to confirm the female dominance in hospital admissions.

# 7. Conclusion

The evidence on misuse of psychoactive medicinal products compiled in this dissertation, following the scoping review that was performed, focuses on opioids, benzodiazepines/z-drugs, gabapentinoids, antidepressants and antiepileptics around the European Union.

The use/misuse of prescription opioids (mainly codeine, morphine, tramadol, oxycodone, and buprenorphine), benzodiazepines/z-drugs (particularly diazepam, alprazolam, zolpidem and zopiclone), antidepressants (such as SSRI family), and antiepileptics (such as, gabapentin, pregabalin, clonazepam) over the years has been increasing in the EU. The same trend is possible to observe regarding the consequences of their misuse, mainly ADR reports of abuse and dependence, hospitalisations, and deaths. Gabapentinoid misuse has also been associated with more ADR reports and deaths. Females are at higher risk of misuse of PPD, mainly benzodiazepines/z-drugs, and males are more related to opioid misuse, despite women being prescribed opioids for longer treatment periods. For all therapeutic classes, the main population of misusers are adults. Apparent gaps for future research were identified, such as in the prison population and elderly population.

In what concerns published research, France was the leading country with consistent data on this topic due to the existence of an Addictovigilance System that systematically and periodically collects data from several sources, providing a global and updated overview of the misuse of medicines and their associated consequences. Other EU countries should take France as an example and invest more systematically in research on the apparently rising problem of PPD misuse, in order to be able to monitor, manage, and prevent misuse of PPD.

In Portugal, this lack of published evidence is even more striking. A problem that my dissertation and the MisuMedPT project wishes to improve with the two additional articles on the use of PPD and the morbi-mortality consequences of their misuse, using consumption, poisoning and forensic PPD-related data, gathered in the frame of the MisuMedPT project.

To conclude this dissertation, a detailed overview of the EU state of the art on misuse of psychoactive medicines and its morbi-mortality consequences was accomplished. Although, data in Portugal remained scarce in this dissertation, research on this topic, is an ongoing project with perspectives of at least two articles to be submitted for later this year and during 2023.

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## Annex I – Search Strategy

| Date of Search | Database | # | Query Search | Results |
|---|---|---|---|---|
| **04/07/2021** | PubMed | 1 | ("prescription drug abuse"[Title/Abstract] OR "prescription drug overdose"[Title/Abstract] OR "prescription drug addiction"[Title/Abstract] OR "prescription opioid misuse"[Title/Abstract] OR "prescription drug misuse"[Title/Abstract] OR prescription drugmisuse[MeSH Terms]) | 15,435 |
| **04/07/2021** | | 2 | (hospitalization*[Title/Abstract] OR hospitalisation*[Title/Abstract] OR hospitalization[MeSH Terms]) | 375,801 |
| **04/07/2021** | | 3 | "emergency room"[Title/Abstract] OR "emergency department"[Title/Abstract] | 111,632 |
| **04/07/2021** | | 4 | (death*[Title/Abstract] OR death[MeSH Terms]) OR (poisoning*[Title/Abstract] OR poisoning[MeSH Terms]) OR (morbidit*[Title/Abstract] OR morbidity[MeSH Terms]) OR (mortalit*[Title/Abstract] OR mortality[MeSH Terms]) | 2,633,545 |
| **04/07/2021** | | 5 | dependence*[Title/Abstract] | 237,185 |
| **04/07/2021** | | 6 | "doctor shop*"[Title/Abstract] | 239 |
| **04/07/2021** | | 7 | "medical misuse"[Title/Abstract] | 15 |
| **04/07/2021** | | 8 | "nonmedical use"[Title/Abstract] OR "non-medical use"[Title/Abstract] | 1,209 |
| **04/07/2021** | | 9 | #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 | 3,153,729 |
| **04/07/2021** | | 10 | (opioid*[Title/Abstract] OR analgesic*[Title/Abstract] OR analgesics, opioid[MeSH Terms]) | 183,631 |
| **04/07/2021** | | 11 | (benzodiazepine*[Title/Abstract] OR benzodiazepines[MeSH Terms]) | 82,200 |
| **04/07/2021** | | 12 | (antidepressant*[Title/Abstract] OR antidepressive agents[MeSH Terms]) | 94,706 |
| **04/07/2021** | | 13 | (anticonvulsant*[Title/Abstract] OR antiepileptic*[Title/Abstract] OR anticonvulsants[MeSH Terms]) | 75,759 |
| **04/07/2021** | | 14 | (hypnotic*[Title/Abstract] OR sedative*[Title/Abstract] OR hypnotics and sedatives[MeSH Terms]) | 51,752 |
| **04/07/2021** | | 15 | (anxiolytic*[Title/Abstract] OR anxiolytics[MeSH Terms]) | 28,561 |

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|---|---|---|---|---|
| **04/07/2021** | | 16 | ("benzodiazepine-like"[Title/Abstract] OR "benzodiazepine related drugs"[Title/Abstract] OR z-drug*[Title/Abstract]) | 674 |
| **04/07/2021** | | 17 | "sleep medication*"[Title/Abstract] | 731 |
| **04/07/2021** | | 18 | 10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 | 447,286 |
| **04/07/2021** | | 19 | #1 AND #9 AND #18 | 3,868 |
| **04/07/2021** | | 20 | ("prescription medicines"[Title/Abstract] OR "psychoactive medicines"[Title/Abstract] OR "prescription medication*" [Title/Abstract] OR "prescription drugs"[Title/Abstract] OR prescription drugs[MeSH Terms]) | 14,172 |
| **04/07/2021** | | 21 | "controlled medication*"[Title/Abstract] OR "controlled medicines"[Title/Abstract] OR "controlled substances"[Title/Abstract] | 1,443 |
| **04/07/2021** | | 22 | #20 OR #21 | 15,476 |
| **04/07/2021** | | 23 | (death*[Title/Abstract] OR death[MeSH Terms]) OR (poisoning*[Title/Abstract] OR poisoning[MeSH Terms]) OR (overdose*[Title/Abstract] OR overdoses[MeSH Terms]) OR (morbidit*[Title/Abstract] OR morbidity[MeSH Terms]) OR (mortalit*[Title/Abstract] OR mortality[MeSH Terms]) | 2,648,639 |
| **04/07/2021** | | 24 | (dependence*[Title/Abstract] OR addiction*[Title/Abstract]) | 283,368 |
| **04/07/2021** | | 25 | (misuse*[Title/Abstract] OR abuse*[Title/Abstract]) | 161,437 |
| **04/07/2021** | | 26 | #2 OR #3 OR #6 OR #7 OR #8 OR #23 OR #24 OR #25 | 3,316,852 |
| **04/07/2021** | | 27 | #22 AND #26 AND #18 | 1,903 |
| **04/07/2021** | | 28 | (#19 AND #27) AND ("2011/01/01"[Date - Publication] :"2020/12/31"[Date - Publication]) NOT ("2021/01/01"[Date -Publication] : "2021/07/04"[Date - Publication]) AND(english[Language] OR french[Language] OR spanish[Language] ORportuguese[Language]) | 374 |
| **04/07/2021** | | 29 | (#28 AND humans[mesh:noexp]) OR (#28 NOTanimals[mesh:noexp]) | **374** |
| **04/07/2021** | Web of Science | 1 | TS=("prescription drug abuse" OR "prescription drug overdose" OR "prescription drug addiction" OR "prescription drug misuse" OR "prescription opioid misuse") | 1,482 |
| **04/07/2021** | | 2 | TS=(hospitalization* OR hospitalisation*) | 167,764 |

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|---|---|---|---|---|
| **04/07/2021** | | 3 | TS=("emergency room" OR "emergency department") | 114,089 |
| **04/07/2021** | | 4 | TS=(death* OR poisoning* OR morbidit* OR mortalit*) | 2,123,402 |
| **04/07/2021** | | 5 | TS=(dependence*) | 1,002,706 |
| **04/07/2021** | | 6 | TS=("doctor shop*") | 242 |
| **04/07/2021** | | 7 | TS=("medical misuse") | 21 |
| **04/07/2021** | | 8 | TS=("nonmedical use" OR "non-medical use") | 2,153 |
| **04/07/2021** | | 9 | #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 | 3,287,307 |
| **04/07/2021** | | 10 | TS=(opioid* OR analgesic*) | 176,322 |
| **04/07/2021** | | 11 | TS=(benzodiazepine*) | 44,207 |
| **04/07/2021** | | 12 | TS=(antidepressant*) | 80,993 |
| **04/07/2021** | | 13 | TS=(anticonvulsant* OR antiepileptic*) | 53,482 |
| **04/07/2021** | | 14 | TS=(hypnotic* OR sedative*) | 28,547 |
| **04/07/2021** | | 15 | TS=(anxiolytic*) | 16,246 |
| **04/07/2021** | | 16 | TS=("benzodiazepine-like" OR "benzodiazepine related drugs" OR z-drug*) | 674 |
| **04/07/2021** | | 17 | TS=("sleep medication*") | 728 |
| **04/07/2021** | | 18 | #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 | 363,177 |
| **04/07/2021** | | 19 | #1 AND #9 AND #18 | 606 |
| **04/07/2021** | | 20 | TS=("prescription medicines" OR "psychoactive medicines" OR "prescription medication*" OR "prescription drugs") | 9,299 |
| **04/07/2021** | | 21 | TS=("controlled medication*" OR "controlled medicines" OR "controlled sub-stances") | 1,204 |
| **04/07/2021** | | 22 | #20 OR #21 | 10,435 |
| **04/07/2021** | | 23 | TS=(death* OR overdose* OR poisoning* OR morbidit* OR mortalit*) | 2,139,902 |
| **04/07/2021** | | 24 | TS=(dependence* OR addiction*) | 1,064,403 |
| **04/07/2021** | | 25 | TS=(misuse* OR abuse*) | 237,691 |

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|---|---|---|---|---|
| **04/07/2021** | | 26 | #2 OR #3 OR #6 OR #7 OR #8 OR #23 OR #24 OR #25 | 3,538,465 |
| **04/07/2021** | | 27 | #22 AND #26 AND #18 | 1,380 |
| **04/07/2021** | | 28 | (#19 AND #27) AND PY=(2011-2020) NOT PY=(2021) AND LA=(English OR French OR Spanish OR Portuguese) | **127** |
| **04/07/2021** | Scopus | 1 | TITLE-ABS-KEY("prescription drug abuse" OR "prescription drug overdose" OR "prescriptiondrug addiction" OR "prescription drug misuse" OR "prescription opioid misuse") | 3,458 |
| **04/07/2021** | | 2 | TITLE-ABS-KEY(hospitalization* OR hospitalisation*) | 430,250 |
| **04/07/2021** | | 3 | TITLE-ABS-KEY("emergency room" OR "emergency department") | 134,541 |
| **04/07/2021** | | 4 | TITLE-ABS-KEY(death* OR poisoning* OR morbidit* OR mortalit*) | 2,950,121 |
| **04/07/2021** | | 5 | TITLE-ABS-KEY(dependence*) | 1,289,299 |
| **04/07/2021** | | 6 | TITLE-ABS-KEY("doctor shop*") | 316 |
| **04/07/2021** | | 7 | TITLE-ABS-KEY("medical misuse") | 16 |
| **04/07/2021** | | 8 | TITLE-ABS-KEY("nonmedical use" OR "non-medical use") | 1,522 |
| **04/07/2021** | | 9 | #2 OR #4 OR #5 OR #6 OR #7 OR #8 | 4,584,109 |
| **04/07/2021** | | 10 | TITLE-ABS-KEY(opioid* OR analgesic*) | 302,586 |
| **04/07/2021** | | 11 | TITLE-ABS-KEY(benzodiazepine*) | 97,524 |
| **04/07/2021** | | 12 | TITLE-ABS-KEY(antidepressant*) | 157,117 |
| **04/07/2021** | | 13 | TITLE-ABS-KEY(anticonvulsant* OR antiepileptic*) | 89,756 |
| **04/07/2021** | | 14 | TITLE-ABS-KEY(hypnotic* OR sedative*) | 75,285 |
| **04/07/2021** | | 15 | TITLE-ABS-KEY(anxiolytic*) | 33,443 |
| **04/07/2021** | | 16 | TITLE-ABS-KEY("benzodiazepine-like" OR "benzodiazepine related drugs" OR z-drug*) | 818 |
| **04/07/2021** | | 17 | TITLE-ABS-KEY("sleep medication*") | 813 |
| **04/07/2021** | | 18 | #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 | 643,359 |

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|---|---|---|---|---|
| **04/07/2021** | | 19 | #1 AND #9 AND #18 | 1,343 |
| **04/07/2021** | | 20 | TITLE-ABS-KEY("prescription medicines" OR "psychoactive medicines" OR "prescription medication*" OR "prescription drugs") | 52,134 |
| **04/07/2021** | | 21 | TITLE-ABS-KEY("controlled medication*" OR "controlled medicines" OR "controlled substances") | 2,892 |
| **04/07/2021** | | 22 | #20 OR #21 | 54,359 |
| **04/07/2021** | | 23 | TITLE-ABS-KEY(death* OR overdose* OR poisoning* OR morbidit* OR mortalit*) | 2,976,883 |
| **04/07/2021** | | 24 | TITLE-ABS-KEY(dependence* OR addiction*) | 1,390,086 |
| **04/07/2021** | | 25 | TITLE-ABS-KEY( misuse* OR abuse*) | 377,901 |
| **04/07/2021** | | 26 | #2 OR #3 OR #6 OR #7 OR #8 OR #23 OR #24 OR #25 | 4,953,967 |
| **04/07/2021** | | 27 | #22 AND #26 AND #18 | 6,846 |
| **04/07/2021** | | 28 | (#19 AND #27) AND PUBYEAR > 2010 AND PUBYEAR < 2021 AND LAN-GUAGE(english OR french OR spanish OR portuguese) | **1,148** |