Assessing the extent and characteristics of non-medical use of a range of prescribed drugs: epidemiological and pharmacovigilance approaches

Submitted in partial fulfilment of the requirements of the University of Hertfordshire for the degree of PhD

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Abstract

Introduction: In the last ten years, the growing use of prescription and over-the-counter (OTC) drugs for recreational purposes has been observed. The use of 'psychoactive pharmaceuticals' and 'pharming' are new widespread terms describing a worldwide phenomenon involving the non-medical use of prescription (e.g., pain relievers, tranquilisers, stimulants, sedatives, etc.) and OTC drugs, including cough and cold preparations, particularly those containing dextromethorphan and promethazine. However, although data supporting a growing concern on their misuse and diversion are increasing, there is still a lack of evidence regarding the true extent and nature of such phenomena.

Aim of the study: This project aimed at assessing the misuse and diversion potential of certain pharmaceuticals, known anecdotally to be used in order to achieve psychoactive effects, as well as described by drug users' online fora reporting new trends in abuse and experimentation in drugs. The substances of interest of the programme of research included prescription drugs such as gabapentinoids; antidepressants (e.g., venlafaxine, bupropion, and Selective Serotonin Reuptake Inhibitors/SSRIs); antipsychotics (e.g., olanzapine, clozapine, and quetiapine); Z-drugs (e.g., zolpidem, zopiclone, and zaleplon); image and performance enhancing drugs (e.g., clenbuterol and salbutamol); opioids (e.g., fentanyl, tramadol, codeine, dihydrocodeine, oxycodone, and pentazocine); and, among OTCs, the anti-diarrhoeal drug loperamide, the non-steroidal anti-inflammatory drug benzydamine, and the antihistamine promethazine.

Methods: Firstly, descriptive analyses of data from the European Medicines Agency pharmacovigilance database (EudraVigilance/EV) collecting voluntarily reported Adverse Drug Reactions (ADRs) related to specific pharmaceuticals were performed.

Moreover, to better compare two drugs in the same group, e.g., quetiapine versus olanzapine, the Proportional Reporting Ratio (PRR) approach was used. Inclusion criteria for selecting the ADRs to be studied were all terms containing ‘abuse’, ‘intentional misuse’, ‘dependence’, or ‘drug withdrawal’ as narrow terms according to the Standardised MedDRA Query System; terms relating to events observed with abuse, but which also occurred without abuse (e.g., ‘overdose’ or ‘drug level increased’ or ‘drug toxicity’) were included as broad terms. Finally, in the last section of the PhD, in order to better assess pharmacovigilance issues, statistical analyses included further disproportionality methods, such as the reporting odds ratio, the information component value, and the empirical bayes geometric mean (signals were based on a false discovery rate <0.05). Where possible, EV data, were compared with other pharmacovigilance datasets, such as the United Kingdom (UK) Yellow Card Scheme related to the Medicines and Healthcare products Regulatory Agency (MHRA) data, and the United States Food and Drug Administration Adverse Event Reporting System (FAERS).

Results: From data analysed, diversion, abuse, and dependence are issues which might present with several of the studied drugs, especially if used in large or extremely large dosages, concomitant licit/illicit drugs, and unconventional routes of administration. To give an example, over years 2004–2015, from the EV database some 7,639 (6.6% of a total of 115,616) and 4,301 (4.8% of 90,166) misuse/abuse/dependence ADR were respectively associated to pregabalin and gabapentin, with an overall reporting frequency increasing over time. According to the PRR, abuse, dependence and intentional product misuse were ADR more frequently reported for pregabalin (1.25, 1.39, and 1.58, respectively) compared to gabapentin. A total of 27 (2.1%) and 86 (21.0%) fatalities, respectively associated with pregabalin

and gabapentin, occurred, and mostly in combination with opioids. Among the OTCs, during the years 2005-2017, EV collected a number of 1,983 (out of a total of 7,895; 25.1%) loperamide-related misuse/abuse/dependence/withdrawal ADR reports, with a progressively increasing trend since 2014. Interestingly, most cases were classified as 'drug use disorder' (37.4%) or 'intentional overdose' (25.4%) and recorded supratherapeutic dosages, e.g., up to 800mg, with an average daily dosage of 4 to 8 mg. Loperamide was mostly used on its own (182/434 = 41.9%); conversely, antidepressants, benzodiazepines, opioids, and other OTCs were concomitantly recorded in the remaining cases (252/434 = 58.1%). Some 1,085 (1,085/7,895 = 13.7%) cardiovascular ADRs were reported, being conduction abnormalities and electrocardiogram alterations the most frequently identified. In all studies, populations at risk have been identified, such as patients with a substance abuse history.

Conclusions: Although further studies are needed, both the literature and current data support the principle that some drugs, including both prescription drugs, e.g., gabapentinoids, some antipsychotics and antidepressants, and some OTC drugs, such as loperamide, dextromethorphan, promethazine, etc., should be prescribed with caution owing to the risk of abuse and of idiosyncratic reactions. According to the results presented here, the misuse and abuse of prescription/OTC drugs could be a cause for major concern, especially in vulnerable individuals or in some contexts, such as polysubstance abuse, history of drug abuse or drug addiction. The use of concomitant substances or of high/supra-high doses for recreational purposes may cause unpredictable effects, such as overdoses or drug-related fatalities. Hence, caution should be exercised in prescribing. Healthcare professionals should be warned about the possible misuse of such drugs and be aware of their diversion potential. They should recognise actual cases of abuse; and consider the possibility of polydrug

misuse. The Internet through both social media/fora and rogue online pharmacies might be a means for buying drugs. On the other hand, the Internet and social networks are a promising source of data in order to better understand, monitor and treat substance use issues. The present situation represents a challenge for psychiatry, public health, and drug-control policies with enormous implications for clinical practice in terms of harm reduction strategies, preventable morbidity, and mortality.

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Statement of authorship

This dissertation was written by Stefania Chiappini, and I can confirm that the work presented here was solely reviewed and interpreted by myself and has the relevant ethical clearances. I can confirm that this work is being submitted in fulfilment of the requirements of the School of Life and Medical Sciences - Allied Health Professions, Dentistry, Nursing and Pharmacy - Department of Clinical, Pharmaceutical and Biological Sciences - at the University of Hertfordshire for a Doctorate in Pharmacy, Pharmacology and Postgraduate Medicine.

This dissertation carries no conflict of interest, and the author is responsible for the content and writing of this report. The work has not been submitted elsewhere in any other form for the fulfilment of any other degree or qualification. The thesis does not contain any material or content previously written in another publication except for where such work has been used and referenced as appropriate**.**

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Chapter 2 - Methodology

In this chapter, explanations of methodological theories and frameworks are provided before proceeding to the analysis of the datasets. In addition, an explanation is provided on the data gathering process and the methodological choices made. The chapter also briefly introduces the interpretation and analysis of the data, demonstrating that methodological improvements have been made throughout the study to achieve greater rigour and validity.

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Chapter three presents the results of the study obtained from the analysis process. Findings were presented in consideration of the type of medication studied, firstly reporting data on prescription drugs abuse, e.g., gabapentinoids, antidepressants, antipsychotics, Z-drugs, and opioids, and secondly describing findings regarding over-the-counter (OTC) drugs, e.g., loperamide, promethazine, and benzydamine. Furthermore, through the use of

pharmacovigilance databases, the study of possible other reactions of interest related to psychiatric drugs was investigated, e.g., the problem of adverse urological reactions related to the use of prescribed ketamine. Finally, even though they could not be considered primary objectives of the present project, in order to better understand the diversion and misuse of some other drugs, systematic reviews were carried out prior to further studies using pharmacovigilance data. The first systematic review focused on the study of antihistamines, cough medicines and OTC decongestants; the second one analysed the relevant published data on the abuse of centrally acting anticholinergic drugs, such as benztropine, benzhexol/trihexyphenidyl, cyclobenzaprine, orphenadrine and scopolamine.

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In this chapter, a summary of the main findings is presented together with new learning that evolved from these outcomes and their implications for clinical practice. There is a brief description of the study strengths and limitations followed by recommendations for future research, and my own summative reflections.

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This chapter reports the most important conclusions of the study, including final recommendations for future research and final self-reflections.

Chapter 1 - Introduction: prescription and OTC drugs misuse

1.1 Background

1.1.1 The new phenomenon of '*pharming*'

In the past fifteen years, the drug abuse scene has been changing due to the appearance on the market of molecules known as new psychoactive substances (NPS) and the recreational use of pharmaceuticals, that are not already controlled, as theoretically considered without a diversion potential, but have shown a potential abuse liability[1–5]. They include several commonly used molecules: some gabapentinoids, such as pregabalin and gabapentin[5–9]; some antidepressants, such as bupropion and venlafaxine[10–13]; some antipsychotics, such as quetiapine[14,15]; several over-the-counter (OTC) drugs[16–20], such as codeine-containing products, the antidiarrhoeic drug loperamide or the antihistamine promethazine; and derivatives of prescription medicines, such as novel synthetic opioids, e.g., fentanyl analogues[21–23], and designer benzodiazepines[24–26].

'Pharming' and 'psychoactive pharmaceuticals' are terms defining a newly increasing phenomenon involving the non-medical use of prescription (e.g., pain relievers, tranquilisers, stimulants, and sedatives) and OTC drugs, including cough and cold preparations, in order to obtain psychoactive effects[1,5,27]. In general, even though they are considered as a single phenomenon and used interchangeably, the terms *non-medical use* or *misuse* or *abuse* in relation to a medication refer to specific conditions. In this study, we have considered as a reference the definitions available on the Medical Dictionary for Regulatory Activities-MedDRA (MedDRA)[28], which is a standardised medical terminology used worldwide in pharmacovigilance, where the term *misuse* describes the intentional use for a therapeutic purpose by a patient or consumer of a product, OTC or prescription, other than as prescribed or not in accordance with the authorised product information (see the Glossary). Similarly, the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA) indistinctly uses *diversion*,

misuse, and *non-medical use* of medications, terms referring to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information, e.g., a prolonged and continued use of medications, even after the original health problem for which the drug was prescribed has been resolved; or the use of a molecule in amounts exceeding the therapeutic dosage, outside the indications, and in combination with other drugs or medicines[29]. Similarly, in the United States of America (US/USA), the National Institute on Drug Abuse (NIDA) uses *drug misuse* to distinguish improper or unhealthy use from use of a medication as prescribed, including the repeated use of drugs to produce pleasure, alleviate stress, and/or alter or avoid reality, using prescription drugs in ways other than prescribed, or using someone else's prescription[30]. NIDA uses the term *misuse*, as it is roughly equivalent to the term *abuse*, which is considered a diagnostic term that is increasingly avoided by professionals because it can be shaming and stigmatising[30], whereas the MedDRA considers *drug abuse* as the habitual use of drugs that are not needed for therapeutic purposes (e.g., to alter mood); to effect a body function unnecessarily (e.g., laxative); and non-medical use of drugs[28]. Interestingly, highlighting its consequences, the United Kingdom (UK) Advisory Council on the Misuse of Drugs (ACMD), characterised *problematic drug use* as a condition that may cause an individual to experience social, psychological, physical, or legal problems related to intoxication and/or regular excessive consumption, and/or dependence[31]. Indeed, misusing prescription drugs involves not only risks associated with the drugs themselves, but also with the general context in which they are consumed. These include side-effects, interactions between licensed medicines and other unlicensed substances or products (food and environmental chemicals), and individual variation in responses (genetic differences and possible comorbidities), which might be associated with a range of severe adverse reactions and fatalities[27,29,32–34]. Finally, their abuse appeared facilitated by: i) their easy accessibility, e.g., from friends or relatives for free, from a doctor through doctor-shopping practices, from drug dealers or strangers, and finally from the Internet; ii) the low cost; and iii) a decreased perception of potential for harm[1,5,27]. Emphasising health, legal and social implications, *prescription drug diversion* is defined as the unlawful channelling of regulated pharmaceuticals

from legal sources to the illicit marketplace, which includes transferring drugs to people they were not prescribed for[28,35].

1.1.2 Size of the phenomenon

Data regarding the abuse/misuse/non-medical use of both prescription and OTC drugs can be derived from several sources, including i) Emergency Departments (ED) visits and hospital admissions related to acute intoxication states; ii) addiction treatment admissions; iii) Internet/treatment centres/schools surveys; iv) national poison data; v) voluntary reports to pharmacovigilance authorities; vi) fatalities recorded by coroners, medical examiners, and other investigators. Despite these multiple sources of information, global- or European-related numbers on the abuse/misuse/non-medical use of medications are only partially available, possibly due to several factors, including difficulties in collating them all together, the above-described heterogeneity in terms describing the same phenomenon, public awareness regarding these issues which might affect their detection and differences in drug scheduling/classification between countries. Thus, studies on the use of prescription and OTC drugs are scarce. Moreover, they often do not distinguish prescription from OTC drugs and prescribed from non-prescribed use, e.g., as in the case of analgesic opioids [36]. Furthermore, the USA/US Food and Drug Administration (FDA) and the EMCDDA, which respectively collate drug-related information worldwide and in the European Union (EU), are mainly focused on illicit drugs and, among prescription molecules, on already known abused molecules such as benzodiazepines and opioids, rather than on other medications such as antidepressants, antipsychotics, OTC drugs, etc. In general, the non-medical use of prescription drugs is becoming a major threat to public health and law enforcement worldwide with opioids causing the most harm, and accounting for 76% of deaths where drug use disorders were implicated[37]. Information from the European Drug Emergencies Network (Euro-DEN Plus), which monitors drug-related presentations in sentinel hospitals in a number of European countries, shows that around one-fifth of presentations involve the non-medical use of prescription or OTC medicines

(most commonly opioids and benzodiazepines)[29]. Similarly, in the USA increases in prescription drug misuse over the last 15 years are reflected in increased ED visits, overdose deaths associated with prescription drugs, and treatment admissions for prescription drug use disorders, including addiction[38]. A useful source of the most recent data for drug use prevalence estimates in the USA is available through an online dashboard from the Survey of Non-Medical Use of Prescription Drugs (NMURx) Program of the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System which is a surveillance system that collects product-and geographically-specific data on abuse, misuse, and diversion of prescription drugs, focusing on pain relievers, opioids, sedatives, stimulants, gabapentinoids, and cannabis or other illicit drugs e.g., heroin, illicit fentanyl, cocaine powder/crack cocaine, etc [39]. Unfortunately, even though groupings do not include OTC medications, such data might be considered as a reliable source of information regarding the increasing misuse and the non-medical use of those prescription and illicit drugs over the past ten years. Similarly, the Crime Survey for England and Wales (CSEW) monitors the extent of crime in the general population of England and Wales[40], including since 2014/2015 a specific question on the diversion and misuse of prescription medication and the reason of this misuse (e.g., “for medical reasons or for the feeling or experience it gave them”). The 2015/16 survey estimated that in the last year 7.5% of adults aged 16 to 59 had taken a prescription-only painkiller which was not prescribed to them, and 7.4% (around 2.4 million adults) said that they had taken the painkillers purely for medical reasons, while a small proportion (0.2%, or 33,000 adults) said it was just for the feeling or experience it gave them. This tendency was also true for young adults aged 16 to 24[40]. Similarly, in order to understand non-medical prescription drug use in five European countries Denmark, Germany, Great Britain, Spain, and Sweden, parallel series of self-administered, cross-sectional, general population surveys were conducted in 2014 on a total of 22,070 non-institutionalised participants, aged 12 to 49 years. According to this study, estimates of lifetime and past-year non-medical use of prescription medications including stimulants, opioids, and sedatives were highest for opioids (13.5 and 5.0%), followed by sedatives (10.9 and 5.8%), and stimulants (7.0 and 2.8%), with Germany

exhibiting the lowest levels, and Great Britain, Spain, and Sweden the highest levels[41]. Interestingly, the survey evaluated mental and sexual health risk factors, and found in about 32, 28, and 52% of opioid, sedative, and stimulant non-medical users (respectively) a concomitant use of illicit drugs. Social sources (sharing by friends/family) were the most commonly stated methods of acquisition, ranging from 44% (opioids) to 62% (sedatives). Of interest is that Internet pharmacies were a common source of medications for opioids (4.1%), stimulants (7.6%), and sedatives (2.7%)[41].

Several prescription drug monitoring programmes are available worldwide aiming at preventing prescription drug abuse, misuse and overdose, particularly prescription opioids[42], e.g., in the US there are several state-wide programmes consisting of electronic databases that contain information from pharmacies about prescriptions they dispense for controlled substances. These monitoring programmes serve several functions, such as identifying drug-seeking behaviours or *doctor shopping* practices, when patients attempt to obtain controlled substances from several prescribers. They also can be used by professional licensing boards to identify inappropriate clinician prescribing and dispensing, and to help law enforcement agencies investigate possible illegal activity, depending on the state[43]. Similarly, in the UK the National Health System (NHS) provides information on prescribing and dispensing medications[44]. In the EU there are several nationwide programmes, and all are members of the World Health Organization (WHO) Programme for International Drug Monitoring, which now includes over 170 countries[45] collaborating in monitoring drug safety and in advancing pharmacovigilance practices in countries across the world.

Commonly prescribed and OTC medicines that may be used for non-medical purposes are: opioids, including natural, synthetic and semi-synthetic substances that act on opioid receptors to produce pain relief and euphoria and are available on prescription only (e.g., tramadol, oxycodone, fentanyl, etc.) or OTC (e.g., codeine-containing products or the antidiarrheal drug loperamide); central nervous system (CNS) depressants, including tranquilisers, sedatives, and hypnotics, e.g., benzodiazepines and non-benzodiazepine hypnotics such as the Z-drugs (zaleplon, zopiclone, and zolpidem); and finally stimulants,

which may be used as cognitive enhancers such as Attention-Deficit/Hyperactivity Disorder (ADHD) medications, or to reduce weight/improve a person's performance, such as some beta2 agonists such as clenbuterol and salbutamol, etc.[29,38]. Other drugs causing concern with respect to their non-medical use might include a large and varied array of medicines, such as pregabalin and gabapentin, medicines currently prescribed for the control of seizures and the treatment of neuropathic pain, and, besides them, some antipsychotic drugs, e.g., quetiapine, or olanzapine; and some antidepressants, including the selective norepinephrine and dopamine reuptake inhibitor (NDRI) bupropion and the selective serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine, but also a range of Selective Serotonin Reuptake Inhibitors (SSRI), such as paroxetine, fluoxetine, citalopram, escitalopram, etc.

In this context, the Corona Virus Disease (CoViD)-19 pandemic, impacting on drug markets, through shortages of numerous types of drugs at the street level and increased prices[46], may have resulted in a further increase in risks for people who use drugs, for example by increasing variability in drug purity through the adulteration with other molecules unknown to the user or by encouraging: i) shifts to more risky drug using behaviours, such as the use of the available medications and powerful drugs as street benzodiazepines and synthetic opioids, if the access to those previously used become limited; ii) changes in levels of drug use - an increase is often seen as a reactive behaviour to negative impact of disasters; or iii) a relapse, if drug diversion/addiction has already been treated [47]. Notably, as more users turned from street drugs to prescription/OTC products, health services have been overloaded with requests to obtain prescription medicines or opioid treatments, the supply of the latter is tightly regulated, hence further increasing the possibility of drug diversion [2,47–49]. Moreover, in parallel to the problem of *doctor shopping*, even if this practice was limited by CoViD-related constraints and the need to reduce face-to-face encounters, some countries intervened with *ad hoc* changes in legislation to encourage non-medical prescribers, e.g. in the UK pharmacist supplementary prescribers or pharmacist independent prescribers, owning the right to supply certain controlled drugs to patients without a prescription, who became unwittingly a source of drugs for abuse [50–52].

1.2 Pharmacovigilance as an assessment approach for detecting drug abuse and dependence issues

The WHO Programme for International Drug Monitoring was developed after the thalidomide disaster in 1961 in order to address medicine safety issues at a global level, and promote pharmacovigilance worldwide. The WHO definition of pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem[45,53]. Its aims are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines. Under the Programme for International Drug Monitoring, systems have been developed in member states for the collection of individual case safety reports (ICSRs) and their evaluation. As of June 2013, there were 144 countries participating in the programme, and all reports are held in a central database, known as VigiBase[54], which is the largest pharmacovigilance database in the world, with over 30 million reports of suspected adverse effects of medicines, submitted, since 1968 up to date, by member countries of the WHO Programme for International Drug Monitoring. Vigibase is managed and maintained by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) in Sweden. The work of the UMC, with policy directives from WHO, serves the important function of contributing to the work of national drug regulatory authorities and other relevant stakeholders, by improving the knowledge of safety profiles of medicines. It includes the public datasets of the US FDA Adverse Event Reporting System (FAERS)[55], the European Medicines Agency (EMA)'s EudraVigilance (EV)[56], the UK-Medicines and Healthcare products Regulatory Agency (MHRA)'s data collected through the Yellow Card Scheme (YCS)[57], and many national databases from across Asia, Africa, Latin America, and Oceania, collecting information related to human adverse events reported respectively by the pharmaceutical industry, healthcare providers and consumers. They all promote the safe and effective use of

medicinal products, collecting voluntarily reported ADRs related to specific pharmaceuticals. According to the WHO, an ADR is considered a voluntary and unsolicited communication reported by both Regulatory Authorities and/or by the Marketing Authorisation Holders on an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product[58]. Similarly, but in more detail, the EMA describes an adverse reaction as a response to a medicinal product which is noxious and unintended, which arises from the use of a medicinal product within the terms of the marketing authorisation (in accordance to the product information); the use outside the terms of the marketing authorisation, including overdose, misuse, abuse and medication errors; and occupational exposure[59].

During the past twenty years pharmacovigilance has evolved from a reactive system responding to emerging risks, to a planned, proactive and risk-balanced approach supported by a scientific discipline[60]. As the intended and actual uses of medicines differ between clinical trials and real-world use, the post-marketing phase is essential to monitor the emergence of new patterns of use and misuse of molecules, as happened in the past with benzodiazepines, which were thought to be safer compared to barbiturates, and then associated with problems of tolerance and dependence. By monitoring drug consumption, pharmacovigilance is now addressing a *new wave of drug abuse*[61]. Thus, a *proactive pharmacovigilance* means a multimodal approach of drug monitoring, drawing on clinical, epidemiologic, basic science, and social science expertise, which may intervene proactively and effectively, in anticipation of changes in drug abuse[61].

1.3 Aims of the programme of research

This research originates from the observation of a recent change in the drug abuse scene, which has seen the appearance of new and emerging substances, called NPS, but also of pharmaceuticals commonly prescribed in clinical practice, which, on the basis of different reasons, such as a recreational purpose, or related dependence after long-term use, might be unsafely used, accompanied by risky behaviours consisting in buying drugs online/on the

street or a polydrug consumption where users might mix licit and illicit substances in order to reach recreational effects. Even though known with benzodiazepines and opioids, these features have appeared being reported in the literature and are emerging in the clinical practice even with pharmaceuticals not known to have such effects, e.g., the antiepileptic pregabalin, the antidepressant bupropion, the antidiarrheal loperamide, the anticholinergic biperiden, the antipsychotic quetiapine, etc., which have been described as diverted, misused, or abused. Moreover, this type of phenomenon has been recorded by health professionals in various settings, not only those related to substance abusers, including EDs, primary care centres, and mental health services. However, in being limited the number of cases recorded and the related knowledge on this phenomenon, and in consideration of the rigorous process needed for the marketing of a drug in order to ensure its safe use, this research aimed to analyse data from pharmacovigilance datasets of voluntary reports, such as the EV; the UK YCS; and the FAERS, focusing on the abuse/misuse/dependence and withdrawal issues of several molecules.

Objectives of the study:

- To assess the misuse and diversion potential of the following prescription drugs:

  -gabapentinoids, e.g., pregabalin and gabapentin;

  -selected antidepressants, e.g., bupropion and venlafaxine, and the SSRI drugs fluoxetine, paroxetine, citalopram, escitalopram, and sertraline;

  -selected antipsychotics, e.g., quetiapine, olanzapine, and clozapine;

  -Z-drugs, e.g., zolpidem, zaleplon, and zopiclone;

  - among image and performance-enhancing drugs (IPEDs), salbutamol and clenbuterol;

  -selected opioids, including fentanyl, tramadol, codeine, dihydrocodeine, oxycodone and pentazocine.

- To assess the misuse and diversion potential of selected OTCs, including loperamide, promethazine, and benzydamine.

Secondary objectives of the present project included the study of possible other reactions of interest related to psychiatric drugs was investigated, e.g., the problem of adverse urological reactions related to the use of prescribed ketamine, through the use of pharmacovigilance databases. Moreover, in order to have a better understanding of the diversion and misuse of some other drugs, systematic reviews were carried out prior to further study using pharmacovigilance data. The first systematic review focused on the study of antihistamines, cough medicines and OTC decongestants; the second one analysed the relevant published data on the abuse of centrally acting anticholinergic drugs, such as benztropine, benzhexol/trihexyphenidyl, cyclobenzaprine, orphenadrine and scopolamine.

Overall, the analysis and description of these cases finally aimed to understand if any prescription drugs are abused/used recreationally, if there were vulnerable populations and risk categories, and if there is a range of possibilities/potentialities for abuse depending on the pharmacodynamic action of drugs, supporting physicians in prescribing.

Research areas included:

- Epidemiology of *pharming* and drug misuse, including drug-related mortality;
- Pharmacovigilance/toxicovigilance approaches in assessing the abuse potential of prescription and OTC drugs;
- Post-marketing and surveillance issues.

Chapter 2 - Methodology

2.1 Data

2.1.1 Sources of pharmacovigilance data

In order to access pharmacovigilance data to analyse the mentioned issues, we contacted the UMC and requested access to VigiBase. However, even though they did not charge for the data itself (as it is the property of the WHO Programme member countries), there were some fees to cover for the manual work going into the request, which could not be afforded due to funding unavailability. Similarly, VigiLyze, which is the software used by the UMC for the statistical analysis of the dataset, is reserved for the use of national pharmacovigilance centres only. Thus, other pharmacovigilance datasets freely available were considered. EV is the dataset through which the EMA manages and analyses information on suspected ADRs to medicines authorised in the European Economic Area (EEA), according to Directive 2001/83/EC and Regulation (EC) No 726/2004[59]. Since November 2017, EV launched an extensive web access to data on suspected ADRs and the possibilities for academic research institutions to request a more extensive dataset for the purposes of health research[62]. Data analysed were available from the EMA upon a drug-specific request to access the EV related dataset (for each request of data and each medical product there is a numerical code of identification 'EMA request reference ASK-'). Our request involved the provision of data elements for abuse/misuse/dependence individual case safety reports related to an identified substance according to the EV Access Policy. A copy of the approval of the research protocol by the ethics committee of the University of Hertfordshire, copies of the confidentiality form were signed by the research group, and the details of a corresponding author were provided to the EMA.

Similarly, the FAERS dataset, which supports the FDA's post-marketing safety procedures, collecting information on adverse event and medication error reports submitted to

the FDA, was considered a useful tool for the aim of this project. Its data were available through the FAERS Public Dashboard, which is a highly interactive web-based tool allowing for the querying of FAERS data[55]

Moreover, for the UK, the YCS collects information on a range of ADRs voluntarily reported from healthcare professionals, members of the public, and pharmaceutical companies, and publishes cumulative listings of all suspected ADRs received through interactive Drug Analysis Profiles (iDAPs)[63]. Its data have been used here for comparison with the other datasets. In fact they were easily accessible online: after selecting the iDAP related to the index molecule, a general overview of data relating to: age, gender, and type of reactions (organised as in the EV and the FAERS by System Organ Class-SOC and MedDRA Preferred Terms – PTs[28]) was made available. A range of filters were then applied to the database, with the timeframe and reactions selected being those used for the other two datasets.

Finally, the Italian Medicines Agency was contacted in order to request information on access to the national pharmacovigilance dataset for academic purposes, but this could not be obtained.

2.1.2 Selection of drugs to be analysed

A range of both prescription medicines and OTCs which were previously reported as possibly being misused according to the literature (e.g., experimental and observational studies; case reports; case series; and fatality reports) and online sources, such as drug monitoring reports and users' fora, have been preselected. In addition, the research group's expertise in previous projects, including the European-wide Monitoring, Analysis and knowledge Dissemination on Novel Emerging Psychoactives (EU-MADNESS) project was taken into account. Compared with opioids and benzodiazepines or any other prescription drugs that are already known to be prone to abuse, which are traditionally misused and thus already mostly controlled, those agents might potentially be diverted, associated with risky behaviours and fatalities. They are: gabapentinoids (e.g., pregabalin and gabapentin); some antidepressants (e.g., bupropion and venlafaxine, and the SSRI drugs fluoxetine, paroxetine,

citalopram, escitalopram, sertraline); among antipsychotics, quetiapine, olanzapine, and clozapine; among IPEDs, clenbuterol and salbutamol; among OTCs, loperamide, promethazine, and benzydamine; Z-drugs, such as zolpidem, zaleplon, and zopiclone; and, finally, among opioids, fentanyl, tramadol, codeine, dihydrocodeine, oxycodone and pentazocine.

Due to the new EMA restrictions on the acquisition of data (December 2019), some substances which have been mentioned in the first phase have not been studied, including: noopept and citicoline (nootropic supplements); aripiprazole (antipsychotics); triptans (sumatriptan, zolmitriptan, eletriptan, frovatriptan, rizatriptan, naratriptan); oxytocin; atomoxetine; optalidon; acetaminophen; metamizole/dipyrone; and flupirtin.

2.1.3 Pharmacovigilance data

Information requested from the EMA dataset were provided within three months through a hyperlink that was valid for two months. Data were provided as large Excel files divided into information sections reporting in a standardised format. EV data allowed the access to Level 2A information, which included: general information on the ADR (sender type; sender organisation; type of report; date when the report was first received; primary source country; reporter qualification; seriousness of the case; and medical confirmation of the case); information on the patient (age, sex, weight, and height); type of reaction/event; drug information, including concomitant licit and illicit drugs (the information provided enclosed indicated: type of drug; dosages; administration route; and duration), medical history and comments; outcome of the reaction and any death; and literature references when available[59].

ADRs were recorded according to the MedDRA, and selected through Preferred Terms (PT), defined as distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic. PTs included were the following: ‘dependence’, ‘drug abuse’, ‘drug abuser’, ‘drug diversion’, ‘drug use disorder’, ‘drug withdrawal’, ‘drug withdrawal

syndrome', 'intentional product misuse', 'intentional product use issue', 'overdose', 'product use in unapproved indication', 'product use issue', 'substance use disorder', 'substance abuser', 'withdrawal syndrome', within the standardised MedDRA 'drug abuse, dependence and withdrawal' section. The following ADRs were excluded from the analysis: 'toxicity to various agents', 'medication error', 'drug level increased', 'drug tolerance', 'drug administration error', 'drug dispensing error', 'off-label use', 'drug prescribing error', 'drug tolerance', 'accidental overdose/exposure', 'drug disease interaction', 'inappropriate prescribing', and 'incorrect dose administration'.

Information from the EV dataset is provided in line listings with the names 'Safety Report', 'Reporter', Literature Study', 'Patient', 'Parent', 'Reaction', 'Test', 'Drug', 'Diagnosis Summary'. The line listings 'Safety Report' provides the total number of cases. Each case report may refer to one or more reporter, study, or suspected ADRs as well as to one or more medicinal products. Therefore, a single case may be represented by more than one row in the other line listings, having the same 'EV Local Report Number', assigned by the EV, by which the listings are sorted.

Similarly, the FAERS dataset included ADRs unequivocally identified through 'Report Number'. Then the data items in both datasets were searched for duplicates by report ID and duplicated reports then excluded from the analysis[59]. FAERS datasets contained i) patient demographic and administrative information; ii) drug/biologic information for all medications reported for the event; iii) all MedDRA terms coded for the adverse event; iv) report sources for the ADR; v) drug therapy start and end dates for the reported drug(s); and vi) all MedDRA terms for the reported drug's indications/diagnoses[8]. When the two datasets were compared (e.g., with opioids and SSRIs), a merged data file for each data source (i.e., EMA, FAERS) was created in SPSS® for the selected drugs. In order to compare several drugs with each other, PhiVid in R software® [64] on both datasets was run for the ADRs of interest.

2.2 Disproportionality methods

Detecting safety signals for marketed medicinal products from individual case reports ultimately relies on both accurate assessment by trained pharmacovigilance professionals and statistical and computational methods. In fact, due to pre-marketing clinical trials including too few patients from groups that are too homogeneous to capture a drug's full spectrum of possible adverse effects, post-marketing surveillance is needed in order to detect a previously unknown safety issue of a drug[65]. As the complete safety profile of a drug can be described only after its marketing approval, surveillance systems have been developed, collecting suspected ADRs in very large databases, such as the EV, VigiBase, and FAERS. As the volume of these data is continuously growing, data mining with measures of disproportionality is being used more and more in order to detect new, previously unknown, ADRs as soon as possible after a drug is marketed[66]. Currently, despite the availability of numerous more advanced methods, e.g., Bayesian methods, such as the Multi-Item Gamma Poisson Shrinker (MGPS) [67–69], disproportionality analysis is still the predominant one due to its high sensitivity, easy access, and affordability[65,70]. Disproportionality analysis is primarily a tool to generate hypotheses on possible causal relations between drugs and adverse effects, to be followed up by clinical assessment of the underlying individual case reports. These methods use 'measures of disproportionality' which quantify unexpectedness. 'Unexpectedness' in this context implies that the observed number of reports for a specific drug-adverse event combination is higher than expected, the latter derived from the total database[70]. In fact, disproportionality analyses are based on statistical calculations that detect drug–adverse event/reaction associations that occur at higher-than-expected frequencies. These methods compare the actual count for an association between a drug and an adverse event/reaction with the background count for the adverse event/reaction for all other drugs or drug combinations in the database[71]; this produces a proportional reporting ratio (PRR), which indicates the degree of disproportionality occurring for a drug–adverse event/reaction association, compared with all other products in the database. If a high number of drug–

adverse event/reaction associations are detected compared with the back- ground count, a signal for a potential cause–effect relationship between a drug and the adverse event/reaction has been detected[59,71,72]. It is based on the contrast between observed and expected numbers of reports, for any given combination of drug and adverse event, and is generally recommended and necessary for large databases[73]. The PRR is a disproportionality measure that is defined as 'the ratio between the frequency with which a specific adverse event is reported for the drug of interest (relative to all adverse events reported for the drug) and the frequency with which the same adverse event is reported for the drug(s) in the comparison group (relative to all adverse events for drugs in the comparison group)'[72]. The PRR was computed with the help of the following formula:

$$\frac{W/W+X}{Y/Y+Z}$$

where:

W=number of suspected drug x cases relating to the chosen adverse event(s);

X=number of suspected drug x cases involving any other adverse events;

Y=number of suspected drug y cases relating to the chosen adverse event(s);

and Z=number of suspected drug Y cases involving any other adverse events.

In this case, signals are disproportionality measures based on a 2 × 2 contingency table and determine whether a drug-adverse event pair occurs more often than expected by comparing signal values to published thresholds (Table 1)[14,66,74].

Table 1. Two-by-two contingency table for a combination 'drug X' (or 'drug of interest') and 'Adverse Drug Reaction/ADR Y' (or 'ADR of interest') and framework for the calculation of the disproportionality

	ADR of interest (*Y*)	Other ADRs	
Drug of interest (*X*)	*a*	*b*	*a + b*
Other drugs	*c*	*d*	*c + d*
	a + c	b + d	*n = a + b + c + d*

Frequentist or classical methods, including the PRR and the Reporting odds ratio (ROR), are particularly appealing and therefore widely used due to the fact that they are relatively easy to understand, interpret and compute as they are based on the same principles of calculation [68]. As compared to the view of "frequency probability", Bayesian methods interpret the concept of probability as the degree to which a person believes a proposition. Bayesian inference starts with a pre-existing subjective personal assessment of the unknown parameter and the probability distribution (called prior distribution). Bayesian methods such as the MGPS and Bayesian Confidence Propagation Neural network (BCPN) are based on Bayes' law to estimate the probability (posterior probability) that the suspected event occurs given the use of suspect drug [68]. The Bayes' law assumes that there are two events of interest (D and E), which are not independent. From the basic theory of probability, it is known that the conditional probability of E given that D has occurred is represented as P(E/D)=P(E,D)/P(D), where:

P(D)=probability of a suspected drug being reported in a case report;

P(E)= probability of a suspected event being reported in a case report;

P(E,D)= probability that suspected drug and event being simultaneously reported in a case report;

P(E/D)= probability that suspected event being reported given the suspected drug being reported;

Assuming that the probability that D and E simultaneously occur is the same as the probability that D and E occur and rearranging the formula, we have P(E/D)=P(E,D)/P(D)=P(E)P(D/E)/P(D), which is Bayes' law. The signal metric or signal score in BCPN is the information component (IC) = log2 P(E,D)/P(E)P(D). If drug and event are statistically independent, the ratio of the joint probability of drug and event [P(E,D)] to the product of the individual probabilities [P(E)P(D)] will equal 1 and the IC will equal zero. The IC can be conceptualized as the additional information obtained on the probability of the event (or

the additional uncertainty eliminated) by specifying a drug. A signal usually requires that the lower 95% confidence interval (CI) of the IC exceed zero[68,72].

Although several studies have been conducted to examine and compare the performance of different methods applied in pharmacovigilance in terms of sensitivity, specificity, accuracy, and early identification of safety issues, actually, there is no recognised gold standard methodology, e.g., the PRR approach resulted to be more sensitive than MGPS, although the estimation from the MGPS is believed to be more robust when the number of reports is small [75,76]. Conversely, the ROR is an easily applicable technique, which allows adjustment through logistic regression analysis; moreover, its value is not influenced by non-selective underreporting of a drug or ADR compared with the population of patients experiencing an ADR. An overview on the most frequently used methods in pharmacovigilance is provided in Table 2 to summarize operative information for the reader.

Table 2. Summary of major methods used for signal detection in pharmacovigilance

Method	Computation	Published threshold criteria	Advantage	Limitations
Bayesian methods				
Multi-item Gamma Poisson Shrinker (MGPS)	$\frac{a\,(a+b+c+d)}{(a+c)\,(a+b)}$	EBGM05 > 2 N>0	-Always applicable -More specific as compared to frequentist method*	-Relatively nontransparent for people non familiar with Bayesian statistics -Lower sensitivity
Bayesian Confidence Propagation Neural network (BCPN)	$\log_2 \frac{a\,(a+b+c+d)}{(a+c)\,(a+b)}$	IC-2 SD>0	-Always applicable -More specific as compared to frequentist method* -Can be used for pattern recognition in Higher dimension	-Relatively nontransparent for people non familiar with Bayesian statistics -Lower sensitivity
Frequentist methods				
Proportional Reporting Ratio (PRR)	$\frac{a/(a+b)}{c/(c+d)}$ $95\%CI = e^{\ln(PRR) \pm 1.96 \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	PRR≥2, χ2≥4, N≥3	-Easily applicable .Easily interpretable -More sensitive as compared to Bayesian method*	-Cannot be calculated for all drug-event combinations -Lower specificity
Reporting Odds Ratio (ROR)	$\frac{a/c}{b/d}$ $95\%CI = e^{\ln(ROR) \pm 1.96 \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	95%CI> 1, N≥2	-Easily applicable -Easily interpretable -More sensitive as compared to Bayesian method* -Different adjustment for covariates in logistic Regression analysis	-Odds ratio not calculated if denominator is zero (specific ADRs) -Lower specificity

* when commonly cited thresholds are used.

ADR: adverse drug reaction; CI=Confidence Interval; EBGM=Empirical Bayesian Geometric Mean; 05=fifth percentile of the posterior distribution, i.e., there is a 95% probability that the "true" relative reporting ratio exceeds the EBGM05; IC= Information Component; N= number of cases; SD=Standard Deviation; χ2= chi-squared.

The arbitrary nature of threshold criteria for signal detection could cause the identification of potential false positive or false negative associations. A recent review of published threshold criteria for defining signals of disproportionate reporting highlighted a considerable variation in defining a significant disproportionality among practitioners of pharmacovigilance data miners. Indeed, changing the thresholds or selecting a methodology based on sensitivity considerations alone can have major implications: a more stringent

criterion increases the sensitivity of the test by lowering the number of false positives, with the risk of missing credible signals. It is necessary to find an optimum balance, not just with regard to the use of statistics (frequentist vs Bayesian) but also among thresholds used for signal detection [68].

In the present research we retrospectively analysed ADRs reported and available in the databases performing a descriptive analysis of ADRs and cases. ADR reports were analysed with respect to age and sex of patient/consumer, source/reporter country (EEA or non-EEA) and reporter qualification (i.e., pharmacist, physician, etc); type of ADR; seriousness (fatal, recovered, or resolved outcomes); drug dosage; possible concomitant drug(s); and diagnosis; reporter's comments and references, if recorded. The analysis included cases of overdoses, suicides, and fatalities. In the datasets, each case report may refer to one or more reporter; one or more ADR(s); as well as to one or more medicinal product(s). Therefore, a case may be represented by more than one row in the other line listings. Moreover, the data files received were searched for duplicates by report ID through the 'EV Local Report Number', which unequivocally identified an individual case. Thus, the number of suspected ADRs appeared to be different from the number of case reports as one case report might refer to several suspected ADRs. Moreover, the number of patients was different from the number of case reports as a patient might have been described in more than one case. Finally, ADRs' numbers differed from those referring to case reports/single patients since different reporters/senders could have independently flagged the same ADR.

The first analysis included both a descriptive study of the dataset and the CI values[59] performed through IBM® SPSS® Statistics (version 26) software. Moreover, in order to better compare two molecules in the same group, the PRR approach was used. From its computation, a PRR greater than 1 suggested that the adverse event was more commonly reported for individuals taking the drug of interest relative to the comparison drug(s), while, if the PRR value was less than 1, there was a disproportion of reporting in the sense that the specific event was less frequently reported in association with the suspect drug than with the

others. PRR confidence intervals were computed as well indicating with PRR- and PRR + respectively the lower and upper bounds of the 95% CI[72].

Secondly, according to the examiners' comments on the first Doctoral phase, a study of the literature related to pharmacovigilance approach was performed. Derived from previously published studies on the FAERS dataset, due to an external collaboration, the methodology of the study was improved for calculating the following pharmacovigilance signal measures ROR, PRR, IC, and empirical Bayes geometric mean/EBGM for abuse/dependence/withdrawal-related adverse events[8]. This type of analysis was performed for both the SSRI and opioids datasets trying to compare EMA and FDA data in order to have a worldwide view of related abuse/dependence and withdrawal issues. In this instance, data mining algorithms, including the ROR, the PRR, the EBGM, and the IC were retrospectively applied to both the FAERS and EV databases to detect drug event combinations due to their different sensitivity, specificity, and early detection potential[68,77]. Specifically, the EB05 meaning the 5% quantile of the posterior distribution of the EBGM and the IC025 meaning the 2.5% quantile of the posterior distribution of IC were here studied. Signals for ADR where there were less than 5 events were removed from the analysis. Moreover, signals based on a false discovery rate (FDR) <0.05 were here taken into account [78–80].

2.3 Software systems

In the first phase of the PhD the Excel Programme in Microsoft Office 365® and the IBM SPSS® statistics software (version 26, 2019) were used for the descriptive analysis of data. SPSS® was freely available from the University of Hertfordshire, user-friendly and quickly performed data preparation and management and their analysis[81].

Secondly, due to the improved pharmacovigilance approach, various commercially available software programmes generating disproportionality signals and/or performing Bayesian analysis[69], such as R®, MGPS, e.g., Empirica Signal™, PV Analyser™, Molecular Analysis of Side Effects (MASE™), and Statistical Analysis Systems (SAS™), were considered

for the present project. R® is a free software environment for statistical computing and graphics, which compiles and runs on a wide variety of UNIX platforms, Windows and MacOS. Specifically, the PhiVid package in R® is used to analyse pharmacovigilance data, and obtain the following measures PRR, ROR, EBMG and IC[64]. R (4.1.3) was the software selected for the present study together with SPSS®, while due to several reasons, such as economical and practical advantages, excluding the following softwares: PV-Analyzer™[82], SAS Analytics Software™ [83], MASE™ [84], and VigiMethods developed by the Uppsala Monitoring Centre[85].

2.4 Ethics

In compliance with applicable Personal Data Protection legislation (Regulation (EC) No 45/2001 and Regulation (EC) No 1049/2001, the protection of privacy and integrity of individuals was guaranteed, and in order to safeguard the identity of individuals certain data elements, including names/identifiers of individuals involved or country-specific information were not disclosed by the EMA[59]. Similarly, the informatic structure of the MHRA and the FAERS databases adheres to the international safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B)[55,86]. The study was ethically approved in March 2018 by the University of Hertfordshire Ethics' Committee, with reference number LMS/PGR/UH/03234 (notified on 5th March 2018).

In order to easily investigate substances that by the time become abused or misused, or at least anecdotally reported as misused, and eventually compare two molecules each other, without limitations in the selection of the molecule, after our request, in June 2018 we obtained amendments of the first ethics approved, which then included broad categories of drugs, such as *antipsychotics, antidepressants, hormones, neurological medications, and supplements*. Similarly, in March 2019, in consideration of the related abuse recorded, an extension was requested to include promethazine and benzydamine, and then approved.

Chapter 3 - Results of the research programme

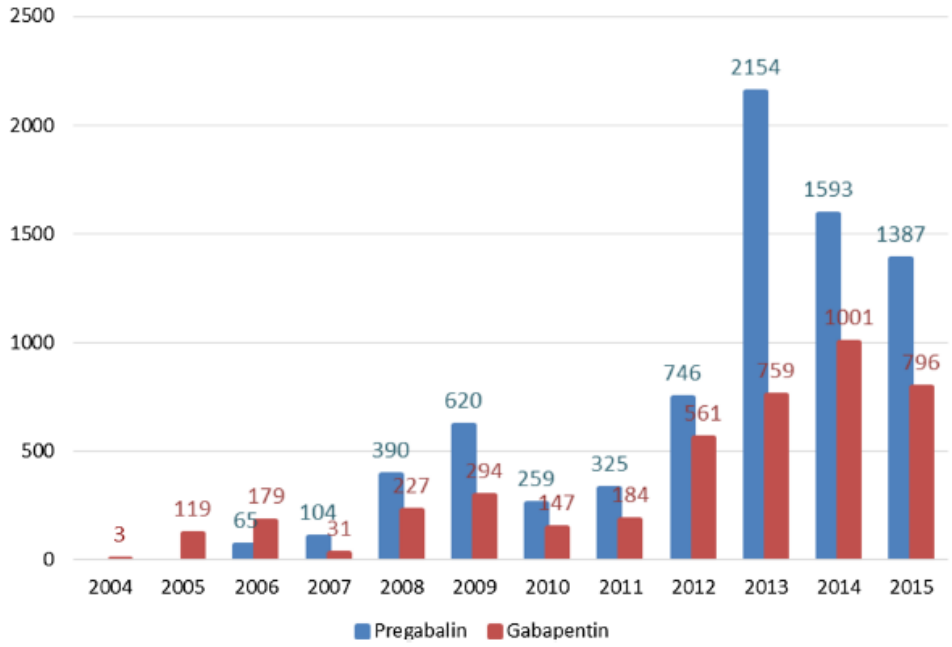
3.1 Findings regarding prescription drugs

Considering the specific type of drug investigated, from the datasets analysed, the following results were obtained:

3.1.1 Study 1: Gabapentinoids

The first pharmacovigilance study performed during our research was related to gabapentinoids, specifically pregabalin and gabapentin, and analysed levels of abuse, misuse and dependence of both pregabalin and gabapentin as reported to the EMA. In addition, their frequencies in being reported for each issue were compared through the PRR computed in association with the ADRs selected, e.g., 'drug abuse', 'drug dependence', 'drug withdrawal', etc. [7,87]. Data received by the EV reported a range of parameters, including socio-demographic characteristics; source/reporter country; reporter qualification; outcomes; and possible concomitant drug(s) ingested. They recorded a number of cases increasing year after year, since 2004 (Figure 1), confirming the increasing prescription numbers of both molecules. In fact, over the period 03/2006–15/07/2015, the EMA received 115,616 ADRs reports relating to pregabalin; this molecule had been approved by the EMA in 2006, when gabapentin was already available. Of them, a number of 7,639 reports were relating to abuse/dependence/product misuse issues, corresponding to 1,315 patients and 6.6% of all ADRs recorded. In the same period, the EMA received 90,166 ADR reports relating to gabapentin. Of these, 4,301 were relating to abuse/dependence issues, corresponding to 410 patients and 4.8% of all ADRs recorded.

Figure 1. Number of gabapentinoid abuse/ dependence adverse drug reactions (ADR) per year as recorded by the EV dataset



According to the MedDRA dictionary, the ADRs involved in the majority of cases were, in order, 'drug abuse', 'drug dependence', and 'intentional product misuse', respectively in 22.3%, 31.9% and 32.2% of pregabalin cases, and in 24.8%, 31.8%, and 28.3% of gabapentin cases. Both pregabalin and gabapentin datasets reported concurrently misused drugs, such as opioids (involved in 10.4% of pregabalin ADRs, and 12.9% of gabapentin ADRs), antidepressants, and benzodiazepines. Fatalities have been reported with both pregabalin (2.1%) and gabapentin (21.0%), especially with supratherapeutic dosages of drugs, e.g., pregabalin > 750mg/day (the licensed dose range is 150 to 600mg per day), with maximum dosage 12,000mg/day, and idiosyncratic intake routes, such as nasal or intravenous. Following the PRR computation, pregabalin compared with gabapentin emerged as more prone to determine abuse, misuse, and dependence issues, being PRR values 1.25, 1.39, and 1.58, respectively (Table 3). In order to give an example, the PRR was computed as follows:

$$\frac{A/A + B}{C/C + D}$$

where:

A is the number of individual cases with pregabalin involving the adverse events drug abuse/drug dependence/intentional product misuse;

B is the number of individual cases related to pregabalin involving any other adverse events;

C is the number of individual cases involving the events drug abuse/drug dependence/intentional product misuse in relation to gabapentin;

and D is the number of individual cases involving any other adverse events associated with gabapentin.

As described above, for example, the PRR for drug abuse was computed as follows (Table 3):

$$\frac{1706/(1706+109007)}{1066/(1066+86513)} = \frac{0.015}{0.012} = 1.25$$

Table 3. Pregabalin and gabapentin abuse/dependence/product misuse Adverse Drug Reactions (ADRs) frequency relative to all adverse events reported for each drug

Pregabalin ADRs	**ADRs (Number of reactions)**	**Proportion of pregabalin ADRs (A/A + B)**	**PRR**
Drug abuse (A1)	1,706	0.015	1.25
Drug dependence (A2)	2,440	0.021	1.39
Intentional product misuse (A3)	2,463	0.021	1.58
Other adverse events (B)	109,007	0.943	
Total adverse events (A1+ A2+A3+B)	115,616	1.000	
Gabapentin ADRs	**ADRs (Number of reactions)**	**Proportion of gabapentin ADRs (C/C + D)**	**PRR**
Drug abuse (C1)	1,066	0.012	
Drug dependence (C2)	1,368	0.015	
Intentional product misuse (C3)	1,219	0.014	
Other adverse events (D)	86,513	0.959	
Total adverse events (C1+C2+C3+D)	90,166	1.000	

Abbreviations: ADRs: adverse drug reactions; PRR: proportional reporting ratio

3.1.2 Study 2: Antidepressants

3.1.2.1 Bupropion versus Venlafaxine

Studying bupropion and venlafaxine related misuse-/abuse-/dependence- and withdrawal- cases reported to EMA, out of 20,720 (bupropion) and 47,516 (venlafaxine) total number of ADRs, some 2,232 (10.8%), and 4,071 (8.5%) misuse/abuse/dependence ADRs were respectively associated with bupropion and venlafaxine. Conversely, bupropion withdrawal-related ADRs were reported in 299/20,720 (1.4%) cases and in 914/47,516 (1.9%) cases for venlafaxine (Table 4). Overall, all bupropion and venlafaxine misuse-/abuse-/dependence- and withdrawal-ADRs were related to a respective number of 264 and 447 patients. According to our analysis, the most represented ADRs described in the bupropion dataset were ‘drug abuse’ (61.6%); ‘drug dependence’ (26.6%); and ‘drug withdrawal syndrome’ (11.8%), while the respectively calculated percentages for venlafaxine were: ‘drug abuse’ (47.4%); ‘drug dependence’ (34.3%); and ‘drug withdrawal syndrome’ (18.3%) (Table 4). The male gender was mostly involved in bupropion cases, whereas the female gender emerged among venlafaxine cases. In both bupropion- and venlafaxine- related datasets opioids were the most concurrently used drugs, respectively in 46.5% of bupropion cases and 33.56% of venlafaxine cases. Supratherapeutic dosages, e.g., bupropion > 800mg/day (maximum total daily dose must not exceed 300mg), and idiosyncratic intake routes, such as nasal or intravenous, emerged (Table 4).

Table 4. Overview of data relating to bupropion and venlafaxine ADRs as reported to the EudraVigilance (EV) database.

	BUPROPION ADRs	**VENLAFAXINE ADRs**
Time-frame considered	01/2005–05/2016	06/2003–07/2016
Total number of ADRs	20,720	47,516
Misuse-/abuse-/dependence- and withdrawal- related ADRs	2,531 (including misuse-/abuse-/dependence-related ADRs 2,232 and withdrawal-related ADRs 299)	4,985 (including misuse-/abuse-/dependence-related ADRs 4,071 and withdrawal-related ADRs 914)
Number of unique patients being reported to the database	264	447
Age range most typically represented	18-64 yy (64.5%)	18-64 yy (61.5%)
ADRs most typically represented within the misuse-/abuse-/dependence- and withdrawal- related ADRs' group	Drug abuse (61.6%), Drug dependence (26.6%), Drug withdrawal syndrome (11.8%)	Drug abuse (47.4%), Drug dependence (34.3%), Drug withdrawal syndrome 18.3(%)
Gender most typically represented	Male (F/M ratio: 1,155/1,257=0.91)	Female (F/M ratio: 2,483/2,406= 1.03)
Concomitant drugs most typically represented	Opiates/opioids (in n=123/264; 46.5%); other antidepressants (in n=116/264; 43.9% of cases, with SSRIs-citalopram, escitalopram, fluoxetine, paroxetine and sertraline being those most typically reported); other psychotropic substances, such as amphetamine, caffeine, cannabis, cocaine, alcohol, nicotine (in n=68/264; 25.7%)	Opiates/opioids (in n=150/447,33.55% of cases); benzodiazepines (in n=138/447; 30.8%); and other antidepressants (in n=114/447; 25.5% with SSRIs being those most typically reported)

Abbreviations: ADR: adverse drug reaction; yy: years

Comparing the two antidepressants through the PRR computation, bupropion was more frequently misused/abused (PRR = 1.50), but less frequently associated with both dependence (PRR = 0.92) and withdrawal (PRR = 0.77) issues in comparison with venlafaxine (Table 5).

Table 5. Bupropion and venlafaxine misuse/abuse-; dependence-; withdrawal and remaining-related ADRs': occurrence and Proportional Reporting Ratio (PRR)

BUPROPION ADRs	**No of reactions ADRs**	**Proportion of Bupropion ADRs**	***Bupropion vs Venlafaxine PRR***
Misuse/abuse-related ADRs (A1)	1,558	0.075	***1.50***
Dependence–related ADRs (A2)	674	0.032	***0.92 (reverse: 1.09)***
Withdrawal-related ADRs (A3)	299	0.014	***0.77 (reverse: 1.30)***
Other Adverse Events (B)	18,189	0.878	
Total (A1+A2+A3 +B)	20,720	1	
VENLAFAXINE ADRS	**No of reactions ADRs**	**Proportion of Venlafaxine ADRs**	
Misuse/abuse-related ADRs (C1)	2,361	0.05	
Dependence–related ADRs (C2)	1,710	0.036	
Withdrawal syndrome-related ADRs (C3)	914	0.019	
Other Adverse Events (D)	42,531	0.895	
Total (C1+C2+C3+D)	47,516	1	

Abbreviations: ADR: adverse drug reaction; PRR: proportional reporting ratio

To better assess withdrawal issues, we carried out a further comparison with paroxetine and fluoxetine, two SSRIs being characterised by different levels of withdrawal presentation during a tapering down regime. In doing so, we took into account the January 2000-December 2016 data available from the YCS MHRA, finding similar results, which then supported the EMA findings (Table 6)[10].

Table 6. Reported withdrawal adverse drug reactions for bupropion; fluoxetine; paroxetine; and venlafaxine (source: UK-based Yellow Card scheme; 2000-2016) and related proportional reporting ratio (PRR) computations

	Number of reactions	**Proportion**	PRR computation	
BUPROPION		0.0014	Venlafaxine vs Bupropion	**29.64**
Withdrawal reactions	30		Fluoxetine vs Bupropion	**6.71**
Total reactions	20,585		Paroxetine vs Bupropion	**51.07**
FLUOXETINE		0.0094	Venlafaxine vs Fluoxetine	**4.41**
Withdrawal reactions	74		Paroxetine vs Venlafaxine	**1.72**
Total reactions	7,905		Paroxetine vs Fluoxetine	**7.61**
PAROXETINE		0.0715		
Withdrawal reactions	1,358			
Total reactions	18,988			
VENLAFAXINE		0.0415		
Withdrawal reactions	471			
Total reactions	11,350			

Abbreviation: PRR: proportional reporting ratio

3.1.2.2 SSRIs (fluoxetine, paroxetine, citalopram, escitalopram, and sertraline)

This study was performed in the second phase of the PhD, and aimed at analysing the EV and the FAERS datasets, in order to describe how abuse, misuse, dependence, and withdrawal issues were recorded for most SSRIs, i.e., citalopram, escitalopram, fluoxetine, paroxetine, and sertraline, and detect possible signals of disproportionality, calculating the PRR, ROR, IC025, and EB05 measures. Both datasets showed increasing trends of yearly reporting and similar signals regarding abuse and dependence. EV misuse/abuse/dependence/withdrawal observations totalled 5,335 cases/patients; higher numbers referred to paroxetine (1,592/5,335; 29.8%), citalopram (1,419; 26.6%) and sertraline (1,149; 21.5%), whilst fewer to fluoxetine (771; 14.4%) and escitalopram (404; 7.5%). Regarding the FAERS dataset, a total of 144,395 misuse/abuse/dependence cases were identified, with some 39,091/144,395 (27.1%) cases reported for paroxetine; 38,532 (26.7%) for sertraline; 25,744 (17.8%) for citalopram; 22,793 (15.8%) for fluoxetine; and 18,235 (12.6%) for escitalopram. Comparing SSRIs, EV misuse/abuse related ADRs were mostly recorded for citalopram, fluoxetine, and sertraline; conversely, dependence was mostly associated with

paroxetine, and withdrawal with escitalopram. For FAERS, citalopram and fluoxetine were the most mentioned antidepressants for drug abuse; conversely, dependence/withdrawal were more frequently reported for paroxetine (Table 7). Moreover, with the lack of reliable worldwide prescription data, a representative sample of national data regarding prescriptions dispensed in the community in England from the Prescription Cost Analysis (PCA), was considered. According to this sample, a continuous rise during years 2004-2018, and especially so for the single antidepressants citalopram, fluoxetine, and sertraline was registered, while paroxetine gradually reduced over the years, and escitalopram remained almost stable; citalopram was the most prescribed antidepressant, whilst sertraline prescriptions have risen rapidly, overtaking paroxetine. Similarly, from the US, results from the latest National Health and Nutrition Examination Survey (NHANES) showed a consistent overall rise in the US prevalence of antidepressant use over the period 2003-2018, with peaks observed during 2011-2012 and 2013-2014 (Table 7).

Table 7. Signal scores regarding abuse/dependence and withdrawal issues for citalopram, escitalopram, fluoxetine, paroxetine, and sertraline (European Medicines Agency/EMA and the Food and Drug Administration-FDA Adverse Event Reporting System/FAERS datasets)

EMA DATASET																				
Preferred terms (PT)	**CITALOPRAM**				**ESCITALOPRAM**				**FLUOXETINE**				**PAROXETINE**				**SERTRALINE**			
	PRR	**ROR**	**IC025**	**EB05**	**PRR**	**ROR**	**IC025**	**EB05**	**PRR**	**ROR**	**IC025**	**EB05**	**PRR**	**ROR**	**IC025**	**EB05**	**PRR**	**ROR**	**IC025**	**EB05**
Drug abuse	**4.12 (<0.01)**	**5.00 (<0.01)**	**1.39 (<0.01)**	**2.67 (<0.01)**	0.48 (0.42)	0.46 (0.42)	-1.31 (0.30)	0.43 (0.47)	**1.77 (<0.01)**	**1.88 (<0.01)**	**0.54 (<0.01)**	**1.49 (<0.01)**	0.12 (0.43)	0.10 (0.43)	-2.49 (0.42)	0.19 (0.53)	**1.57 (<0.01)**	**1.64 (<0.01)**	**0.37 (<0.01)**	**1.32 (<0.01)**
Drug abuser	**3.00 (0.03)**	**3.00 (0.03)**	-2.58 (0.42)	0.46 (0.44)	**5.74 (<0.01)**	**5.75 (<0.01)**	-2.33 (0.41)	0.48 (0.42)	NA	NA	NA	NA	NA	NA	NA	NA	2.22 (0.08)	2.22 (0.08)	-2.72 (0.43)	0.45 (0.46)
Drug diversion	NA	NA	NA	NA	**5.74 (<0.01)**	**5.75 (<0.01)**	-1.30 (0.30)	0.57 (0.31)	NA	NA	NA	NA	0.56 (0.31)	0.56 (0.31)	-2.77 (0.43)	0.41 (0.48)	**2.22 (0.02)**	**2.22 (0.02)**	-1.85 (0.37)	0.52 (0.37)
Drug use disorder	NA	NA	NA	NA	**11.49 (<0.01)**	**11.49 (<0.01)**	-2.33 (0.41)	0.48 (0.41)	**7.30 (<0.01)**	**7.30 (<0.01)**	-2.47 (0.42)	0.48 (0.43)	NA	NA	NA	NA	NA	NA	NA	NA
Intentional product misuse	**3.20 (<0.01)**	**3.32 (<0.01)**	**1.05 (<0.01)**	**2.09 (<0.01)**	**1.23 (<0.01)**	**1.23 (<0.01)**	**-0.13 (0.02)**	**0.95 (0.02)**	**1.78 (<0.01)**	**1.81 (<0.01)**	**0.41 (<0.01)**	**1.36 (<0.01)**	0.20 (0.42)	0.19 (0.42)	-1.97 (0.38)	0.28 (0.52)	**1.18 (<0.01)**	**1.18 (<0.01)**	**-0.09 (0.01)**	**0.97 (0.01)**
Substance abuse	**3.85 (<0.01)**	**3.88 (<0.01)**	**0.87 (<0.01)**	**1.76 (<0.01)**	0.66 (0.39)	0.66 (0.39)	-1.74 (0.36)	0.44 (0.46)	**1.24 (0.04)**	**1.24 (0.04)**	-0.54 (0.09)	0.76 (0.13)	0.23 (0.42)	0.23 (0.42)	-2.14 (0.40)	0.29 (0.52)	**1.38 (<0.01)**	**1.38 (<0.01)**	**-0.30 (0.05)**	0.88 (0.05)
Substance use	**3.00 (0.03)**	**3.00 (0.03)**	-2.58 (0.42)	0.46 (0.44)	NA	NA	NA	NA	**3.65 (<0.01)**	**3.65 (<0.01)**	-2.50 (0.42)	0.47 (0.43)	NA	NA	NA	NA	2.22 (0.09)	2.22 (0.09)	-2.72 (0.43)	0.45 (0.46)
Dependence	0.16 (0.42)	0.16 (0.42)	-3.58 (0.47)	0.17 (0.53)	0.31 (0.40)	0.31 (0.40)	-2.78 (0.43)	0.27 (0.52)	0.28 (0.41)	0.28 (0.41)	-2.73 (0.43)	0.25 (0.53)	6.45 (<0.01)	6.51 (<0.01)	0.53 (<0.01)	1.53 (<0.01)	0.27 (0.42)	0.27 (0.42)	-2.50 (0.42)	0.25 (0.53)
Drug dependence	0.41 (0.41)	0.41 (0.41)	-1.89 (0.37)	0.35 (0.51)	1.02 (0.19)	1.02 (0.19)	-0.68 (0.14)	0.69 (0.19)	0.57 (0.39)	0.57 (0.39)	-1.44 (0.32)	0.45 (0.46)	**1.84 (<0.01)**	**1.84 (<0.01)**	**0.09 (<0.01)**	**1.13 (<0.01)**	0.84 (0.39)	0.84 (0.39)	-0.73 (0.16)	0.66 (0.21)

Substance dependence	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.56 (0.28)	0.56 (0.28)	-3.46 (0.47)	0.40 (0.49)	**8.89 (<0.01)**	**8.89 (<0.01)**	-1.61 (0.34)	0.56 (0.32)
Drug withdrawal syndrome	1.01 (0.19)	1.01 (0.19)	**-0.29 (0.05)**	0.85 (0.06)	**1.68 (<0.01)**	**1.71 (<0.01)**	**0.34 (<0.01)**	**1.29 (<0.01)**	0.90 (0.36)	0.90 (0.36)	-0.48 (0.08)	0.76 (0.12)	1.01 (0.19)	1.01 (0.19)	**-0.18 (0.02)**	**0.92 (0.03)**	0.75 (0.40)	0.74 (0.40)	-0.65 (0.13)	0.67 (0.20)
Intentional overdose	**1.56 (<0.01)**	**1.57 (<0.01)**	**-0.25 (0.04)**	**0.89 (0.05)**	0.80 (0.30)	0.80 (0.30)	-1.52 (0.33)	0.49 (0.40)	**2.58 (<0.01)**	**2.59 (<0.01)**	**0.37 (<0.01)**	**1.25 (<0.01)**	0.31 (0.42)	0.31 (0.42)	-1.82 (0.36)	0.36 (0.51)	**1.48 (<0.01)**	**1.48 (<0.01)**	**-0.27 (0.04)**	**0.89 (0.05)**
Off-label use	1.09 (0.16)	1.09 (0.16)	-1.22 (0.29)	0.57 (0.31)	**1.69 (<0.01)**	**1.69 (<0.01)**	-0.88 (0.19)	0.64 (0.23)	**3.24 (<0.01)**	**3.25 (<0.01)**	**0.20 (<0.01)**	**1.07 (<0.01)**	0.38 (0.40)	0.38 (0.40)	-1.89 (0.37)	0.39 (0.49)	0.81 (0.28)	0.81 (0.28)	-1.54 (0.33)	0.50 (0.39)
Overdose	**1.53 (<0.01)**	**1.54 (<0.01)**	**-0.02 (0.01)**	**1.02 (0.01)**	**1.26 (0.01)**	**1.26 (0.01)**	-0.42 (0.07)	0.80 (0.10)	**1.35 (<0.01)**	**1.35 (<0.01)**	**-0.22 (0.03)**	**0.91 (0.04)**	0.40 (0.42)	0.40 (0.42)	-1.28 (0.30)	0.46 (0.44)	**1.69 (<0.01)**	**1.70 (<0.01)**	**0.12 (<0.01)**	**1.13 (<0.01)**
FAERS DATASET																				
PREFERRED TERMS (PT)	**CITALOPRAM**				**ESCITALOPRAM**				**FLUOXETINE**				**PAROXETINE**				**SERTRALINE**			
	PRR	**ROR**	**IC025**	**EB05**	**PRR**	**ROR**	**IC025**	**EB05**	**PRR**	**ROR**	**IC025**	**EB05**	**PRR**	**ROR**	**IC025**	**EB05**	**PRR**	**ROR**	**IC025**	**EB05**
Drug abuse	**3.35 (<0.01)**	**3.39 (<0.01)**	**1.18 (<0.01)**	**2.31 (<0.01)**	0.52 (0.63)	0.51 (0.63)	-1.04 (0.27)	0.50 (0.27)	**1.22 (<0.01)**	**1.22 (<0.01)**	**0.13 (<0.01)**	**1.11 (0.01)**	0.32 (0.63)	0.32 (0.63)	-1.44 (0.33)	0.38 (0.34)	0.86 (0.63)	0.86 (0.63)	-0.27 (0.06)	0.85 (0.07)
Drug abuser	**1.32 (0.01)**	**1.32 (0.01)**	**-0.18 (0.03)**	**0.95 (0.02)**	0.74 (0.56)	0.74 (0.56)	-1.08 (0.28)	0.52 (0.26)	**1.46 (<0.01)**	**1.46 (<0.01)**	**-0.06 (0.01)**	**1.03 (0.01)**	0.70 (0.60)	0.70 (0.60)	-0.86 (0.23)	0.60 (0.22)	1.01 (0.35)	1.01 (0.35)	-0.45 (0.12)	0.79 (0.10)
Drug diversion	0.19 (0.58)	0.19 (0.58)	-4.20 (0.49)	0.11 (0.47)	1.61 (0.11)	1.61 (0.11)	-0.99 (0.26)	0.62 (0.21)	0.69 (0.49)	0.69 (0.49)	-2.16 (0.40)	0.31 (0.38)	0.41 (0.58)	0.41 (0.58)	-2.47 (0.43)	0.25 (0.41)	**3.11 (<0.01)**	**3.11 (<0.01)**	**-0.07 (0.01)**	**1.14 (<0.01)**
Drug use disorder	0.18 (0.58)	0.18 (0.58)	-4.24 (0.49)	0.11 (0.47)	**1.93 (0.01)**	**1.93 (0.01)**	-0.70 (0.20)	0.74 (0.13)	**9.96 (<0.01)**	**9.96 (<0.01)**	**0.95 (<0.01)**	**2.19 (<0.01)**	0.09 (0.61)	0.09 (0.61)	-4.97 (0.50)	0.07 (0.47)	0.22 (0.60)	0.22 (0.60)	-3.58 (0.48)	0.14 (0.46)
Intentional product misuse	**2.22 (<0.01)**	**2.23 (<0.01)**	**0.71 (<0.01)**	**1.68 (<0.01)**	0.86 (0.58)	0.86 (0.58)	-0.46 (0.13)	0.75 (0.12)	**1.43 (<0.01)**	**1.43 (<0.01)**	**0.22 (<0.01)**	**1.20 (<0.01)**	0.45 (0.63)	0.45 (0.63)	-1.12 (0.28)	0.48 (0.28)	0.80 (0.62)	0.80 (0.62)	-0.44 (0.12)	0.76 (0.12)
Substance abuse	**1.83 (<0.01)**	**1.83 (<0.01)**	**0.11 (<0.01)**	**1.17 (<0.01)**	0.39 (0.61)	0.39 (0.61)	-2.29 (0.41)	0.25 (0.41)	0.80 (0.52)	0.80 (0.52)	-1.02 (0.26)	0.55 (0.24)	0.89 (0.48)	0.89 (0.48)	-0.66 (0.19)	0.70 (0.16)	1.10 (0.23)	1.10 (0.23)	-0.45 (0.12)	0.80 (0.09)

Substance use	**1.90 (0.01)**	**1.90 (0.01)**	-0.58 (0.16)	0.80 (0.09)	0.25 (0.56)	0.25 (0.56)	-3.93 (0.49)	0.13 (0.46)	1.44 (0.15)	1.44 (0.15)	-0.98 (0.26)	0.62 (0.21)	0.08 (0.61)	0.08 (0.61)	-5.01 (0.50)	0.07 (0.48)	**2.35 (<0.01)**	**2.35 (<0.01)**	-0.27 (0.06)	**0.99 (0.01)**
Dependence	0.07 (0.63)	0.07 (0.63)	-4.45 (0.50)	0.05 (0.48)	0.06 (0.63)	0.06 (0.63)	-5.09 (0.50)	0.04 (0.48)	0.11 (0.63)	0.11 (0.63)	-3.67 (0.48)	0.09 (0.47)	**27.42 (<0.01)**	**27.51 (<0.01)**	**1.46 (<0.01)**	**2.86 (<0.01)**	0.11 (0.63)	0.11 (0.63)	-3.36 (0.47)	0.11 (0.47)
Drug dependence	0.33 (0.63)	0.33 (0.63)	-1.77 (0.37)	0.31 (0.38)	0.44 (0.63)	0.44 (0.63)	-1.43 (0.33)	0.39 (0.33)	0.34 (0.63)	0.34 (0.63)	-1.73 (0.36)	0.32 (0.37)	**3.61 (<0.01)**	**3.62 (<0.01)**	**0.88 (<0.01)**	**1.90 (<0.01)**	0.79 (0.62)	0.79 (0.62)	-0.45 (0.12)	0.75 (0.12)
Substance dependence	NA	NA	NA	NA	NA	NA	NA	NA	1.84 (0.15)	1.84 (0.15)	-1.86 (0.37)	0.42 (0.32)	1.41 (0.25)	1.41 (0.25)	-1.78 (0.37)	0.44 (0.30)	1.73 (0.15)	1.73 (0.15)	-1.63 (0.35)	0.48 (0.28)
Drug withdrawal syndrome	0.13 (0.63)	0.13 (0.63)	-2.89 (0.45)	0.14 (0.46)	0.17 (0.63)	0.17 (0.63)	-2.57 (0.43)	0.17 (0.45)	0.19 (0.63)	0.19 (0.63)	-2.37 (0.42)	0.20 (0.43)	**13.68 (<0.01)**	**14.19 (<0.01)**	**1.47 (<0.01)**	**2.80 (<0.01)**	0.19 (0.63)	0.19 (0.63)	-2.16 (0.40)	0.23 (0.42)
Intentional overdose	**1.65 (<0.01)**	**1.65 (<0.01)**	**0.46 (<0.01)**	**1.40 (<0.01)**	**1.59 (<0.01)**	**1.59 (<0.01)**	**0.44 (<0.01)**	**1.38 (<0.01)**	**1.30 (<0.01)**	**1.30 (<0.01)**	**0.19 (<0.01)**	**1.17 (<0.01)**	0.50 (0.63)	0.50 (0.63)	-0.90 (0.24)	0.55 (0.25)	0.74 (0.63)	0.74 (0.63)	-0.46 (0.12)	0.74 (0.13)
Off-label use	**1.14 (<0.01)**	**1.14 (<0.01)**	**-0.02 (0.01)**	**1.01 (0.01)**	**2.13 (<0.01)**	**2.14 (<0.01)**	**0.73 (<0.01)**	**1.71 (<0.01)**	**2.00 (<0.01)**	**2.00 (<0.01)**	**0.63 (<0.01)**	**1.59 (<0.01)**	0.36 (0.63)	0.36 (0.63)	-1.38 (0.32)	0.40 (0.33)	0.65 (0.63)	0.65 (0.63)	-0.66 (0.19)	0.65 (0.19)
Overdose	**1.88 (<0.01)**	**1.89 (<0.01)**	**0.62 (<0.01)**	**1.56 (<0.01)**	**1.25 (<0.01)**	**1.25 (<0.01)**	**0.16 (<0.01)**	**1.14 (<0.01)**	**1.06 (0.01)**	**1.06 (0.01)**	**-0.04 (0.01)**	**0.99 (0.01)**	0.62 (0.63)	0.62 (0.63)	-0.61 (0.17)	0.67 (0.18)	0.75 (0.63)	0.75 (0.63)	-0.42 (0.11)	0.76 (0.12)

Boldface denotes signals based on FDR<0.05; Minimum number of events to compute signal statistics = 1 for all measures.

Abbreviations: EMA: European Medicines Agency; EB05 = 5% quantile of the posterior distribution of the empirical Bayesian geometric mean (estimated FDR); FAERS: Food and Drug Administration Adverse Event Reporting System; FDR = false discovery rate; IC025 = 2.5% quantile of the posterior distribution of information component (estimated FDR); NA = not available = no events for this pair; PRR = observed relative risks (estimated FDR); ROR = observed odds ratios (estimated FDR)

3.1.3 Study 3: Antipsychotics

3.1.3.1 Quetiapine versus olanzapine

A study on antipsychotics compared quetiapine and olanzapine cases of abuse, misuse, dependence, and withdrawal reported to the EMA. Over the period July 2005 to July 2016, the EMA received 209,571 ADR reports relating to quetiapine (Table 8); of these, 18,112 reports were related to misuse/abuse/dependence/withdrawal issues, corresponding to 884 patients and 8.6% of all ADRs recorded. Most patients (87.2%) were in the 18- to 64-year age range. The number of reports increased consistently year per year, The most commonly reported quetiapine ADRs were ‘drug abuse’ (52.2%); ‘drug dependence’ (26.4%); and ‘substance abuse’ (7.6%). The most concurrently used drugs were antidepressants (46.9%); benzodiazepine (44.0%); and opioids (43.3%). Similarly, over the period September 2004 to July 2016, EMA received 55,100 ADR reports relating to olanzapine (Table 8). Of these, 4,178 were relating to misuse/abuse/dependence/withdrawal issues, corresponding to 237 patients and 7.6% of all ADRs recorded. Most patients (71.6%) were in the 18- to 64-year age range. Olanzapine ADRs most often described in the EV dataset were ‘drug abuse’ (55.4%) and ‘drug dependence’ (29.9%), antidepressants, benzodiazepines, and opioids being the most used concomitant drugs (48.1%, 43.9%, and 35.9%). In both antipsychotics’ datasets male adults were mostly involved, and supratherapeutic dosages of drugs, e.g., quetiapine > 800mg/day, emerged. According to the PRR computation, quetiapine has been more frequently associated with abuse/misuse-, dependence- and withdrawal-related reactions compared with olanzapine (PRR values were 1.07, 1.01, 5.25 respectively). Fatalities were more represented in the quetiapine dataset, being mostly in the context of a polydrug consumption. Other illicit substances have been reported as consumed concurrently with quetiapine and olanzapine (Table 8).

Table 8. Overview of data relating to quetiapine and olanzapine Adverse Drug Reactions (ADRs) as reported to the EudraVigilance (EV) database

	QUETIAPINE ADRs	OLANZAPINE ADRs
TIMEFRAME CONSIDERED	07/2005–07/2016	09/2004–07/2016
TOTAL NUMBER OF ADRS	209,571	55,100
MISUSE-ABUSE-/DEPENDENCE-/WITHDRAWAL-RELATED ADRS	18,112	4,178
NUMBER OF UNIQUE PATIENTS BEING REPORTED TO THE DATABASE	884	237
AGE RANGE MOST TYPICALLY REPRESENTED	18-64 yy (87.21%)	18-64 yy (71.6%)
ADRS MOST TYPICALLY REPRESENTED	Drug abuse (52.2%), Drug dependence (26.4%), Substance abuse (7.6%)	Drug abuse (55.9%), Drug dependence (29.9%)
GENDER MOST TYPICALLY REPRESENTED	Male (F/M ratio=0.96)	Male (F/M ratio=0.96)
CONCOMITANT DRUGS MOST TYPICALLY REPRESENTED	Antidepressants (in n=415/884, 46.9% of cases, with citalopram, trazodone and sertraline being those most typically reported); benzodiazepines (in n=392; 44.3%); opiates/opioids (in n=383; 43.3%)	Antidepressants (in n=114/288, 48.1% of cases, with sertraline, fluoxetine and trazodone being those most typically reported); benzodiazepines (in n=104; 43.9%); and opiates/opioids (in n=82; 35.9%)
FATALITIES	368 patients	79 patients

Abbreviations: ADRs: adverse drug reactions; F: female; M: male; yy: years.

3.1.3.2 Clozapine

In the case of clozapine, the 2005–2018 EMA dataset was analysed to identify and describe possible clozapine withdrawal- and even misuse-/abuse-/dependence-related in consideration of discontinuation/withdrawal syndrome anecdotally described[88]. Out of 11,847 clozapine-related ADRs recorded, some 599 (5.1%) were related to misuse/abuse/dependence/withdrawal issues, including 258 withdrawal-related (43.1%); 241 abuse-related (40.2%); and 80 intentional product misuse-related (13.3%) ADRs. Patients were typically males (379/559 = 67.8% CI 95% 378–380), in the 18–65 years age range (Table 9). A small number of overdose- and suicide-related ADRs were reported as well. Oral intake occurred here in 533/559 cases (95.3% CI 95% 532.5–533.5); when recorded, clozapine dosages varied from 12.5mg/day to high/unlicensed levels (i.e., 2,800–5,600mg/day; normal

dosage can be adjusted up to maximum 900mg/day). Only a few cases (n = 7), however, reported high (e.g., >1,000mg) levels. When the relevant clinical data were made available, these cases were typically described as 'intentional self-injury', 'completed suicide', and 'drug abuse'). Clozapine was typically (69.2%) identified alone, and most (84.7%) fatalities/high-dosage intake instances were reported in association with a history of substance abuse (Table 9).

Table 9. Analysis of the EudraVigilance (EV) clozapine-related misuse/abuse/dependence and withdrawal Adverse Drug Reactions (ADRs) (2005-June 2018)

	N
TOTAL "SUSPECT" CLOZAPINE-RELATED ADRS RECORDED	**11,847**
CLOZAPINE-RELATED 'ABUSE, DEPENDENCE AND WITHDRAWAL' ADRs	**599 (*CI* 95% 595-603)** (N individual cases = 559)
Drug abuse	198
Drug abuser	1
Substance abuse	42
Dependence	7
Drug dependence	6
Drug diversion	1
Intentional product misuse	80
Product use issue	4
Drug withdrawal convulsions	1
Drug withdrawal neonatal syndrome	1
Drug withdrawal syndrome	91
Withdrawal syndrome	165
FURTHER ISSUES EMERGING FROM THE ANALYSIS OF CLOZAPINE ADRS' DATASET	
Intentional overdose	12
Overdose	17
Completed suicide	9
Intentional self-injury	4
Suicidal behaviour	1
Suicidal ideation	4
Suicide attempt	7
Self-injurious ideation	4

Abbreviations: ADRs: adverse drug reactions; CI: confidence interval

3.1.4 Study 4: Z-drugs (zolpidem, zaleplon, and zopiclone)

In this study, the Z-drugs Zolpidem, Zopiclone and Zaleplon, were studied and compared with regard to abuse/misuse/dependence issues through EV data. An overall total of 33,240 (e.g., 23,420 zolpidem; 9,283 zopiclone; and 537 zaleplon) misuse/abuse/dependence/withdrawal-related ADRs was identified[89]. Cases were described including demographic characteristics and clinical data, such as concomitant drugs, doses, and outcomes recorded of the reactions, including fatalities (Tables 10-11).

Table 10. Z-drugs (zaleplon, zolpidem and zopiclone) misuse-/abuse-/dependence/withdrawal- and overdose-related Adverse Drug Reactions (ADRs) and proportional reporting ratio (PRR) computation

ZALEPLON ADRS	**N OF REACTIONS ADRs TOTAL N = 4,270**	**PROPORTION OF ZALEPLON ADRs**
Drug abuser (A1) + Drug diversion (A2) + Drug use disorder(A3) + Intentional product use issue (A4) + Intentional product misuse (A5) +Prescription drug used without prescription (A6) + Product use in unapproved indication (A7) + Product use issue (A8) + Substance abuser (A9) + Substance use disorder (A10)	367	0.089
Dependence (A11)	5	0.001
Withdrawal syndrome (A12) + Drug withdrawal syndrome (A13) + Drug withdrawal headache (A14) + Drug withdrawal (A15)	89	0.023
Intentional overdose (A16) + Overdose (A17)	76	0.019
Other Adverse Events (B)	3,733	0.868
ZOPICLONE ADRs	**N OF REACTIONS ADRs TOTAL N = 65,140**	**PROPORTION OF ZOPICLONE ADRs**
Drug abuser (C1) + Drug diversion (C2) + Drug use disorder(C3) + Intentional product use issue (C4) + Intentional product misuse (C5) + Prescription drug used without prescription (C6) + Product use in unapproved indication (C7) + Product use issue (C8) + Substance abuser (C9) + Substance use disorder (C10)	2,507	0.043
Dependence (C11)	138	0.002
Withdrawal syndrome (C12) + Drug withdrawal syndrome (C13) + Drug withdrawal headache (C14) + Drug withdrawal (C15)	718	0.013
Intentional overdose (C16) + Overdose (C17)	5,920	0.096
Other Adverse Events (D)	55,857	0.846
ZOLPIDEM ADRs	**N OF REACTIONS ADRs TOTAL N = 206,315**	**PROPORTION OF ZOLPIDEM ADRs**
Drug abuser (E1) + Drug diversion (E2) + Drug use disorder (E2) + Intentional product use issue (E4) + Intentional product misuse (E5) +Prescription drug used without prescription (E6) + Product use in unapproved indication (E7) + Product use issue (E8) + Substance abuser (E9) + Substance use disorder (E10)	9,744	0.050
Dependence (E11)	423	0.002
Withdrawal syndrome (E12) + Drug withdrawal syndrome (E13) + Drug withdrawal headache (E14) + Drug withdrawal (E15)	2,433	0.018
Intentional overdose (E16) + Overdose (E17)	10,820	0.056

Other Adverse Events (F)	182,895	0.874

Abbreviations: ADR: adverse drug reaction

For the three Z-drugs the most recorded concomitant prescription drugs were antidepressants; benzodiazepines; and opiates; moreover, a range of recreational drugs were identified (e.g., alcohol; cannabis; cocaine; amphetamines); and intravenous and subcutaneous intake modalities were reported as well.

Table 11. Z-drugs (zaleplon, zolpidem and zopiclone) proportional reporting ratio (PRR) values

	PRR ZOLPIDEM VS ZALEPLON (PRR- AND PRR+)	**PRR ZOPICLONE VS ZALEPLON (PRR- AND PRR+)**	**PRR ZOLPIDEM VS ZOPICLONE (PRR- AND PRR+)**
Misuse/abuse ADRs	0.57 (0.55-0.59)	0.48 (0.43-0.53)	1.16 (1.11-1.21)
Dependence ADRs	2.00 (0.82-4.8)	2.00 (0.81-4.80)	1.00
Withdrawal ADRs	0.79 (0.76-0.81)	0.56 (0.29-1.06)	1.38 (1.27-1.49)
Overdose ADRs	2.90 (2.31-3.60)	5.00 (4.00-6.2)	0.58 (0.56-0.60)

Abbreviations: ADR: adverse drug reaction; PRR: proportional reporting ratio

The analyses of the EV databases confirmed the diversion potential and the possibility of abuse/misuse/dependence and withdrawal issues related to three Z-drugs, albeit some differences have emerged within this group. Considering PRR values, in comparison with zopiclone, zolpidem was more frequently involved in both misuse/abuse and withdrawal issues. Zolpidem and zopiclone presented with the same dependence risk (PRR = 1), but zopiclone was the most involved in overdose ADRs. When compared with zaleplon, zopiclone presented higher dependence (PRR = 2.00) and overdose-related issues (PRR = 5.00), but slightly lower misuse/abuse (PRR = 0.48) and withdrawal PRR values (PRR = 0.56).

3.1.5 Study 5: Performance and enhancing drugs (clenbuterol versus salbutamol)

Comparing clenbuterol and salbutamol EV datasets on misuse, abuse, dependence cases, a number of 55 misuse/abuse/dependence/withdrawal/overdose/off-label ADRs on a total number of 920 ADRs (6.0%, corresponding to 25 of 138 individual patients) and 1,310 ADRs on 62,879 ADRs (2.1%, corresponding to 474 of 6,923 individuals) were respectively associated with clenbuterol and salbutamol. The most frequently reported clenbuterol cases were ‘drug/substance abuse’ (n = 27/55: 50.5%), while in the salbutamol ADR dataset ‘overdose’ emerged as the most represented (n = 720/1,310: 55.0%) (Table 12). For clenbuterol, subjects typically involved were adult males; conversely, adult females were mostly represented in salbutamol cases. Clenbuterol has been used alone in 44% of cases reported, while in the remaining cases the most concurrently used drugs included anabolic steroids (e.g., testosterone, trenbolone, stanozolol, and nandrolone). Similar data have been described with salbutamol. Some fatalities have been recorded with both clenbuterol (2.2%) and salbutamol (0.5%), all in the context of a polydrug use, together with other IPEDs (anabolic steroids, thyroid hormone, and tamoxifen) (Table 12). From the PRR computation of clenbuterol versus salbutamol abuse/misuse numbers, emerged a value of 18.38, meaning those reactions were more frequently associated with clenbuterol than salbutamol [90].

Table 12. Overview of data relating to clenbuterol and salbutamol adverse drug reactions (ADRs) as reported to the European Medicines Agency (EMA) database in the timeframe July 2006–July 2016

	CLENBUTEROL ADRS	**SALBUTAMOL ADRS**
TOTAL NUMBER OF ADRs	920	62,879
N OF MISUSE/ABUSE/DEPENDENCE/ WITHDRAWAL/ OVERDOSE/OFF LABEL-RELATED ADRs	55	1,310
N OF INDIVIDUALS WITH MISUSE/ABUSE/ DEPENDENCE/WITHDRAWAL/OVERDOSE/ OFF LABEL- RELATED ADRs	25	474
AGE RANGE MOST TYPICALLY REPRESENTED	18–64 years	18–64 years
ADRs MOST TYPICALLY IDENTIFIED	Drug/substance abuse (49.0%), intentional product misuse (31.0%), overdose (14.5%), off-label (5.5%)	Overdose (55.0%), off label (20.8%), intentional product misuse (8.1%), drug withdrawal (6.6%), drug dependence (5.0%), drug/substance abuse (4.7%)
GENDER MOST TYPICALLY REPRESENTED	Male (F/M ratio = 0.09) (22 males, 2 females, and one unknown)	Female (F/M ratio = 1.2) (253 females, 207 males, and 14 unknown)
CONCOMITANT DRUGS	45.8% individuals were in monotherapy with clenbuterol; anabolic steroids, antipsychotics, and analgesic drugs were recorded	39.9% individuals were in monotherapy with salbutamol; steroids, antidepressants, and analgesic drugs were recorded
FATALITIES	3 subjects	34 subjects

Abbreviations: ADR: adverse drug reaction

3.1.6 Study 6: Opioid molecules: fentanyl, tramadol, codeine, dihydrocodeine, oxycodone, and pentazocine

In an initial study[91], fentanyl misuse/abuse/dependence-related issues were assessed using the EV database and compared with UK-MHRA and US FAERS data. The analysis of the three datasets showed increasing levels of misuse/abuse/dependence issues over time. During the period 2004-2018 some 127,313 ADRs (n = 6,161 patients/single cases) related to fentanyl's misuse/abuse/dependence/withdrawal were reported to the EMA. Among them, were considered as 'suspect' a total number of 14,287 ADRs, corresponding to 559 individual cases. The most represented ADRs were: 'drug dependence' (76.9%); 'intentional product misuse' (13.1%); and 'drug abuse' (7.5%). Most cases involved adult males and the concomitant use of other prescription/illicit drugs. A range of idiosyncratic (i.e., ingestion/injection of transdermal patches' fentanyl) and very high-dosage intake cases were identified. Significant numbers of cases required either a prolonged hospitalisation (34.35%) or resulted in death (33.1%). Similarly, within the same timeframe, the MHRA collected some 3,566 reports (n = 1,165 single patients/cases), with the most frequently reported ADRs being 'withdrawal' (24.9%); 'intentional product misuse' (19.6%); and 'overdose' (17.6%), and FAERS identified a total of 19,145 misuse/abuse/dependence/withdrawal-related cases, with 'overdose', 'withdrawal', and 'drug use disorder/drug abuse/drug diversion' being the most represented ADRs (respectively, 43.1%, 20.8%, and 20.3%) (Table 13).

Table 13. Data relating to fentanyl misuse/abuse/dependence/withdrawal-related Adverse Drug Reactions (ADRs) reported to the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency (MHRA) and the Food and Drug Administration (FDA) pharmacovigilance databases; 2004-2018

CHARACTERISTICS	EMA EV DATA	MHRA YCS DATA	FAERS DATA
FENTANYL MISUSE/ABUSE/ DEPENDENCE/WITHDRAWAL -RELATED ISSUES	14,287 ADRs (559 cases)	3,566 reactions (1,165 individual cases)	19,145 individual cases
MOST FREQUENTLY REPORTED ADRS' ISSUES	Drug dependence (76.9%), Intentional product misuse (13.1%), Drug abuse (7.5%)	Withdrawal (24.9%), Intentional product misuse and use issues (19.6%), Overdose (17.6%)	Overdose (42.1%), Withdrawal (20.5%), Drug abuse (20.0%)
AGE (years)	Adult Age group 35-64 (229/559 = 41.0%)	Adult Age group: 50-59 (164/1,165 = 14.1%) 40-49 (144/1,165 = 12.4%) 60-69 (141/1,165 = 12.1%)	N/A
GENDER MOST RAPRESENTED	Male (M/F: 319/209 = 1.52)	Female (M/F: 434/657 = 0.66)	N/A
FENTANYL AS SOLE DRUG OR IN COMBINATION	**Fentanyl sole drug:** 54.9% (307/559 cases). **Concomitant drugs reported**: other opioids (69.0%), cocaine (9.5%), benzodiazepines (6.8%), cannabis (5.6%), and alcohol (5.2%)	N/A	N/A

Abbreviations: ADR: adverse drug reaction; EMA: European Medicines Agency; FAERS: Food and Drug Administration (FDA) adverse event report system; MHRA: Medicines and Healthcare products Regulatory Agency

A follow-up study aimed to determine whether there were pharmacovigilance signals of abuse, misuse, and dependence and their nature for the prescription opioids codeine; dihydrocodeine; fentanyl; oxycodone; pentazocine; and tramadol, using both the pharmacovigilance datasets EV and FAERS. After a descriptive analysis of the selected ADRs, pharmacovigilance signal measures (i.e., ROR, PRR, IC025, and EB05) were computed.

During fifteen years (2003-2018), abuse-, misuse-, dependence-, and withdrawal-ADRs regarding the selected opioids were increasingly reported in both datasets. Overall, some 16,507 and 130,283 unique ADRs were submitted respectively to EV and FAERS relating to the selected opioids misuse/abuse/dependence/withdrawal issues. Compared with other opioids, abuse issues (e.g., ‘drug abuse’, ‘drug abuser’, ‘intentional product misuse’, and ‘substance abuse’) were mostly recorded in relation to fentanyl and oxycodone, while tramadol and oxycodone had significantly greater odds of drug dependence and withdrawal (Table 14). Benzodiazepines, antidepressants, other opioids, and antihistamines, and recreational drugs such as cocaine and alcohol, and several NPS, including mitragynine, and cathinones, were the most recorded concomitant drugs reported in both datasets (Tables 14-15).

Table 14. Analysis of opioid drugs abuse/misuse/dependence/withdrawal cases recorded by the European Medicines Agency (EMA) EudraVigilance (EV) dataset (up to 2018) and the Food and Drug Administration (FDA) Adverse Event Reporting System (up to 2020)

	CODEINE		DIHYDROCODEINE		FENTANYL		OXYCODONE		PENTAZOCINE		TRAMADOL	
	EMA	**FAERS**	**EMA**	**FAERS**	**EMA**	**FAERS**	**EMA**	**FAERS**	**EMA**	**FAERS**	**EMA**	**FAERS**
Individual cases	**814**	**6,764**	**53**	**575**	**5,443**	**54,640**	**7,442**	**45,672**	**136**	**112**	**2,619**	**22,530**
Mean Age in years (SD)	38.3 (13.6)	50.7 (19.6)	37.9 (12.7)	43.4 (22.2)	43.3 (16.0)	53.2 (19.2)	38.0 (13.6)	45.6 (18.2)	46.3 (16.5)	51.4 (21.1)	42.7 (15.7)	52.8 (20.4)
M (%) **F (%)**	73.8% (540) 26.2% (19	32.2% (1,983) 67.8% (4,167)	36.2% (17) 63.8% (30)	48.2% (244) 51.8% (262)	53.0% (2,459) 47.0% (2,178)	40.5% (19,354) 59.5% (28,382)	61.4% (3,929) 38.6% (2,468)	54.2% (22,504) 45.8% (19,036)	20.7% (28) 79.3% (107)	51.9% (54) 48.1% (50)	48.9% (1,142) 51.1% (1,195)	38.7% (7,890) 61.3% (12,479)
Country of origin (five most recorded countries, %)	US (58.6) Germany (12.1) France (7.4) Canada (6.5) Australia (4.7)	US (67.1) UK (10.8) Canada (5.4) Australia (3.6) Norway (2.6)	UK (31.8) Germany (22.7) France (18.2) Austria (9.1) New Zealand (6.8)	UK (78.0) US (8.0) Japan (4.5) Italy (2.4) Germany (1.6) New Zealand (1.6)	US (51.8) Canada (22.8) Germany (8.3) France (4.9) Estonia (2.2)	US (71.3) Japan (8.6) France (3.9) UK (3.0) Australia (2.1)	US (74.9) Canada (10.5) Australia (9.6) France (1.3) Germany (1.2)	US (86.8) France (2.6) Japan (2.1) Canada (1.9) UK (1.3) Australia (1.3)	Canada (63.0) US (18.5) India (10.9) Japan (4.2) UK (0.8)	Japan (65.6) US (14.0) India (12.9) Turkey (2.2) Germany (1.1)	US (48.4) Germany (13.3) France (7.6) Denmark (4.6) Sweden (3.8)	US (48.9) France (16.8) UK (11.9) Germany (2.5) Italy (2.3)
Most common indications recorded for the index opioid when reported (%)	-Drug abuse (1.9) -Pain/back pain (2.4) -Cough (1.4) -Headache (1.0) -Drug dependence (1.0)	-Pain (7.2) -Rheumatoid arthritis (4.9) -Cough (2.6) -Analgesic therapy (1.8) -Back Pain (1.6)	-Pain/ procedural pain (30.0) -Drug dependence (6.7) -Toothache (3.3) -Headache (3.3) -Drug abuser (3.3) -Analgesic therapy (3.3) -Drug withdrawal maintenance therapy (3.3)	-Pain/ back pain (18.2) -Rheumatoid arthritis (5.4) -Cough (2.5) -Psoriatic arthropathy (1.9) -Neuralgia (1.9)	-Pain (25.0) -Intentional product misuse (7.3) -Back pain (4.7) -Drug abuse (2.2) -Cancer pain (2.0)	-Pain/ back pain (40.9) -Cancer pain (6.2) -Breakthrough pain (4.2) -Anaesthesia (2.0) -Fibromyalgia (1.9)	-Drug abuse (15.3) -Pain/ back pain (18.5) -Intentional product misuse (3.5) -Drug abuser (1.2) -Drug dependence (0.6)	-Pain/ back pain (36.3) -Drug abuse (4.0) -Cancer Pain (3.5) -Breakthrough pain (2.2) -Drug abuser (1.3)	-Pain (24.4) -Drug/ substance abuse (9.0) - Migraine (3.8) - Abdominal pain (2.6) -Analgesic therapy (2.6) -	-Pain (17.3) -Analgesic therapy (14.3) -Drug abuse (8.2) -Induction of anaesthesia (5.1)	-Pain/ back pain (26.5) -Headache (2.7) -Arthralgia (2.2) -Drug abuse (1.7) -Procedural pain (1.0) -Migraine (1.0) -Fibromyalgia (1.0)	-Pain/ back pain (27.4) -Depression (6.1) -Fibromyalgia (2.1) -Analgesic therapy (2.0) -Rheumatoid arthritis (1.9)
Median dose (mg)	50.0- 500.0	NA	25.0- 210.0	NA	75.0- 800.0	NA	30.0- 90.0	NA	35.0- 750.0	NA	50.0- 1000.0	NA
ROA (%)	Oral (26.9) Parenteral (9.6) Naal/inhalation (1.8) Rectal (0.2)	NA	Oral (63.0) Parenteral (0) Nasal/inhalation (0) Rectal (0)	NA	Transdermal (44.9) Oral (22.6) Parenteral (8.3) Nasal/inhalation (3.1)	NA	Oral (56.0) Parenteral (3.6) Nasal/inhalation (2.5) Rectal (0)	NA	Parenteral (791.7) Oral (2.5)	NA	Oral (86.5) Parenteral (1.1)	NA
Most important concomitant prescription psychotropic drugs recorded (%)												
ANTIDEPRESSANTS	170 (20.9)	1,582 (23.4)	5 (9.4)	271 (47.1)	781 (14.3)	6,051 (11.1)	1,022 (13.7)	6,032 (13.2)	2 (1.5)	11 (9.8)	461 (17.6)	5,982 (26.6)
ANTIPSYCHOTICS	42 (5.2)	445 (6.6)	5 (9.4)	123 (21.4)	149 (2.7)	1,697 (2.9)	245 (3.3)	1,850 (4.1)	2 (1.5)	8 (7.1)	85 (3.2)	1,485 (6.6)
BENZODIAZEPINES	254 (31.2)	1,323 (19.6)	13 (24.5)	202 (35.1)	992 (18.2)	7,423 (13.6)	1,711 (23.0)	8,587 (18.8)	7 (5.1)	31 (27.7)	403 (15.4)	4,110 (18.2)
GABAPENTINOIDS	18 (2.2)	637 (9.4)	1 (1.9)	117 (20.3)	273 (5.0)	3,086 (5.6)	235 (3.2)	2,817 (6.2)	1 (0.7)	2 (1.8)	112 (4.3)	2,781 (12.3)

MOOD STABILIZERS	16 (2.0)	354 (5.2)	0 (0)	71 (12.3)	121 (2.2)	1,188 (2.2)	118 (1.6)	1,133 (2.5)	1 (0.7)	2 (1.8)	64 (2.4)	1,213 (5.4)
OTCs:												
Anticholinergics	11 (1.4)	167 (2.5)	2 (3.4)	9 (1.6)	37 (0.7)	1,190 (2.2)	33 (0.4)	533 (1.2)	0 (0)	11 (9.8)	23 (0.9)	609 (2.7)
Antihistamines	160 (19.7)	820 (12.1)	5 (9.4)	0 (0)	325 (6.0)	2,042 (3.7)	495 (8.7)	2,398 (5.3)	7 (5.1)	38 (33.9)	147 (5.6)	2,032 (9.0)
Dextrometorphan	102 (12.5)	200 (3.0)	0 (0)	2 (0.3)	37 (0.7)	96 (0.2)	112 (1.5)	268 (0.6)	0 (0)	0 (0)	26 (1.5)	95 (0.4)
Loperamide	0 (0)	51 (0.8)	0 (0)	2 (0.3)	4 (0.1)	63 (0.1)	11 (0.1)	92 (0.2)	0 (0)	1 (0.9)	6 (0.2)	106 (0.5)
Paracetamol/Acetaminophen	116 (14.3)	1,186 (17.5)	2 (3.8)	147 (25.1)	165 (3.0)	1,491 (2.7)	411 (5.5)	2,612 (5.7)	3 (2.2)	10 (8.9)	151 (5.8)	3,143 (14.0)
Pseudoephedrine and pseudoephedrine-containing products	3 (0.4)	63 (0.9)	0 (0)	0 (0)	3 (0.1)	26 (0)	26 (0.3)	72 (0.2)	0 (0)	0 (0)	3 (0.1)	56 (0.2)
OTHER OPIOIDS	550 (67.6%)	2,688 (39.7)	11 (20.8)	215 (37.4)	1,172 (21.5)	23,490 (43.0)	2,304 (31.0)	10,392 (22.8)	8 (5.9)	16 (14.3)	436 (16.6)	3,755 (16.7)
Z-DRUGS	34 (4.2)	279 (4.1)	2 (3.8)	14 (2.4)	145 (2.7)	1,201 (2.1)	184 (2.5)	1,341 (2.9)	1 (0.7)	6 (5.4)	68 (2.6)	1,270 (5.6)
Most important concomitant recreational drugs recorded (%)												
ALCOHOL	66 (8.1)	246 (3.6)	6 (11.3)	50 (8.7)	168 (3.1)	475 (0.9)	645 (8.7)	1,929 (4.2)	3 (2.2)	1 (0.9)	94 (3.6)	595 (2.6)
AMPHETAMINES AND METAMPHETAMINES	37 (4.5)	192 (2.8)	2 (3.4)	11 (1.9)	95 (1.7)	241 (0.4)	284 (3.8)	783 (1.7)	0 (0)	0 (0)	38 (1.5)	208 (0.9)
CANNABIS and CANNABINOIDS	22 (2.7)	64 (1.0)	0 (0)	3 (0.5)	58 (1.1)	164 (0.3)	346 (4.7)	803 (1.8)	1 (0.7)	1 (0.9)	40 (1.5)	97 (0.5)
COCAINE	149 (19.3)	296 (4.4)	1 (1.9)	4 (0.7)	190 (3.5)	421 (0.8)	652 (8.8)	1,481 (3.2)	0 (0)	0 (0)	69 (2.6)	196 (0.9)
HALLUCINOGENS	16 (2.0)	43 (0.6)	0 (0)	4 (0.7)	5 (0.1)	31 (0.1)	70 (0.9)	166 (0.4)	0 (0)	0 (0)	18 (0.7)	41 (0.2)
HEROIN	0 (0)	614 (9.1)	0 (0)	23 (4.0)	0 (0)	542 (1.0)	0 (0)	804 (1.8)	0 (0)	1 (0.9)	0 (0)	94 (0.4)
KETAMINE	3 (0.4)	7 (0.1)	0 (0)	2 (0.3)	9 (0.2)	177 (0.3)	13 (0.2)	30 (0.1)	0 (0)	0 (0)	0 (0)	48 (0.2)
NPS	0 (0)	5 (0.1)	0 (0)	0 (0)	0 (0)	5 (0)	0 (0)	8 (0)	0 (0)	0 (0)	4 (0.2)	19 (0.1)

Abbreviations: AE: Adverse Event; EMA: European Medicines Agency; FAERS: Food and Drug Administration Adverse Event Reporting System; NA: not available; NPS: new psychoactive substances; OTC: over the counter drugs; ROA: route of administration; SD: Standard Deviation; UK: United Kingdom; US: United States

*parenteral administration include intravenous and intramuscular routes of administrations

Table 15. Description of cases involving opioids and new psychoactive substances (NPS) recorded in both the European Medicines Agency (EMA) and the Food and Drug Administration Adverse Event Reporting System (FAERS) databases

Total number	Opioid drug *	Concomitant drugs *	*Traditional* illicit drugs *	NPS *	Country of occurrence	ADR recorded (PT)	Outcome
EMA CASES							
N = 4 (unspecified gender)	**TRAMADOL**	Loperamide (n = 1) Aripiprazole (n = 1) Haloperidol (n = 1) Hydroxyzine (n = 1)	Not recorded (n = 3) 3,4-methylenedioxymethamphetamine (n=1) Cocaine (n=1)	Mitragynine (n = 2) 4-methylethcathinone (n=1) Mephedrone (n=1) Methylenedioxypyrovalerone (n=1)	USA (n = 3) France (n = 1)	Drug abuse (n = 3) Accidental drug overdose (n = 2) Cardiomegaly (n = 2) Possible drug interaction (n =2) Drug use disorder (n = 1) Delirium (n = 1) Multiple drug abuse (n = 1) Tachycardia (n = 1) Intentional drug misuse (n = 1) Drug addiction (n = 1) Product used for unknown indication (n = 1) Toxicity to various agents (n = 1)	Fatal (n = 3); Prolonged hospitalization (n = 1)
FAERS CASES							
N = 5 (M/F = 4/1)	**CODEINE**	Benzodiazepines (n = 4) Doxylamine (n = 2) Morphine (n = 2) Ibuprofen (n = 1) Levomethadone (n =1)	Heroin (n = 2) Cocaine (n = 1) Not recorded (n = 2)	Mephedrone (n = 2) Methylenedioxypyrovalerone (n = 3)	NA	Drug abuse (n = 2) Toxicity to various agents (n = 4) Product used for unknown indication (n = 4) Disturbance in attention (n = 3) Dysarthria (n = 2) Daydreaming (n =1) Somnolence (n =1) Accident (n =1) Toxicity to various agents (n = 2) Gait Disturbance (n = 1) Vestibular disorder (n = 1) Thinking Abnormal (n =1) Slow response to stimuli (n =1) Fine motor skill dysfunction (n =1) Logorrhoea (n =1) Memory impairment (n =1) Mood swings (n =1) Nervous system disorder (n =1) Aggression (n =1) Behaviour disorder (n =1)	Fatal (n = 2); Not recorded (n = 3)

N = 5 (M/F=3/2)	**FENTANYL**	Benzodiazepines (n = 3) Not recorded (n = 2) Quetiapine (n =1) Doxepin (n =1) Methadone (n =1) Pseudoephedrine (n =1) Pregabalin (n =1) Trimipramine (n =1) Morphine (n =1) Alcohol (n =1)	Not recorded (n = 2) Methamphetamine (n =1)	Methylenedioxypyrovalerone (n = 4) Mitragynine (n =1)	NA	Aggression (n = 3) Toxicity to various agents (n = 3) Hypertonia (n = 2) Clonus (n = 2) Product used for unknown indication (n = 2) Bacteraemia (n = 2) Pneumonia aspiration (n = 1) Cognitive disorder (n = 1) Blood pressure diastolic decreased (n = 1) Serotonin syndrome (n = 1) Pneumothorax (n = 1) Hallucination (n =1) Confusional state (n = 1) White blood cell count increased (n = 1) Agitation (n =1) Urinary retention (n = 1) Left ventricular hypertrophy (n = 1) Respiratory arrest (n = 1) Accidental death (n = 1) Drug screen positive (n = 1) Pulmonary congestion (n = 1) Crime (n = 1) Somnolence (n = 1)	Hospitalised (n = 2); Fatal (n = 2); Not recorded (n = 1)
N = 6 (M/F=6/0)	**OXYCODONE**	Benzodiazepines (n = 2) Propoxyphene (n = 1) Naproxen (n = 1) Not recorded (n = 1) Hydromorphone (n = 1) Dronabinol (n = 1)	Not recorded (n = 4) Amphetamine (n = 1)	Alpha-Pyrrolidinopropiophenone (n =2) Phenethylamine (n = 1) Mitragynine (n = 1) Mephedrone (n = 1) Flubromazolam (n = 1) 3-Methoxyphencyclidine (n =1) 4-Methoxyphencyclidine (n = 1)	NA	Product used for unknown indication (n = 3) Completed suicide (n = 2) Cardiac arrest (n = 2) Respiratory arrest (n = 2) Toxicity to various agents (n = 2) Substance abuse (n = 1) Drug withdrawal syndrome (n = 1) Pain (n = 1) Accidental overdose (n = 1) Drug diversion (n = 1) Unresponsive to stimuli (n = 1) Intentional overdose (n = 1) Suicide attempt (n = 1) Loss of consciousness (n = 1) Brain oedema (n = 1)	Fata (n = 4); Not recorded (n = 1); Hospitalised (n = 1=
N = 18 (M/F=16/2)	**TRAMADOL**	Benzodiazepines (n = 7) Venlafaxine (n = 3)	Not recorded (n = 11) Cannabis (n = 2) Amphetamine (n = 1)	Mitragynine (n = 11) Methylenedioxypyrovalerone (n = 6)	NA	Toxicity to various agents (n = 10) Cardiac arrest (n = 10)	Fatal (n = 16); Hospitalised (n = 1); Not

		Trimipramine (n = 2) Mirtazapine (n = 2) Buprenorphine (n = 2) Alcohol (n = 2) Loperamide (n = 2) Pregabalin (n = 1) Fluoxetine (n = 1) Citalopram (n = 1) Olanzapine (n = 1) Zopiclone (n = 1) Doxepin (n = 1) Not recorded (n = 5)		3-Methoxyphencyclidine (n = 1)		Product used for unknown indication (n = 10) Pulmonary oedema (n = 7) Drug abuse (n = 4) Loss of consciousness (n = 4) Overdose (n = 3) Accidental overdose (n = 3) Brain oedema (n = 3) Respiratory depression (n = 2) Accidental death (n = 2) Tachycardia (n = 2) Drug level increased (n = 1) Pain (n = 1) Rib fracture (n = 1) Blood ethanol increased (n = 1) Death (n = 1) Arrhythmia (n = 1) Poisoningdeath (n = 1) Drug interaction (n = 1) Aggression (n = 1) Logorrhoea (n = 1) Dysarthria (n = 1) Restlessness (n = 1) Abnormal behaviour (n = 1)	recorded (n = 1)

*Dosages and routes of administration were not recorded

Abbreviations: ADR: adverse drug reaction; EV: EudraVigilance; NA: not available; NPS: new psychoactive substance; PT: preferred term; USA: United States of America

Finally, regarding other PTs recorded, in both datasets, compared with the other opioids, oxycodone was associated with aggression and euphoric mood; and tramadol was associated with visual and auditory hallucinations, psychotic disorder, and substance-induced-psychotic disorder (Table 16).

Table 16. Signal scores regarding opioid drugs other than abuse/dependence and withdrawal issues (European Medicines Agency/EMA and the Food and Drug Administration-FDA Adverse Event Reporting System/FAERS datasets)

PREFERRED TERMS (PT)	CODEINE				DIHYDROCODEINE				FENTANYL				OXYCODONE				PENTAZOCINE				TRAMADOL			
	PRR	ROR	IC025	EB05	PRR	ROR	IC025	EB05	PRR	ROR	IC025	EB05	PRR	ROR	IC025	EB05	PRR	ROR	IC025	EB05	PRR	ROR	IC025	EB05
ACUTE PSYCHOSIS																								
EMA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FAERS	NA	NA	NA	NA	NA	NA	NA	NA	1.03 (0.13)	1.04 (0.13)	-1.25 (0.29)	0.58 (0.24)	NA	NA	NA	NA	NA	NA	NA	NA	**3.07 (<0.01)**	**3.07 ()**	-0.31 (0.06)	**0.93 (0.03)**
AGGRESSION																								
EMA	0.84 (0.31)	0.84 (0.31)	-1.56 (0.33)	0.50 (0.37)	NA	NA	NA	NA	0.48 (0.71)	0.48 (0.71)	-1.35 (0.30)	0.46 (0.42)	**1.96 (<0.01)**	**1.97 (<0.01)**	**0.06 (<0.01)**	**1.12 (<0.01)**	NA	NA	NA	NA	0.88 (0.38)	0.88 (0.38)	-0.81 (0.20)	0.65 (0.23)
FAERS	**1.14 (<0.01)**	**1.14 (0.02)**	-0.32 (0.06)	0.85 (0.06)	**1.33 (0.04)**	**1.33 (0.04)**	-1.00 (0.25)	0.60 (0.23)	0.33 (0.43)	0.33 (0.43)	-1.38 (0.31)	0.41 (0.37)	**1.90 (<0.01)**	**1.90 (<0.01)**	**0.35 (<0.01)**	**1.32 (<0.01)**	NA	NA	NA	NA	**1.42 (<0.01)**	**1.42 (<0.01)**	**0.16 (<0.01)**	**1.16 (<0.01)**
CONFUSIONAL STATE																								
EMA	NA	NA	NA	NA	NA	NA	NA	NA	0.99 (0.23)	0.99 (0.23)	-0.44 (0.11)	0.80 (0.12)	0.87 (0.47)	0.87 (0.47)	-0.47 (0.12)	0.78 (0.13)	NA	NA	NA	NA	**1.40 (<0.01)**	**1.40 (<0.01)**	**-0.12 (0.02)**	**0.97 (0.02)**
FAERS	0.45 (0.42)	0.45 (0.42)	-1.47 (0.32)	0.38 (0.38)	**1.14 (0.05)**	**1.14 (0.05)**	-0.55 (0.13)	0.74 (0.13)	0.72 (0.42)	0.72 (0.42)	-0.40 (0.09)	0.77 (0.11)	0.83 (0.41)	0.83 (0.41)	-0.29 (0.05)	0.84 (0.07)	NA	NA	NA	NA	**2.10 (<0.01)**	**2.11 (<0.01)**	**0.69 (<0.01)**	**1.64 (<0.01)**
DELIRIUM																								
EMA	NA	NA	NA	NA	NA	NA	NA	NA	0.96 (0.23)	0.96 (0.23)	-1.03 (0.24)	0.62 (0.25)	0.54 (0.62)	0.54 (0.62)	-1.41 (0.31)	0.50 (0.37)	NA	NA	NA	NA	**1.44 (<0.01)**	**1.44 (<0.01)**	-0.78 (0.19)	0.70 (0.18)
FAERS	0.43 (0.41)	0.43 (0.41)	-1.80 (0.36)	0.33 (0.41)	NA	NA	NA	NA	0.97 (0.22)	0.97 (0.22)	**-0.19 (0.03)**	**0.90 (0.03)**	**1.21 (<0.01)**	**1.21 (<0.01)**	**0.01 (<0.01)**	**1.04 (0.01)**	NA	NA	NA	NA	0.95 (0.23)	0.95 (0.23)	-0.29 (0.06)	0.85 (0.06)
EUPHORIC MOOD																								
EMA	0.47 (0.57)	0.47 (0.57)	-2.28 (0.40)	0.36 (0.47)	NA	NA	NA	NA	0.11 (0.70)	0.11 (0.70)	-3.48 (0.47)	0.13 (0.49)	**2.66 (<0.01)**	**2.68 (<0.01)**	**0.29 (<0.01)**	**1.29 (<0.01)**	NA	NA	NA	NA	**1.49 (<0.01)**	**1.49 (<0.01)**	**0.06 (<0.01)**	**1.09 (<0.01)**
FAERS	0.34 (0.40)	0.34 (0.40)	-2.34 (0.40)	0.25 (0.44)	NA	NA	NA	NA	0.33 (0.43)	0.33 (0.43)	-1.39 (0.31)	0.40 (0.37)	**4.41 (<0.01)**	**4.42 (<0.01)**	**0.85 (<0.01)**	**1.86 (<0.01)**	NA	NA	NA	NA	0.44 (0.42)	0.44 (0.42)	-1.37 (0.31)	0.41 (0.36)
FEELING OF RELAXATION																								
EMA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

FAERS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HALLUCINATIONS, VISUAL																								
EMA	NA	NA	NA	NA	NA	NA	NA	NA	0.78 (0.40)	0.78 (0.40)	-1.43 (0.31)	0.53 (0.34)	0.41 (0.69)	0.41 (0.69)	-1.86 (0.36)	0.42 (0.45)	NA	NA	NA	NA	**3.63 (<0.01)**	**3.64 (<0.01)**	**0.20 (<0.01)**	**1.10 (<0.01)**
FAERS	**1.26 (<0.01)**	**1.26 (<0.01)**	-0.34 (0.07)	0.84 (0.06)	NA	NA	NA	NA	0.38 (0.42)	0.38 (0.42)	-1.31 (0.30)	0.43 (0.35)	0.52 (0.42)	0.52 (0.42)	-1.02 (0.25)	0.53 (0.28)	NA	NA	NA	NA	**4.50 (<0.01)**	**4.51 (<0.01)**	**1.17 (<0.01)**	**2.33 (<0.01)**
HALLUCINATIONS, AUDITORY																								
EMA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**1.24 (<0.01)**	**1.24 (<0.01)**	-0.79 (0.20)	0.72 (0.17)	NA	NA	NA	NA	**1.83 (<0.01)**	**1.83 (<0.01)**	-0.67 (0.16)	0.74 (0.16)
FAERS	NA	NA	NA	NA	NA	NA	NA	NA	0.35 (0.41)	0.35 (0.41)	-1.66 (0.34)	0.37 (0.39)	0.81 (0.28)	0.81 (0.28)	-0.71 (0.18)	0.68 (0.17)	NA	NA	NA	NA	**4.04 (<0.01)**	**4.04 (<0.01)**	**0.89 (<0.01)**	**1.95 (<0.01)**
PSYCHOTIC DISORDER																								
EMA	NA	NA	NA	NA	NA	NA	NA	NA	0.46 (0.57)	0.46 (0.57)	-2.08 (0.38)	0.40 (0.46)	0.67 (0.47)	0.67 (0.47)	-1.25 (0.28)	0.56 (0.31)	NA	NA	NA	NA	**3.40 (<0.01)**	**3.40 (<0.01)**	**0.21 (<0.01)**	**1.12 (<0.01)**
FAERS	0.31 (0.37)	0.31 (0.37)	-2.91 (0.44)	0.22 (0.45)	NA	NA	NA	NA	0.47 (0.42)	0.47 (0.42)	-1.11 (0.27)	0.50 (0.30)	0.81 (0.33)	0.81 (0.33)	-0.57 (0.14)	0.72 (0.14)	NA	NA	NA	NA	**3.13 (<0.01)**	**3.13 (<0.01)**	**0.82 (<0.01)**	**1.84 (<0.01)**
SUBSTANCE-INDUCED PSYCHOTIC DISORDER																								
EMA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FAERS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.81 (0.20)	0.81 (0.20)	-1.58 (0.34)	0.49 (0.31)	NA	NA	NA	NA	**4.21 (<0.01)**	**4.22 (<0.01)**	**0.02 (<0.01)**	**1.12 (<0.01)**

Boldface denotes signals based on FDR<0.05; Minimum number of events to compute signal statistics = 1 for all measures.

Abbreviations: EMA: European Medicines Agency; EB05: 5% quantile of the posterior distribution of the empirical Bayesian geometric mean (estimated FDR); FAERS: Food and Drug Administration Adverse Event Reporting System; FDR: false discovery rate; IC025: 2.5% quantile of the posterior distribution of information component (estimated FDR); NA: not available (no events for this pair); PRR: proportional reporting ratio (observed relative risks, estimated FDR); ROR: observed odds ratios (estimated FDR)

3.2 Findings regarding over-the-counter (OTC) drugs

Considering the specific type of drug investigated, from the datasets analysed, the following results were obtained:

3.2.1 Study 7: Loperamide

Studying the loperamide-related EV dataset, out of a total number of 7,895 suspect ADRs, the misuse/abuse/dependence/withdrawal ADRs were 1,983 (25.1%; relating to 434 unique subjects), with 'drug use disorder' (37.4%), 'intentional overdose' (25.3%), and 'intentional product misuse' (14.9%) being the most represented ADRs. The number of ADRs remained flat until 2014, and then rose in 2015 (853 ADRs), 2016 (931 ADRs) and 2017 (3,867 ADRs until August 2017). Most ADRs involved adult females (female/male ratio: 1.29) and were reported by pharmaceutical companies (67.8%) which were typically located in non-EEA countries (64.1%), and especially in North America (Table 17). The abuse of loperamide high dosages (up to 800mg/day, where the maximum daily dose should not exceed 12 mg) was detected; loperamide was reported as having been ingested in the 2-800mg range as the sole drug in 182/434 (41.9%) cases; of them, some 48 cases recorded a loperamide dosage beyond 16mg (Table 18). Most frequently mentioned compounds in polydrug cases included antidepressants, benzodiazepines, and opioids. However, a range of medications known to increase loperamide effects was here reported as well and included: dextromethorphan (25 cases), diphenhydramine (20 cases), cimetidine (13 cases), quinidine-quinine (5 cases), and omeprazole (3 cases). Cardiotoxicity issues (Table 18) related to loperamide abuse were retrieved and analysed, conduction abnormalities or electrocardiogram (ECG) alterations ADRs, e.g., 'tachycardia', 'ventricular tachycardia', 'torsade de pointes', and 'increased QTc levels' being more frequently reported. Data available online from other pharmacovigilance datasets, such as the YCS and FAERS, have been considered as well, in order to have a broader view of the phenomenon[92]. Results of our studies are summarised in Tables 17 and 18.

Table 17. Overview of loperamide misuse-abuse-/dependence-/withdrawal-related Adverse Drug Reactions (ADRs) as reported to the EudraVigilance (EV) database

	LOPERAMIDE ADRs
TIME-FRAME CONSIDERED	08/2005–08/2017
TOTAL NUMBER OF 'SUSPECT' ADRs	7,895
MISUSE-ABUSE-/DEPENDENCE-/WITHDRAWAL-RELATED ADRs	**1,983 (1,983/7,895= 25.1%)**
NUMBER OF UNIQUE PATIENTS REPORTED TO THE DATABASE	434
AGE-RANGE MOST TYPICALLY REPRESENTED	18-64 yy (4,577/ 7,895= 57.9%)
ADRs MOST TYPICALLY REPRESENTED	Drug use disorder 742 (742/1,983=37.4%), Intentional overdose 502 (502/1,983=25.3%), Intentional product misuse 296 (296/1,983=14.9%)
GENDER MOST TYPICALLY REPRESENTED	Female (F/M ratio:4,401/3,397=1.29)
LOPERAMIDE IDENTIFIED AS THE SOLE DRUG	182 cases (182/434=41.9%)
CONCOMITANT DRUGS MOST TYPICALLY REPRESENTED IN THE REMAINING (434-182 = 252) CASES	Antidepressants in 44 cases (44/252= 17.5%); Benzodiazepines in 40 cases (40/252=15.9%); Opioids in 23 cases (23/252=9.13%); Other psychotropic drugs in 21 cases (21/252=8.3%); Antipsychotics in 11 cases (11/252=4.4%); Mood stabilizers in 9 cases (9/252=3.6%)
RESULTED IN DEATH	305/1,983 (15.34%, corresponding to 94/434 cases: 21.6%)
SUICIDES	373 ADRs, corresponding to 42/434 cases; 9.7%

Table 18. Overview of data relating to loperamide cardiovascular Adverse Drug Reactions (ADRs)

LOPERAMIDE Suspect CV ADRs: 1,085/7,895: 13.7% (160/434: 36.9% unique cases)		**N OF REACTIONS/ADRs**
CONDUCTION ABNORMALITIES		**494** (494/1,085= 45.5%)
-Tachycardia	123	
-Ventricular Tachycardia	106	
-Torsades de Pointes	64	
-Arrhythmia	44	
-Conduction Disorder	34	
-Bradycardia	36	
- Ventricular Arrythmia	23	
-Ventricular Fibrillation	16	
-AV block II Degree	15	
-Brugada Syndrome	7	
-AV block	6	
-HR Decreased	5	
-AV block I Degree	3	
-Sinus Bradycardia	3	
-Defect Conduction Intraventricular	3	
-HR increased	3	
-HR Irregular	2	
-Sinus Arrhythmia	1	
ECG ALTERATIONS		**322** (322/1,085= 29.7%)
-ECG QT Prolonged	216	
-ECG QRS Prolonged	72	
-Long QT Syndrome	10	
-ECG abnormal	6	
-ECG QRS Shortened	6	
-ECG PR Shortened	5	
-QRS Axis Abnormal	2	
-ECG P Abnormal	1	
-ECG PR Prolongation	1	
-ECG QT Abnormal	1	
-ECG QRS Abnormal	1	
-ECG ST-T change	1	
LOSS OF CONSCIOUSNESS	36	**97** (97/1,085= 8.9%)
SYNCOPE	51	
DYASTOLIC HYPOTENSION	10	
CARDIAC ARREST/CARDIORESPIRATORY ARREST/ SINUS ARREST		**77** (77/1,085= 7.1%)
HYPOKALAEMIA		**76** (76/1,085=7%)
CARDIOTOXICITY		**11** (11/1,085= 1%).
No of CV ADRs according to loperamide dosages	0-100mg 122 ADRs 101- 200mg 80 ADRs 201- 400mg 57 ADRs 401-800mg 20 ADRs	
FATALITIES AMONG CV CASES (15/160 cases= 9.4%)		
Loperamide reported alone		12 cases out of 15; 80.0%
Cause of death:		
Cardiac arrest/Cardiorespiratory arrest	10 cases	
Arrythmias and cardiotoxicity	3 cases	
Long QT syndrome	1 case	
Ventricular tachycardia	1 case	

Abbreviations: ADR: Adverse Drug Reaction; AV; atrioventricular; CV: cardiovascular; ECG: electrocardiogram; HR: heart rate.

3.2.2 Study 8: Promethazine

Similarly, among OTCs, in consideration of the popular *purple drank* phenomenon[93], consisting in the abuse of promethazine mixed with opioids and other sedatives (e.g., alcohol) in a purple colour drink[2,94,95] for its euphoric effects, promethazine data regarding its misuse, abuse, and dependence as recorded in fifteen years (2003-2018) to the EMA were analysed (Table 19)[96]. From a total of 1,543 individual cases, some 557 abuse/misuse/dependence-related cases were reported (1,543/557: 36.0%), the most represented ADRs being ‘drug abuse’ (300/557: 53.8%) and ‘intentional product misuse’ (117/557: 21.0%), showing increasing levels over time.

Table 19. Analysis of promethazine abuse/misuse/dependence/withdrawal cases recorded by the EudraVigilance (EV), 2003-2019

	Individual cases (% of total within parentheses)
TOTAL ABUSE/MISUSE/DEPENDENCE CASES	1,543 single cases; Number of ADRs:11,796
AGE RANGE **Adult (**19-64yrs, mean age: 31.8yrs, SD 26.55-37.05) **Adolescent (**10-18yrs, mean age, 15.9yrs, SD 14.3-17.77) **Elderly** (> 65yrs, mean age, 72.3yrs, SD 70.85-73.7) **Neonatal** (hours-days, mean age, 24hh, SD 16.6-27.4) **Infant** (months-1yr, mean age, 10months, SD 7-13) **Child** (< 10yrs, mean age 5yrs, SD 3.6-6.3)	 648 (42.0%) 23 (1.5%) 25 (1.6%) 14 (0.9%) 7 (0.5%) 4 (0.4%)
MALE/FEMALE	235/461: 0.51
MOST REPRESENTED ABUSE/MISUSE/DEPENDENCE-RELATED ADRS ACCORDING TO THE PTS:	557 (557/1,543: 36.1%)
ABUSE-RELATED ADRs	458(458/557: 82.2%)
Drug abuse	300
Drug abuser	15
Drug diversion	1
Intentional product misuse	117
Intentional product use issue	9
Substance abuse	11
Substance abuser	3
Substance use	2
DEPENDENCE-RELATED ADRs	44 (44/557: 7.9%)
Dependence	4
Drug dependence	39
Substance dependence	1
WITHDRAWAL-RELATED ADRs	55 (55/557: 9.8%)
Withdrawal syndrome	19
Drug withdrawal convulsions	1
Drug withdrawal neonatal syndrome	18
Drug withdrawal syndrome	17
OUTCOME	Fatal 310 (310/557: 55.6%) Unknown 161 (161/557: 28.9%) Recovered/Resolved 55 (55/557: 9.9%) Recovering/Resolving 18 (18/557: 3.3%) Not recovered/Not resolved 13 (13/557: 2.3%)
PROMETHAZINE-CASES ALONE	74 (with maximum dosage 2,500mg)
PROMETHAZINE-CASES WITH OTHER DRUGS	Most cases (122) were over 100mg (max 8,000mg)
MOST COMMON *PSYCHOACTIVE SUBSTANCES* USED	Alcohol: 114 Cocaine: 68 Cannabis: 16 Ketamine: 4 Amphetamine: 1
MOST COMMON *PRESCRIPTION DRUGS* USED	Opioids: 1,187 Benzodiazepines: 914 Antidepressants: 871 Antipsychotics: 437 Z-drugs: 222 Mood Stabilisers: 197

Abbreviations: ADR: Adverse Drug Reaction; PT: preferred terms

A high number of fatalities were reported (310/557: 55.6%), mostly recorded as 'drug toxicity/drug abuse' cases, opioids being the most concomitant drug reported together with promethazine (Table 20).

Table 20. Analysis of fatal promethazine abuse/misuse/dependence/withdrawal cases recorded by the EudraVigilance (EV), 2003-2019

FATAL CASES ON ABUSE/MISUSE/DEPENDENCE/WITHDRAWAL REACTIONS	**310** (310/557= 55.6%)
AGE-RANGE	
Adult	303 (97.7%)
Adolescent	7 (2.3%)
Elderly (> 65yrs)	-
Child/Neonatal/Infant	-
Gender	M 103 (33.2%) F 177 (57.1%) Unknown 30 (9.7%)
MOST RECORDED PTs	
Drug abuse/Drug abuser/Substance abuse	228/3/6
Intentional product misuse/Intentional product use issue	77/3
Drug dependence	1
REPORTED DEATH CODE	
Drug toxicity/Drug abuse	197
Toxicity to various agents	48
Intentional product misuse	41
Cardiac arrest	10
Completed suicide/Suicide	7
Intentional overdose/Overdose	5
Respiratory depression	5
MOST REPORTED CONCOMITANT DRUGS	
OPIOIDS	**356**
Methadone	103
Oxycodone	63
Morphine	55
Fentanyl	44
Hydrocodone	33
Codeine	32
Tramadol	22
Hydromorphone	3
Dihydocodeine	1
ANTIDEPRESSANTS	**221**
Citalopram	41
Amitriptyline	**35**
Paroxetine	34
Mirtazapine	33
Fluoxetine	24
Sertraline	16
Venlafaxine	15
Trazodone	9
Nortriptyline	6
Clomipramine	5
Duloxetine	1
Escitalopram	1
Bupropion	1
BENZODIAZEPINES	**141**
Diazepam	60
Alprazolam	42
Clonazepam	21
Temazepam	6
Midazolam	4
Oxazepam	3
Lorazepam	3
MOOD STABILISERS	**11**
Topiramate	8
Gabapentin	3
ANTIPSYCHOTICS	**24**
Quetiapine	20
Haloperidol	1
Amisulpride	1
Levomepromazine	1
Olanzapine	1
Z-DRUGS	**39**
ILLICIT DRUGS	
Heroin	52
Cocaine	40
Amphetamine	15
ALCOHOL	26

Abbreviations: F: female; M: male; PT: preferred terms.

3.2.3 Study 9: Benzydamine

A further study on OTCs, included the anti-inflammatory benzydamine, reportedly being diverted and recreationally used. It investigated the misuse of benzydamine, illustrating its psychotropic molecular mechanism, and studying its psychopathological effects, both through a systematic review of the literature concerning the abuse of benzydamine and analysing benzydamine-related data from the EV database recorded during years 2005-2020. The study has already been published, so we will summarise the most important results here (please refer to the paper for further details on the methodology and results). A systematic electronic search was completed in May 2020 and was set without a time-frame on the following scientific search engines: PubMed, Scopus, and Web of Science. Eleven articles, published during 1997-2019, were included in our systematic review, including five case reports; four surveys, one conducted in Poland among pharmacists and three in Brazil among users; and two retrospective case series analyses. While nine articles dealt with a recreational use of BZY, two described an oral overdose of the drug, and all involved male subjects with a mean age of 18±6.1 years, and recorded both physical and mental side-effects, the latter including visual and somatic hallucinations, in the form of terrifying images of aliens, symmetrical geometric forms, animals and worms crawling on the skin. When specified, dosages of BZY consumed ranged from 500 to 1,500mg. Interestingly, in one case the BZY intoxication led to a chronic psychosis and loss of thought association. These symptoms began immediately after taking the substance for the first time and worsened in the following three months during which the subject reported the BZY consumption to have occurred on some 3-4 occasions; the symptoms decreased after a 3 month-period free from BZY. Beside psychiatric symptoms, physical symptoms included slowed speech; hyperreactivity and muscle weakness. In terms of treatment/management, in most cases the symptoms resolved spontaneously, whilst in one case olanzapine 10mg/day prescribing was associated with a partial improvement of the psychotic features. Differently from the case reports, one retrospective case series included a high number (n = 724) of cases of BZY oral intoxication recorded from 1991 to 2003, mostly involving females (73.4%) older than 14 years (86.2%). Interestingly, in 94.3% of cases the

intoxication occurred at home, with the mean amount of BZY ingested having been 500 mg (range: 10mg – 1,500mg); and the mean time of exposure before calling a clinician of 30 minutes (range: 5 minutes-24 hours). Nearly one-third (31.6%) reported a range of side-effects, including visual or auditory hallucinations (e.g., seeing animals and parasites, coloured lights, and cartoon characters) in 15% of cases. Remaining psychiatric symptoms included agitation, dizziness, drowsiness, and tiredness. Non-psychiatric symptoms were mainly gastrointestinal (48%).

With regard to the EV dataset analysed, it included three cases of benzydamine abuse, consumed in a range from 500 to 1,250mg (Table 21; maximum daily dosage 300mg). Among them, one was recorded as an 'accidental overdose' in a 4-years-old child, while the remanent cases were recorded as 'drug abuse' cases. Interestingly, all cases showed psychotic symptoms, dysphoria, and hallucinations and, after treatments, recovered [97].

Table 21. Description of benzydamine abuse/misuse cases reported to the European Medicines Agency (EMA) dataset

ID	YEAR	AGE	GENDER	Needs heading	PT	DOSAGE	COUNTRY	ROUTE OF ADMINISTRATION	REACTIONS ASSOCIATED	CONCOMITANT DRUGS	OUTCOME	REPORTER
12291259	N/A	4	M	Suspect	Product use for unknown indication; Accidental overdose	500mg	Portugal	N/A	-Psychomotor hyperactivity -Agitation -Visual hallucinations -Tremor -Ataxia -Asphyxia	No other licit/illicit drugs	Recovered/resolved	Physician
12724804	2014	24	F	Suspect	Drug abuse	500mg	Italy	Oral	-Medical history of polydrug abuse -Dysphoria -Hallucinations -Weakness -Memory deficit after recent recreational drug consumption	No other licit/illicit drugs	Recovered/resolved	Consumer or other Non-Health Professional
10000561825	N/A	16	M	Suspect	Intentional drug misuse; Drug abuse	1250mg	Romania	Oral	Hallucination	N/A	Recovered/resolved	Consumer or other Non-Health Professional

Abbreviations: F: female; M: male; N/A: not available; PT: Preferred Terms.

Findings from the whole study with regards to all prescription and OTC drugs are summarised in Table 22.

Table 22. Findings from the EMA Adverse Drug Reactions (ADRs) and the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) datasets related to the abuse/misuse/dependence and withdrawal of certain prescription/over-the-counter (OTC) drugs

SUBSTANCE	EXAMPLES	ALONE	COMBINATION	DOSE	ROUTE OF ADMINISTRATION	EFFECTS	MOST RECORDED ADRs	COMPARISON
GABAPENTINOIDS	**Pregabalin versus gabapentin**	☑	Both were recorded in combination with cannabis, alcohol, amphetamines, ketamine, opioids, and other prescribed drugs (e.g., antidepressants and benzodiazepines)	Between 1,000–4,800mg for gabapentin and 750–12,000mg for pregabalin	Mostly oral, but also idiosyncratic routes were recorded, such as nasal and injecting ones	Well-being/relaxation, euphoria, and even hallucinations; their withdrawal syndrome may include agitation/ anxiety, craving, sweating, insomnia, fatigue, palpitations, tremors, and diarrhoea	Intentional product misuse, drug abuse, and drug dependence. Fatalities were also reported	Pregabalin compared with gabapentin emerged as more prone to determine abuse, misuse and dependence issues (being PRR values 1.25, 1.39, and 1.58, respectively)
ANTIDEPRESSANTS	**Bupropion versus venlafaxine**	☑	Cannabis; opiates/opioids; alcohol; nicotine; caffeine; cocaine; benzodiazepines; and antidepressants	Up to 3,000 mg/day for bupropion and up to 6,300mg for venlafaxine	Mostly oral, but also idiosyncratic routes were recorded, such as nasal and injecting ones	'Amphetamine-like high' for bupropion, with adverse effects including nasal pain, irritability, agitation, cardiac toxicity, hallucinations, seizures, delusions, and tremor. Venlafaxine large quantities intake ("baby ecstasy") and its withdrawal syndrome have been reported	Misuse-/abuse-/dependence- and withdrawal- related ADRs. Fatalities reported	Bupropion resulted to be more frequently misused/abused (PRR = 1.50), but less frequently associated with both dependence (PRR = 0.92) and withdrawal (PRR = 0.77) issues in comparison with venlafaxine

ANTIDEPRESSANTS	**Fluoxetine, paroxetine, citalopram, escitalopram, sertraline**	☑	Cocaine and alcohol were the most recorded recreational drugs in combination with antidepressants. Most described concomitant prescription drugs were opioid and benzodiazepines	EMA: for all drugs, most instances (e.g., ranging from 61.9 to 82.2% of cases, depending on the index molecule) reported both an oral ROA and a median dose reflecting the recommended dosage range. Very high dosages and/or via unusual ROA, such as nasal were recorded. FAERS: N/A	See before	Many cases of abuse and diversion recorded involved fluoxetine, ingested for either appetite suppression/weight loss or for stimulant-like effects (e.g., euphoric mood) in patients, especially with a substance use history. Similarly, with sertraline a recreational high has been reported. Conversely, high levels of paroxetine-related dependence/withdrawal issues have been described. A number of symptoms may resemble the primary disease (e.g., depression/anxiety/agitation/irritability), whereas others can be clearly differentiated from the disorder, with most common symptoms including: flu-like symptoms; disturbed sleep and vivid dreams/nightmares; nausea; sensory disturbances, e.g., electric shock-like sensations and dysesthesia	Misuse-/abuse-/dependence- and withdrawal- related ADRs (Drug abuse, Substance abuse, Intentional product misuse, Dependence, Drug dependence, Drug withdrawal syndrome, Withdrawal, Withdrawal syndrome). Fatalities reported	Comparing SSRIs, the EV misuse/abuse-related ADRs were mostly recorded for citalopram, fluoxetine, and sertraline; conversely, dependence was mostly associated to paroxetine, and withdrawal to escitalopram. Considering FAERS, citalopram and fluoxetine were the most mentioned for drug abuse; conversely, dependence/withdrawal were more frequently reported for paroxetine

ANTIPSYCHOTICS	**Quetiapine versus olanzapine**	☑	Cannabis; cocaine, opioids, alcohol, antidepressants, and benzodiazepines	> 800mg/day for quetiapine (being 19,000mg the highest level reported) and up to 20 mg/day for olanzapine (with 11,000mg the highest level reported)	Mostly oral, but also idiosyncratic routes were recorded, such as nasal and injecting ones	Quetiapine as "Susie Q," "Quell," and "baby heroin for its relaxing and anxiolytic effects. Olanzapine as the "ideal trip terminator/modulator" after a psychedelic drug binge to treat unwanted "comedown" symptoms (depression, dysphoria, anxiety, and insomnia) from drug/alcohol intake	Dependence, drug abuse/ dependence/ withdrawal syndrome, intentional product misuse, substance abuse, substance dependence, and withdrawal syndrome. Fatalities have been also reported	Quetiapine has been more frequently associated with abuse/misuse-, dependence- and withdrawal issues compared with olanzapine (PRR values were 1.07, 1.01, 5.25 respectively)
ANTIPSYCHOTICS	**Clozapine**	☑	Reported alone in 387/559 (69.2% of cases; remaining drugs included: first/second generation antipsychotics; benzodiazepines; antidepressants; and mood stabilisers. Illicit drugs most typically reported were opioids, amphetamines, cannabis, and alcohol	Dosages varied from 12.5mg/day to high/unlicensed levels (i.e., 2,800–5,600mg/day. In 7 cases reported very high (e.g., >1,000mg) levels, typically described as 'intentional self-injury', 'completed suicide', and 'drug abuse')	Oral cases (533/559: 95.3%)	The recreational use of clozapine has not been noted in the literature. Conversely, clozapine withdrawal is a phenomenon which has already been described, even at therapeutic dosages	Dependence/withdrawal/abuse-related ADRs were recoded. Fatalities also reported; suicidal issues identified: completed suicide; intentional self-injury; suicidal behaviour; suicidal ideation; suicide attempt; self-injurious ideation	N/A
Z-DRUGS	**Zaleplon, zolpidem, zopiclone**	☑	Alcohol; cannabis, amphetamines; and other prescription drugs (antidepressants; opioids; and benzodiazepines).	Zaleplon: N/A. Zolpidem: > 20mg in 7,371/23,420 ADRs (in 6,234/7,371: 84.6%, dosage was >100mg; and in 20/7,371: 0.3% it was of 2,000mg). Zopiclone: levels >15mg were	Mostly oral. Nasal and Intravenous intake modalities were also recorded	Problematic use of hypnotic drugs have been described among a first population including male and young recreational users of high-dose drugs, often abused together with other	Dependence, drug abuser, drug diversion, drug use disorder, drug withdrawal convulsions, drug withdrawal headache, drug withdrawal syndrome, intentional	Considering PRR values, in comparison with Zopiclone, Zolpidem was more frequently involved in both misuse/abuse and withdrawal issues. Zolpidem and Zopiclone presented

				described in 577/9,283 ADRs, including 205 ADRs where the dosage was in the 450-2,250mg range		licit/illicit drugs with unusual routes of administration (intranasal/intravenous); while a second abusing population is formed by long-term users, including patients with comorbidity of mood/neurotic disorders and with substance use disorders or elderly who started using Z-drugs hypnotics for treating insomnia and then tried unsuccessfully to cut down dosages needing to manage withdrawal symptoms	overdose, intentional product misuse, intentional product use issue, overdose, prescription drug use without prescription, product use in unapproved indication, product use issue, substance use disorder, substance abuser, and withdrawal syndrome. Fatalities also reported	with the same dependence risk, but Zopiclone was the most involved in overdose ADRs. When compared with Zaleplon, Zopiclone presented higher dependence and overdose-related issues, but slightly lower misuse/abuse and withdrawal PRR values
OPIOIDS	**Fentanyl**	☑	EMA data: Fentanyl sole drug: 307/559 = 54.9% cases. Concomitant drugs reported: other opioids (69.0%), cocaine (9.5%), benzodiazepines (6.8%), cannabis (5.6%), and alcohol (5.2%); MHRA: N/A; FAERS: N/A	EMA: max dosage up to 800mcg 2–3 times/day orally; up to 11.56mg/ Transdermally; MHRA: N/A; FAERS: N/A	EMA: oral (41/559 = 7.3%), transdermal (33/559 = 5.9%), but also a range of idiosyncratic ways of administration/high dosage intake were described, e.g.,: 23 cases of transdermal patch ingestion, 10 cases of fentanyl inhalation, and 10 cases of intravenous intake; MHRA: N/A; FAERS: N/A	Apart from the analgesic characteristics, the fentanyls as a group produce drowsiness, relaxation and euphoria, the latter being less pronounced than with heroin and morphine. Side effects include nausea, dizziness, vomiting, fatigue, headache, constipation. A range of severe toxicity effects, including muscle rigidity, seizures, overdoses, and death due to	Dependence, drug abuse, drug abuser, drug dependence, drug diversion, drug withdrawal syndrome, intentional product misuse, intentional product use issue, intentional overdose, overdose, substance use, substance abuse, and withdrawal syndrome. Fatalities also reported	N/A

						respiratory arrest have been reported as well. Tolerance and dependence develop rapidly after repeated use. Recreational fentanyl consumption seems to be often associated with the use of other drugs, such as heroin, other opiate/opioid medicines, alcohol, cocaine, benzodiazepines, psychostimulants, and antidepressants		
IMAGE AND PERFORMANCE-ENHANCING DRUGS (IPEDS)	**Salbutamol versus clenbuterol**	☑	Anabolic steroids, antipsychotics, and analgesic drugs; antidepressants	N/A	Mostly oral, but also idiosyncratic routes were recorded, such as nasal and injecting ones	Beta2 properties, with athletic performance-enhancing and muscle-building activities. Clenbuterol is widely available from the web as 'the size zero pill', for slimming. Conversely, there are only a few anecdotal reports relating to salbutamol misuse. Overall, adverse effects of b-2 agonists, especially occurring in cases of overdosage and chronic use include tremor, tension, restlessness, anxiety/agitation, tachycardia, atrial	Dependence, drug abuse, drug dependence, drug withdrawal syndrome, intentional product misuse, substance abuse, substance dependence, and withdrawal syndrome overdose, accidental overdose, intentional overdose, and off-label use. Fatalities have been reported more with salbutamol than with clenbuterol (34 versus 3)	Specifically, the PRR value for drug misuse/abuse ADRs was higher for clenbuterol than salbutamol (PRR = 18.38); conversely, both overdose and off-label use ADRs were more frequently represented in salbutamol, as opposed to clenbuterol

						fibrillation and myocardial ischaemia, hypokalaemia, hyperglycaemia		
OPIOIDS	**Fentanyl, tramadol, codeine, dihydrocodeine, oxycodone and pentazocine**	☑	Benzodiazepines, antidepressants, other opioids, and antihistamines, and recreational drugs such as cocaine and alcohol, and several new psychoactive substances, including mitragynine and cathinones, were the most recorded concomitant drugs reported in both datasets	The oral ROA was the most recorded, with the exception of fentanyl, most recorded as trans dermally used, and of pentazocine intravenously used. Idiosyncratic ROA, e.g., nasal, have been recorded	EMA: dosages were normally in range, but supratherapeutic doses have been recorded. FAERS: N/A	Finally, regarding other preferred terms (PTs) recorded, in both datasets, compared with the other opioids, oxycodone has been associated with aggression and euphoric mood; and tramadol has been associated with visual and auditory hallucinations, psychotic disorder, and substance-induced-psychotic disorder.	Misuse-/abuse-/dependence- and withdrawal- related ADRs (Drug abuse, Substance abuse, Intentional product misuse, Dependence, Drug dependence, Drug withdrawal syndrome, Withdrawal, Withdrawal syndrome). Fatalities reported	Compared with other opioids, abuse issues (e.g., drug abuse, drug abuser, intentional product misuse, and substance abuse) were mostly recorded in relation to fentanyl and oxycodone, while tramadol and oxycodone had significantly greater odds of drug dependence/withdrawal. Finally, signals for intentional overdose/overdose were more registered in relation with tramadol
OVER-THE-COUNTER (OTC) DRUGS	**Loperamide**	☑	P-gp substrates (e.g., quetiapine, cetirizine, oxycodone) or inhibitors (e.g., fluoxetine, citalopram, sertraline, omeprazole, quinine, quinidine, propranolol, ritonavir). CYP3A4 inhibitors (e.g., itraconazole, grapefruit juice, omeprazole, tonic water and cimetidine) or CYP2C8 inhibitors	Up to 800mg/day	Oral	Euphoria. Its diversion potential may be associated with its use as a relief from opioid withdrawal (the 'poor's' methadone') as well	Dependence, abuse and withdrawal-related ADRs. Cardiotoxicity issues, such as QTc prolongation and 'torsade de pointes', QRS prolongation, ventricular dysrhythmias, syncope, and cardiac arrest. Fatalities have been reported	N/A

			(e.g., gemfibrozil) can increase loperamide plasma levels					
OVER-THE-COUNTER (OTC) DRUGS	**Promethazine**	☑	Reported alone in 74/557 (13.2%) cases. Concomitant drugs recorded were opioids (e.g., oxycodone and fentanyl), benzodiazepines (e.g., diazepam, lorazepam and alprazolam), and antidepressants (e.g., citalopram, venlafaxine and amitriptyline). Other most represented drugs were alcohol and cocaine	Most cases were associated with 100-500mg promethazine dose, the maximum dosage recorded being 8,000mg	The most common ROA was oral (n= 292/557), even though intramuscular and parenteral ones have been reported in a few cases	Calming and sedating effect, enhancement of co-ingested substances or for recreational use leading to hallucinogenic experiences, possibly related to interaction of antihistamine with receptors other than histamine receptor (e.g., the antagonised binding to GABA, opiate, and muscarinic receptor). Promethazine might be abused mixed with a soft drink and candy with some variants including alcohol ("purple drank") for achieving euphoric effects in the young population	Dependence, drug abuse, drug abuser, drug dependence, drug withdrawal convulsions, drug withdrawal syndrome, drug withdrawal neonatal syndrome, intentional product misuse, intentional product use issue, substance abuse, substance abuser, substance use, and withdrawal syndrome. Fatalities also reported	N/A
OVER-THE-COUNTER (OTC) DRUGS	**Benzydamine**	☑	Not recorded	500-1,250mg	Oral	Psychomotor agitation, dysphoria, hallucinations, tremor, ataxia	Product used with unknown indication; drug abuse; accidental overdose; intentional product misuse	N/A

Abbreviations: ADR: Adverse Drug Reaction; EMA: European Medicines Agency; FAERS: FDA Adverse Event Reporting System (FAERS); GABA: Gamma-AminoButyric Acid; MHRA: Medicines and Healthcare products Regulatory Agency; PRR: Proportional Reporting Ratio; ROA: route of administration

3.3 Other studies

3.3.1 Study 10: Ketamine-induced uropathy recorded by pharmacovigilance datasets

Since ketamine prescribing is being increasingly considered for a range of medical and psychopathological conditions, to assess medicinal ketamine-induced uropathy (KIU) issues, we aimed at analysing both the 2005–2017 EMA and the 2006–2018 UK YCS pharmacovigilance databases. A total number (e.g., all categories) of 11,632 EMA ketamine-related ADR reports were here identified. Out of these, some 9,971 ADRs (i.e., 85.7% of the total) were judged as 'suspect' and were analysed. Some 1,758 ADRs (17.7% of the 9,971, corresponding to 194 individual patients) referred to urological issues, relating to either kidney/ureter (922 ADRs) or bladder/urethra (837 ADRs)[98]. Ketamine was the sole drug administered in 156/194 (80.4%) cases/patients. Although most cases occurred in the 1–12-month timeframe following the start of ketamine prescribing, in 30 cases the ADR occurred within 48 hours. Most cases resolved, although both sequelae (18 cases) and fatalities (79/1,758; 4.5%) were recorded (Tables 23-24).

Table 23. Overview of general data relating to the 'Renal and urinary disorders' Adverse Drug Reaction (ADRs) recorded by the European Medicines Agency (EMA)

Total suspect ADRs (2006- Apr 2017)	**1,758**	%
Occurrence country		
EEA	**906**	**51.5%**
Non-EEA	812	41.8%
Not specified	40	2.3%
Reporter qualification		
Physician	**908**	**51.7 %**
Other health professional	735	41.8%
Consumer or other non-health professional	23	1.3%
Not specified	92	5.2%
Reporter country		
EEA	**944**	**53.7%**
Non-EEA	720	41.0%
Not Specified	94	5.3%
Sender		
Pharmaceutical company	864	49.1%
Regulatory authority	**884**	**50.3%**
Not specified	10	0.6%
Age		
1-8 years	3	0.2%
9-18 years	85	4.8%
>18-64 years	**886**	**50.4%**
>64 years	10	0.6 %
Unknown	774	44.0 %
Gender		
Female	**1157**	**65.8%**
Male	561	31.9%
Not specified	40	2.3%

Abbreviations: ADR: adverse drug reaction; EEA: European Economic Area

Table 24. Characteristics of the most frequently reported 'Renal and urinary disorders' suspect Adverse Drug Reaction (ADRs) recorded by the European Medicines Agency (EMA)

ADRs according to the PT		Total 1,758	%
UPPER URINARY TRACT		TOTAL 922	52.5
	Acute kidney injury/renal impairment/failure	**487**	**27.7%**
	Oliguria/anuria	**277**	**15.8%**
	Hydronephrosis	82	4.7%
	Chronic kidney disease	40	2.3%
	Renal tubular necrosis	21	1.2%
	Proteinuria	9	0.5%
	Renal infarction	1	0.1%
	Hydroureter	4	0.2%
	Urethritis	1	0.1%
	Vesical-ureteral reflux	2	0.1%
LOWER URINARY TRACT		TOTAL 836	47.6%
	Irritative LUTS: pollakiuria/dysuria/polyuria/nicturia/urge incontinence	**296**	**16.8%**
	Haematuria; haemorrhagic cystitis	**249**	**14.2%**
	Suprapubic/bladder pain	145	8.3%
	Hypertonic/contracted bladder; cystitis	139	7.9%
	Sterile pyuria	4	0.2%
	Urethritis	1	0.1%
Routes of administration (where indicated):			
	Unknown	621	
	IV	**93**	
	Respiratory/nasal	**51**	
	Oral	10	
	Intrathecal	5	
	Subcutaneous	1	
Outcome of the ADR (where indicated)			
	Unknown	809	
	Recovering/recovered	**916**	
	Not recovered/not resolved	15	
	Recovered/resolved with sequelae	18	
Action taken after ADR occurrence (when indicated)			
	Not specified	464	
	Drug reduced/withdrawn	**278**	
	Dose not changed	35	
Time interval between start of ketamine administration and occurrence of the index ADR (when indicated)			
	1-31 days	32	
	1 month-1 year	**58**	
	>1 year	10	
Duration of the ADR (when indicated):			
	2-7 days	25	
	14-45 days	12	
Dosages (where indicated):			
	1-25 mg	27	
	26 mg- 1 gr	19	
	>1 gr	**70**	
Possible concomitant drugs (where indicated according to a total of 1,758 ADRs corresponding to 198 cases)			
	Ketamine only	**156**	
	Other, non-psychotropic, drugs	16	
	Gabapentin	9	
	Opiates/Opioids (oxycodone, codeine, hydrocodone, fentanyl, morphine, methadone)	7	
	Benzodiazepines	3	
	Antidepressants (escitalopram, duloxetine)	2	
	Cocaine	1	
	Cannabis	1	
	Alcohol	1	

Abbreviation: ADR: adverse drug reaction

Overall, YCS data were consistent with EMA findings, with some 50/217 (23.0%) ADRs referring to renal/urinary disorders. As current data may represent a gross underestimate of the KIU real prevalence issues, it was then hypothesised that chronic treatment involving higher doses/repeated exposure to ketamine be restricted to the context of controlled trials or clinical audits. The typical abusing ketamine-related urological literature focuses on the lower urinary tract, for example, on the “K bladder” phenomenon. However, present findings from the EV (52.0% of ADRs related to kidney/ureter) and the YCS (the involvement of the upper urinary tract was reported in 18/50: 36.0%) are consistent with the possibility that upper urinary tract ketamine-related issues may be fairly common. Moreover, although the duration of ketamine medicinal use prior to the occurrence of KIU was reported for some 52.0% of patients only, consistent with previous literature focusing on ketamine misusers most ADRs were observed after a chronic (i.e., 1 – 12 months) administration. Conversely, some 30 patients experienced the urological disturbance within the first 2 days of treatment, which may tentatively suggest that even an acute ketamine administration may be associated with levels of urological risks.

3.3.2 Study 11: A systematic review on diversion and abuse of antihistamines, cough medicines, and decongestants over-the-counter (OTC) drugs

In May 2021 a systematic literature review was carried out in order to examine the published clinical data on OTC misuse, focusing on several antihistamines (e.g., diphenhydramine, promethazine, chlorpheniramine, and dimenhydrinate), dextromethorphan, codeine-based cough medicines, and the nasal decongestant pseudoephedrine. The study has already been published, so we will summarise the most important findings here (please refer to the related paper [18] for further details on the methodology and results).

Some 92 articles were taken into consideration, including case reports, surveys, and retrospective case series analyses. OTC recreational intake appeared to be associated with high/very high dosages, e.g., up to 4,920mg for dextromethorphan, normal doses for adults

should not exceed 120mg per day; up to 5,000 for dimenhydrinate, the maximum dose being 400 mg within 24 hours; or 3,000–4,500mg of pseudoephedrine, the maximum daily dose being 240mg/day. In addition, idiosyncratic routes of administration (e.g., snorting; intramuscular; intravenous); and the concomitant ingestion of both licit (e.g., alcohol, prescription opioids, benzodiazepines, other OTCs) and illicit (e.g., cannabis, cocaine, ketamine, etc.) drugs were recorded. OTC drugs were obtained by various means, including family and friends, multiple doctor prescriptions (*doctor shopping*, illegal online pharmacies/shops, and theft/burglary from hospitals, residences, and pharmacies. Interestingly, dextromethorphan pills named “Snurf” were also reported to have been acquired online and in having been marketed as a ‘legal high’.

Overall, two main populations of misusers were identified: i) patients already suffering from a health condition and/or a psychiatric disorder who became dependent on OTC drugs due to prolonged/high-dosage use, e.g., dextromethorphan-based cough mixtures started for sinusitis/cough/ nasal congestion, and then continued for years at higher dosages. Other examples have included dimenhydrinate prescribed for emesis in pregnancy and then continued for 12 years at a higher dosage or diphenhydramine use initiated to assist with initial insomnia and then continued for 6 months up to 1,600mg daily, or pseudoephedrine self-administered to lose weight then causing addiction; ii) individuals, including substance abusers who may have started to misuse/abuse with OTC medications for recreational purposes. In the review, out of a total of n = 185 OTC misusers described in case reports/series surveys, male subjects were the most represented (F/M = 51/134), with a substance use disorder history having been recorded in 53 of them (53/185 = 28.6%). A range of psychiatric diagnoses were reported (45/185 misusers, 24.3%), including mood disorders (e.g., bipolar disorder, depression, dysthymia; n = 26), anxiety disorders (e.g., adjustment disorder, anxiety; n = 5), psychotic disorders (e.g., schizoaffective disorder, schizophrenia, psychosis, delusional disorder; n = 11), attention deficit and hyperactivity disorder (ADHD, n = 1), eating disorders (i.e., bulimia; n = 1), and personality disorders (i.e., dependent disorder; n = 1). Regarding the outcome, most cases recorded were associated with a full recovery after hospitalisation, with

treatment having been either supportive or symptomatic, with the latter consisting of benzodiazepines and antipsychotics. A full detoxification procedure was recorded in cases of dependence and withdrawal. Some cases required specific actions in the ED. OTC-related fatalities were here related to either cases characterised by unusually high dosages or to suicide/self-aggression.

According to the specific OTC recorded, most articles focused on dextromethorphan (n = 54), misused for its dose-dependent sedative, dissociative, and stimulant properties related to the antagonism on the N-methyl-D-aspartate (NMDA) receptors, and several other reasons, such as i) individual's CYP2D6 subtype; ii) body weight; iii) the concomitant use of other CYP2D6 substrates, including SSRIs; the antipsychotics clozapine, haloperidol, risperidone; β-blockers (e.g., atenolol, propranolol, etc.); antiarrhythmics; and opioid analgesics (e.g., codeine, tramadol, methadone, etc.), which may decrease the rate of dextromethorphan metabolism, resulting in a dextromethorphan intoxication; iv) synergistic effects related to other pharmaceutical agents such as chlorpheniramine, usually contained in dextromethorphan formulations, which might produce anticholinergic signs and symptoms.

The two second most recorded drugs, dimenhydrinate (n = 8) and its moiety diphenhydramine (n = 12) are widely used antihistamine molecules originally marketed for their anti-allergy properties and available as sleeping aids. Antihistamines' toxicity appears to be clinically related to both central and peripheral acetylcholine antagonism. In addition, both can acutely block the cell membrane pump mechanism of central 5-hydroxytryptophane and peripheral noradrenaline neurons, causing euphoria and stimulating effects, especially at high dosages and if taken together with other drugs (e.g., alcohol, cannabis, and stimulants). Conversely, promethazine abuse potential appeared related to its calming and sedating effect and enhancement of other co-ingested substances. It has been reported in substance use disorder clients being misused as a substitute for another drug or to increase the effects of inadequate dosing (i.e., to delay the onset of opioid withdrawal or to potentiate the sedating effect of benzodiazepines/Z-drugs). Interestingly, its overdose is associated with an antimuscarinic delirium, agitation, and neuroleptic malignant syndrome. Regarding the toxicity

of codeine, apart from the strictly pharmacological considerations made above, it worth considering idiosyncratic codeine administration procedures have been recorded, e.g., a misuser learned online how the codeine base might be extracted through a process called cold water extraction (CWE) prior to injection (Table 25).

Table 25. Drug classification and main characteristics of misuse of the selected OTC drugs

DRUG/ DRUG CLASSIFICATION	ADMINISTRATION PATH	MECHANISM OF ACTION	EFFECTS	DOES IT CAUSE DEPENDENCE?	STREET NAMES AND BRAND NAMES
Chlorpheniramine (antihistamine)	Oral	• Chlorpheniramine acts primarily as a potent H1 antihistamine drug • Moderate anticholinergic activity • Chlorpheniramine has been found to act as a serotonin reuptake inhibitor	• ACUTE EFFECTS: *psychiatric effects:* i) sedating and anxiolytic properties; ii) its abuse has been related to pleasurable feelings such as euphoria and stimulating effects; iii) it may be associated with psychotic symptoms in predisposed individuals (e.g., people with mental illnesses or individuals concomitantly abusing other drugs) • CHRONIC EFFECTS: dependence	• Drug dependence is recorded after long-term use • Withdrawal symptoms, including excessive irritability, anger outbursts, insomnia, sweating, and craving	'Triple c' refers to Coricidin® cough and cold tablets; the combination of codeine, methyl ephedrine chlorpheniramine, and caffeine is marketed as Bron®; Panadol® is a combination of chlorpheniramine, paracetamol and pseudoephedrine; Advil® includes ibuprofen, chlorpheniramine and phenylephrine; other brand names: Polaramine®, Chlortrimeton®
Codeine (opioid)	Oral, IV	• It is a selective agonist of the mu-opioid receptor; it is a natural isomer of methylated morphine, requiring metabolic activation by O-demethylation to morphine by CYP2D6	• ACUTE EFFECTS: *psychiatric effects:* euphoria, elation, analgesia, calmness; *physical effects:* respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, bradycardia and hypotension. The triad of coma, pinpoint pupils, and respiratory depression is strongly suggestive of opiate	• Codeine has an identified abuse liability potential, given its effect and development of tolerance within a short timeframe on regular or excessive use • Codeine-dependence was here recorded, and associated with daily use of codeine	Street names: 'Captain Cody', 'Cody', 'Little C', 'Schoolboy', 'Doors & Fours'. Common brand names for codeine and codeine containing combinations: Aspalgin® for aspirin and codeine; Nurofen Plus® for ibuprofen and codeine; Panadeine Forte® for paracetamol and codeine

			poisoning. In severe overdosage, death may occur • CHRONIC EFFECTS: dependence		
Dextromethorphan (DXM) (non-competitive NMDA receptor antagonist and sigma 1 agonist antitussive)	Oral; IV and IN use also recorded in misuse cases	• At high doses, acting as a NMDA receptor antagonist, DXM and its potent metabolite dextrorphan inhibit the excitatory amino acid and neurotransmitter glutamate, causing hallucinogenic and dissociative states • DXM also exhibits binding activity at serotonergic receptors	• Neurobehavioural effects begin within 30–60 minutes of ingestion and persist for approximately 6 hours • They are dose-related, starting from a mild to moderate stimulation with restlessness and euphoria (100-200 mg), to a state characterised by hallucinations, paranoia, perceptual distortions, delusional beliefs, ataxia, and out-of-body experiences (> 1000 mg) • ACUTE EFFECTS: i) *psychiatric effects*: euphoria, altered mental status, mania, irritability, dysphoria, insomnia; ii) *physical effects*: tachycardia, hypertension, vomiting, mydriasis, diaphoresis, nystagmus, dystonia, loss of motor coordination; • CHRONIC EFFECTS: i) toxic psychosis and cognitive deterioration; ii) folate deficiency and neuropathy; iii) since DXM is produced as the crystalline hydrobromide salt, bromism is a rare consequence that has been identified in heavy	• Although DXM is not thought to have addictive properties, its chronic use might determine addiction due to GABAergic/antiglutamatergic mechanisms, including substance-taking compulsive behaviours, tolerance, and autonomic withdrawal symptoms • EMCDDA: regarded as NPS	Street names: 'Bromage', 'Brome', 'Candy', 'Dex', 'Dextro', 'DM', 'Drex', 'DXM', 'Red Devils', 'Robo', 'Rojo', 'Skittles', 'Triple C', 'Tussin', 'Velvet', and 'Vitamin D', 'Poor Man's Ecstasy'; the practice of using large amounts of DXM to achieve psychoactive effects is known as 'robotrippin'. Common brand names are: Balminil DM®, Benylin DM®, Bronchophan®, Buckleys D®, Calylin #1, Delsym®, Koffex DM®, Novahistex DM®, Robitussin®

			chronic abusers of DXM (neurotoxic effects, resulting in somnolence, psychosis, seizures, and delirium		
Diphenhydramine (DPH) (antihistamine moiety of dimenhydrinate/DH)	Oral; IV and IN use also recorded in misuse cases	• It is a first generation H1-antihistamine • Diphenhydramine also acts as a potent anticholinergic agent • It can acutely block the cell membrane pump mechanism of central 5-hydroxytryptophane and peripheral noradrenaline neurons	• ACUTE EFFECTS: i) *psychiatric effects*: euphoria, altered mental status, hallucinations, and/or psychosis; ii) *physical effects*: tachycardia, xerostomia, mydriasis, blurred vision, ileus, urinary retention, CNS depression, agitation, and hyperactivity • CHRONIC EFFECTS: dependence	• Reported cases of DPH dependence have resulted from usage of large doses (often over 1,000 mg per day) over periods of months or years. Withdrawal symptoms include craving, worsening of insomnia, rhinorrhoea, nausea, irritability, restlessness, abdominal cramps, sweating, and diarrhoea. Gradual tapering has been the only described detoxification treatment plan	Different brand names, including Benadryl®, Dimedrol®, Daedalon®, Sominex®, Unisom® and Nytol®
Promethazine (antihistamine)	Oral	• It is a phenothiazine derivative and a H1 receptor antagonist; It also acts as a direct antagonist at muscarinic (M1) and dopamine (D2) receptors. It is classified as a first-generation antihistamine molecule which easily penetrates the blood-brain barrier and is associated with adverse effects such as sedation	• ACUTE EFFECTS: from mild sedation and CNS depression to profound hypotension, respiratory depression, unconsciousness, and sudden death; overdosage might determine an antimuscarinic delirium, agitation and neuroleptic malignant syndrome • it can be used to enhance effects of other co-ingested substances, e.g., opioids • CHRONIC EFFECTS: NR	• EMCDDA: regarded as NPS • Dependence might develop after long-term use of promethazine cough mixtures (containing opioids)	Promethazine mixed with a soft drink and/or alcohol is known as 'purple drank', 'lean', 'syzzurp', 'Texas tea'; Phenergan® and Phenadoz® are common brand names
Pseudoephedrine (decongestant)	Oral; IV use also recorded in misuse cases	• Sympathomimetic properties, exerting a stimulating action on alpha, beta1-, and	• ACUTE EFFECTS: stimulant effects, e.g., euphoria, insomnia, diminished sense of fatigue, anorexia, and	• Dependence might be developed after long-term use • Withdrawal symptoms include: dysphoria, restlessness	'Chalk', 'Crank', 'Meth', 'Speed'; 'Russian Cocktail' includes pseudoephedrine consumed together with

		beta2-adrenergic receptors	accelerated thinking; psychotic symptoms with auditory and visual hallucinations, persecutory delusions, fear, disorganised behaviour might develop after high-dose consumption • CHRONIC EFFECTS: dependence	• Due to the possibility to be used to manufacture the class A controlled drug methylamphetamine, restrictions have been in place in the UK to manage the risk of products containing pseudoephedrine and ephedrine; in the US, a prescription is not needed in most States, and in remaining States there are limits on how much an adult subject can buy each month	potassium permanganate and acetylsalicylic acid diluted in water; common brand names: Sudafed®, Nexafed®, Zephrex-D®; Claritin® includes pseudoephedrine and loratadine

CNS: central nervous system; DH: Dimenhydrinate; DPH: Diphenhydramine; EMCDDA: European Monitoring Centre for Drugs and Drug Addiction; GABA: Gamma-Amino-Butyric Acid; H: Histamine; IN: Intranasal; IV: Intravenous; NMDA: N-Methyl-D-Aspartate; NPS: New Psychoactive Substance; OTC: Over-The-Counter; 5-HT: Serotonin

3.3.3 Study 12: A systematic review on anticholinergic drugs diversion and abuse

A systematic review focusing on the diversion and abuse of centrally-acting anticholinergic drugs, such as benztropine, benzhexol/trihexyphenidyl, cyclobenzaprine, orphenadrine, and scopolamine, are used for the treatment of both primary and secondary parkinsonism, bradycardia, asthma and chronic obstructive pulmonary disease, dystonia, urinary incontinence, muscle cramps, nausea, and emesis, was performed in November 2021. The study has already been published, so we will summarise the most important results here (please refer to the paper for further details on the methodology and results)[99]. A total of 48 articles, including case reports, surveys, and retrospective case series analyses, were included, mostly focusing on benzhexol//trihexyphenidyl (n = 25), and benztropine (n = 4). Common anticholinergic agents block the muscarinic acetylcholine receptor, e.g., in the case of an excess of cholinergic activity resulting in extrapyramidal motor effects, which is a typical effect of antipsychotic drugs' block of dopamine receptors. Anticholinergic drugs also act as potent indirect dopamine agonists in the limbic system, which can, in part, explain their misuse potential in both psychiatric and non-psychiatric patients. Anticholinergic toxicity is associated with a wide range of symptoms, due to their non-specific target in terms of cholinergic receptor subtypes. Specifically, apart for psychotropic effects including elevated energy and mood and increased social interaction, they might induce an anticholinergic toxic syndrome, which may feature disorientation, hallucinations, paranoia, and confusion, configuring forms of exogenous psychosis, also with chronic developments. In most cases, due to its relevant symptomatology, anticholinergic intoxication is often seen and treated in emergency settings; toxicity symptoms might include dry mouth and mucosal surfaces, mydriasis, decreased bowel sounds, hot and flushed skin, urinary retention, constipation, tachycardia, hypertension, and tachypnoea, although in severe overdose, hypotension, life-threatening arrhythmias (e.g., supraventricular tachycardias), severe heart blocks, and respiratory depression may occur. Neurological and psychiatric symptoms might include respectively drowsiness, sedation, ataxia, amnesia, and even coma; and paranoia, hallucinations, delirium, and confusion. The diagnosis of anticholinergic intoxication is typically based on the clinical symptomatology presented; moreover, the intravenous use of an

acetylcholinesterase inhibitor such as physostigmine can be used as both a diagnostic and a therapeutic intervention. Toxicity symptoms are explainable through the pharmacological drug effects related to the antimuscarinic action of the index drug at each target tissue. However, the psychotropic, e.g., euphoric, stimulatory, and antidepressant effects of anticholinergic drugs should still be clarified. From the current findings, both the euphoric and toxic effects are dose-dependent, but it was not possible to understand the actual threshold dosages related to each drug due to the possibility of personal variations and idiosyncratic reactions related to use of concomitant drugs and unusual routes of administration. Finally, chronic use was related to tolerance and withdrawal phenomena, possibly related to the reinforcing effect of abused drugs on the mesolimbic dopaminergic system, including the ventral tegmental area (VTA), the nucleus accumbens, and the prefrontal cortex. Therefore, the rapid discontinuation of an anticholinergic drug was associated with a withdrawal syndrome characterised by symptoms including increased anxiety, insomnia, restlessness, sweating, irritability, headache, and tachycardia. Studies retrieved have shown that anticholinergic abusers are mostly young, male, single, and, when recorded, unemployed or marginalised. Moreover, anticholinergic drugs often figured in polydrug abuse since they were possibly used to potentiate the effects of other psychoactive substances, including alcohol, cocaine, benzodiazepines, and opioids. Indeed, regarding the abuse of anticholinergic medications, two distinct groups of abusers have been previously described: i) individuals who consume a medication only for its psychotropic and mind-altering effects; and ii) individuals with a medical indication for the use of, e.g., an anticholinergic drug, who might eventually abuse or misuse it for its psychotropic effects [100]. Misusers/abusers might also be recognised because they might exaggerate extrapyramidal symptoms, repeatedly request unnecessary dose increases, or perform doctor shopping practices. In the present review, although in two studies patients faked extrapyramidal symptoms in order to obtain a prescription for the drug of interest, sources of the drugs were in all cases licit prescriptions and could then be included in the second group.

Chapter 4 - Discussion

Our results supported and increased the levels of knowledge related to previously published data and anecdotal information on the misuse and diversion potential of certain prescribed and OTC drugs, considering a new and increasingly varying context of drug experimentation. Online drug users' fora, related communities and social networks have been contributing through the web to an increasing diffusion of both information and the use of 'new' psychotropics[101,102] and prescription or OTC drugs[27]. Consistently, as previously described for each prescription/OTC drug, an overall increasing number of reports during the past fifteen years has been recorded in several pharmacovigilance datasets, demonstrating awareness and concern have been growing among clinicians and national regulatory authorities, which were mostly involved in the reporting of cases. Differently from most academic papers based on small case series/single case studies, findings from our studies referred to overall much larger numbers of patients (e.g., in the case of opioids 16,507 and 130,283 unique ADRs were submitted respectively to EV and FAERS; similarly, with SSRI antidepressants numbers respectively recorded were 32,344 and 294,500) presenting with drugs' misusing issues. Several other factors might have influenced ADR reporting, including: i) differences in drug regulation and schedule classification, as in the case of opioids; ii) drug availability on the market; iii) pharmaceutical advertising; iv) prescribing attitudes of doctors; v) level of law enforcement and governmental drug policy; vi) regulatory frameworks for pharmaceutical drugs; and vii) cultural reasons[36]. The analysis of pharmacovigilance databases confirmed the diversion potential and the possibility of abuse/misuse/dependence and withdrawal issues related to selected drugs, albeit some differences have emerged within groups, including for example: i) the categories of people most affected, e.g., adult females in the case of gabapentinoids, or young adult males in the case of bupropion or fentanyl; ii) drug-related risks, potential harms, and even fatalities, e.g., in the case of loperamide; iii) the primary recreational value of an index drug, abused together with other substances and by idiosyncratic routes of administration, e.g., in the case of quetiapine; iv) eventual dependence and withdrawal issues, e.g., in the case of SSRIs, especially with paroxetine.

4.1 Issues regarding the abuse/misuse/dependence of the index molecules

4.1.1 Pharmacological issues

4.1.1.1 Opioids characteristics: pharmacokinetic and pharmacodynamic factors influencing opioid abuse and dependence

Possible reasons why some index drugs were recorded more compared to other drugs of the same group in association with abuse/misuse or dependence issues might be found in their pharmacological characteristics, opioids being one of the best examples. Whichever may be the route of uptake, opioids ultimately enter blood circulation and reach the brain. After crossing blood-brain-barrier, opioids enter the brain cells and produce effect by binding to opioid receptors located in brain. The opioid-receptor complex activates the mesolimbic reward system in ventral tegmental area, resulting in release of the neurotransmitter dopamine in nucleus accumbens area of brain. Depending on the intense feeling of pleasure or reward perceived upon administration of opioid, an individual may be more inclined to repeated administration and of addiction[103]. According to our research, among opioids, fentanyl, oxycodone, and then tramadol were in descending order the most recorded drugs being abused, due to the high affinity for the mu opioid receptor and their strong positive reinforcing properties[91,104]. Other physicochemical properties, such as low molecular weight and high lipophilicity, with specific examples made of fentanyl, oxycodone and the di-acetylated morphine pro-drug heroin, lead to faster uptake across blood-brain-barrier and rapid absorption rate, contributing to a low drug effect onset time[103]. As regards pharmacodynamics, oxycodone is a potent semi-synthetic derivative mediating its analgesic properties through both mu and kappa opioid receptors[105]. In the US it is a Schedule II substance like fentanyl, which possesses the highest affinity for the mu opioid receptor[105] and the highest potency (approximately 80 times more than morphine)[106,107]. Due to these properties, fentanyl exposure in opioid-naïve individuals or those with limited opioid tolerance has been associated with significant adverse effects, such as respiratory depression and fatal overdose and in general to higher mortality rates than with use of shorter-acting opioid medications[91,108]. With regard to oxycodone, in the study performed as part of this PhD

programme, in comparison with the other opioids, it has been more associated with the PTs aggression and euphoric mood; it is clear that euphoria might be an effect accompanying the analgesic property of opioids, and specifically mu-opioid agonists, such as oxycodone. These mood-elevating properties recorded here might be hypothetically related to the abuse issue presented above. In fact, subjective euphoric effects, unique energy and even a sense of invincibility and relatively side-effect-free experiences have been recorded by oxycodone abusers [109–111]. Oxycodone's 'likability' and abuse and dependence liability/addictiveness have been related to its rewarding properties, linked to markedly increased active transport across the blood-brain barrier, increased phasic dopaminergic activity in the VTA, nucleus accumbens and related striatal reward centres [104,112,113]. It is worth noting that the liking, the euphoric effect and a higher abuse potential are described as typical of immediate-release formulation compared to the extended release formulation [114,115]. Conversely, increased kappa opioid-mediated withdrawal dysphoria and other unpleasant central nervous withdrawal symptoms, such as aggressiveness, were recorded. Codeine, dihydrocodeine, and tramadol have approximately equianalgesic potencies for oral administration, although tramadol has a different mechanism of analgesia[105]. In fact, tramadol is an atypical opioid thought to work through modulation of serotonin and norepinephrine reuptake, in addition to its action as a mu opioid receptor agonist. Although tramadol displays many of the side-effects associated with mu opioid receptor agonists, it is purported to produce less respiratory depression and fewer gastrointestinal side-effects than pure mu opioid receptor agonists of comparable analgesic potency. For this reason, even though tramadol is used primarily as an analgesic to treat moderate/severe pain and post-operative pain, and off-label in restless leg syndrome in patients who have had little or no success with traditional treatments, it has demonstrated usefulness in treating opioid withdrawal[105,106] due to the low abuse liability and dependency risk initially perceived in comparison to other opioids. However, following its extensive use for chronic pain relief and also in drug abuse cases, dependency and, after long-term use, the occurrence of withdrawal symptoms were observed[116,117]. Consistent with this, in our study, it appeared to be involved in both dependence and withdrawal issues (e.g., drug dependence, drug withdrawal syndrome, and substance dependence) and intentional overdose/overdose. Moreover,

consistent with the literature[116], here it was associated with visual and auditory hallucinations, psychotic disorder, confusional state, and substance-induced-psychotic disorder, which might resemble serotonin reuptake blockers withdrawal symptoms in consideration of tramadol's mechanism of action as a serotonin and epinephrine reuptake blocker and the involvement of other pharmacological mechanisms involved such as muscarinic antagonism, serotonin receptor-mediated dopamine dysregulation, and antagonistic effects on gamma-aminobutyric acid (GABA) receptors[118,119]. Codeine, like oxycodone, is commonly used for chronic pain states, primarily acting on mu opioid receptors. Specifically, codeine's analgesic potency is approximately 50% that of morphine with a half-life of 2.5 to 3 hours, but it first needs to be metabolised to morphine by the body for it to display any activity, and, between 5% and 10% of the population are estimated to lack the ability to perform this conversion, so deriving limited pain relief and effects [105]. In the US codeine in its pure form is a Schedule II substance, whereas in combination with other analgesics and in a dosage less than 90 milligrams, it is Schedule III drug, meaning with a moderate to low potential for physical and psychological dependence[106]. Finally, among opioids, pentazocine is the only member of the benzomorphans opioid class, and is classified as a partial agonist-antagonist having high mu opioid receptor affinity but poor mu opioid receptor efficacy, and thus it may act functionally as a mu antagonist as well as having kappa agonistic properties. Although used as an analgesic, pentazocine has limited effect; psychomimetic effects (e.g., dysphoria, dysesthesias, and hallucinations) might complicate its use, particularly with increasing doses [105,106], as reported here.

4.1.1.2 Addictive use of gabapentinoids

Our study on gabapentinoids through the analysis of pharmacovigilance datasets[7] supported the idea of overall increasing levels of gabapentinoid misuse reports over time, consistent with previous observations made with regard to traditional psychoactives, e.g., benzodiazepines, molecules considered safe for many years before their addictive liability levels were identified. Nonetheless, some considerations on gabapentinoids abuse and dependence issues are needed[120]: firstly, pregabalin is a known potent inhibitor of voltage-dependent calcium channels, reducing the release of excitatory molecules (e.g., glutamate, noradrenaline, and substance P, but not dopamine),

acting against aberrant neuronal stimulation. Hypothetically, a different or unclear range of neurotransmitter involvement, and receptors' activation intensity in high/very high pregabalin dosage ingestion might be here considered. However, although a direct/indirect dopaminergic activity similar to other drugs of misuse cannot be explained, consistent with this, a pleasant stimulation and euphoria have been reported by users in relation to supratherapeutic/mega (e.g., 1,500-12,000 mg) pregabalin dosages. In fact, similar to what was observed with a range of medications such as venlafaxine, bupropion, quetiapine, and loperamide, gabapentinoids may induce a 'liking' subjective feeling, due to their GABA-mimetic action, but more limited levels of 'wanting'/behavioural dependence. Secondly, in line with previous literature recording the misuse of pregabalin may typically be associated with a history of polydrug misuse, gabapentinoids' abuse was identified here in combination with opiates/opioids, which potentiate gabapentinoid analgesic effects or counteract opioids' withdrawal symptoms while also presenting with potentiating effects; similarly, gabapentinoids have been typically prescribed to those affected by anxiety conditions to either 'boost' and/or to replace existing benzodiazepine prescriptions, although there are not any known direct actions on GABA or its receptors; however, therapeutic doses of pregabalin are dose-dependently associated with increase in extracellular GABA levels, driving relaxation and euphoria. iii) In consideration of the recorded abuse issues, both pregabalin and gabapentin were reclassified as Class C controlled substances in the UK in 2018, while in the US, pregabalin is still classified as a Schedule V controlled substance, while gabapentin is a controlled substance only in some states (Tennessee, Kentucky), and finally, in Australia, pregabalin and gabapentin are still classified as prescription only (Schedule 4) medications, similar to drugs like statins and antibiotics, without any special controls on supply or possession.

4.1.1.3 Characteristics of antidepressants associated with abuse, dependence and withdrawal

With regard to the study of abuse/misuse/dependence issues recorded with antidepressants, despite being generally considered a safe drug class, there is a growing, albeit relatively small, literature reporting the misuse and abuse of a range of antidepressants, such as bupropion,

venlafaxine, monoaminoxidase inhibitors, selected tricyclics[121], etc. Consistent with this, bupropion abuse issues recorded here[10] have been ascribed to its dopaminergic and stimulant-like activity, related to a recreational use of high dosages of the molecule, intranasally consumed. Anecdotally known as “welbys,” “wellies,” “dubs,” or “barnies,” its recreational use by oral or nasal routes was first described some 15 years ago[122,123]. Similarly, more recently, reports of high-dose bupropion injecting have appeared as well, with people misusing the drug to get a ‘high’ similar to the one obtained through other stimulants, such as cocaine. Accordingly with its abuse, increasing numbers of rogue, non-prescription required, drug-vending web sites are available. Interestingly, bupropion is a cathinone derivative, working as an inhibitor of catecholamines’ (noradrenaline and dopamine) reuptake, devoid of any serotonergic; antihistamine; or anticholinergic properties[124]. Furthermore, bupropion was notified as an NPS in 2014. Although bupropion causes a non-selective inhibition of both noradrenaline and dopamine reuptake, as well as an antagonism on the neuronal nicotinic acetylcholine receptor, high-dose abuse of bupropion has been previously implicated in several case reports of serotonin toxicity[13], either on its own or in combination with other serotonergic medications. This toxicity may be due to an unknown mechanism which may include a toxicodynamic, downstream, indirect effect, or the effects of bupropion metabolites. Alternatively, whilst acting on both norepinephrine and dopamine pathways, bupropion may lead to a sympathomimetic syndrome (e.g., tachycardia, diaphoresis, altered mental status) with dopaminergic neuromuscular effects (e.g., tremor, extrapyramidal effects), producing symptoms that are similar to those of serotonin toxicity but via a non-serotonin pathway. Furthermore, it is possible that bupropion increases concentrations of other types of serotonergic drugs, such as some SSRI antidepressants (e.g., sertraline and citalopram), but also of opioids (e.g., dextromethorphan, fentanyl, and tramadol), or of other NPS such as mephedrone. Conversely, the occurrence of withdrawal phenomena after the abrupt discontinuation of venlafaxine was here consistent with the extensive literature available, describing a syndrome characterised by nausea, depression, suicidal thoughts, disorientation, stomach cramps, panic attacks, sexual dysfunction, headache, and occasional psychotic symptoms. On the other hand, venlafaxine is a phenylethylamine derivative inhibiting the reuptake of serotonin/5-HT; norepinephrine/NE; and, to a lesser extent, dopamine/DA. The reuptake effects of

venlafaxine are dose-dependent, with action on 5-HT transmission at low doses (<150 mg/day); on both 5-HT and NE systems at moderate doses (>150 mg/day); and on DA at high doses (>300 mg/day). Preclinical studies showed that venlafaxine presents with a high affinity for D2 receptors, whilst its chronic administration is associated as well with D3 receptors' adaptive changes. Finally, venlafaxine desensitises both 5-HT1A and beta-adrenergic receptors, but virtually no affinity has been demonstrated for opiate; benzodiazepine; phencyclidine; N-methyl-D-aspartate; muscarinic; a1- adrenergic; or histaminergic receptors. Although how the withdrawal syndrome develops is unknown, it may well be associated with electrophysiological changes in 5-HT receptors. This is similar to what can be observed with SSRIs, although the severity of withdrawal may be higher with venlafaxine[125]. Finally, according to its putative abuse liability arguably being related to venlafaxine increased dopaminergic turnover at high dosages, the intake of large venlafaxine ('baby ecstasy') dosages has been reported here, consistent with the literature available[12] describing amphetamine/ecstasy-like effects. With regard to remaining SSRIs studied, both the EV and FAERS datasets, the abuse-related signals were mostly recorded here in association with citalopram and fluoxetine, and to a lesser extent with sertraline. This finding was consistent with data from the US RADARS System, suggesting that the most common non-scheduled psychoactive prescription drugs diverted over a 16-year period included sertraline, fluoxetine, and citalopram, along with other psychotropics[126]. Among SSRIs, relatively few cases of abuse and diversion have been recorded in the literature; many of these reports involved fluoxetine, ingested in idiosyncratic ways (e.g., intravenously) and/or at mega-dosages (e.g., up to 120mg), for either appetite suppression/weight loss or for stimulant-like effects in patients with a substance use history [121]. Conversely, whilst citalopram and sertraline are less frequently reported in association with misusing/abusing issues, they have both been identified in overdose-related arrhythmias [127,128]. In this respect, it is worth noting that euphoric mood, which may in itself be associated with a recreational drug-related 'high' [129], was one of the most recorded PTs associated with both fluoxetine and sertraline. There are similarities related to all molecules pertaining to the SSRI class; all of them boost the neurotransmitter serotonin/5HT through a blockade of the serotonin reuptake pump. This is being associated with both a desensitisation of the serotonin receptors, especially serotonin 1A, and overall

increasing levels of serotonergic neurotransmission. However, citalopram, fluoxetine and sertraline show several differences in terms of potency and selectivity. Indeed, citalopram seems to represent the most selective inhibitor of 5HT uptake, having minimal effects on dopamine and noradrenaline transporters and mild antagonist actions at H1 histamine receptors; fluoxetine shows antagonist properties at 5HT2C receptors, which could increase noradrenaline and dopamine neurotransmission; and, finally, sertraline may possess some ability to block the dopamine transporter, hence increasing dopamine neurotransmission, whilst also binding to sigma 1 receptors [124,127]. Despite an abuse liability of these three SSRIs having not been previously suggested, and the related pharmacological mechanisms might not yet be clear, several and complex factors might influence the possible diversion and abuse/misuse of SSRIs. It is generally accepted that drugs with addictive properties act on brain systems subserving reinforcement or reward and involving both multiple brain areas and multiple neurotransmitters. The most important one is the dopaminergic mesocorticolimbic pathway, probably underlying the positive motivational or incentive aspects of reward- and of drug-seeking behaviour[130]. Further interacting systems postulated to be involved in rewarding actions are those related to endogenous opioids; the GABAergic system, involved when substances such as alcohol, barbiturates, and benzodiazepines are being ingested; and a few others, such as the noradrenaline, cholecystokinin, glutamate, and neuropeptide Y pathways [131]. Serotonin appears to play a dual role in reward; in fact, both the VTA and the nucleus accumbens receive serotonergic projections from the dorsal and median raphe nuclei. The serotonergic activity in the VTA appears to be excitatory, resulting in increased levels of dopamine release in the nucleus accumbens [131]. A second point to be considered is the possibility of a current/previous history of substance abuse in patients reported here to have misused SSRIs. Current findings, suggesting high levels of paroxetine-related dependence/withdrawal issues in comparison with remaining SSRIs, are consistent with previous literature suggestions [4,132–135]. Indeed, due to its long half-life, fluoxetine is not typically associated with withdrawal signs/symptoms even when abruptly discontinued; furthermore, sertraline, citalopram, and escitalopram all present with a low risk of withdrawal symptoms [4,14,136–141]. Paroxetine metabolism is linked to cytochrome CYP2D6 [139,142]. At high concentrations, paroxetine inhibits CYP2D6, slowing its own inactivation; hence, a dose increase

might lead to a disproportionate increase in plasma levels. Conversely, abruptly stopping the drug could cause a sharp drop in plasma levels, which may help explain the withdrawal symptoms' intensity[139,142–144]. When discussing both SSRI-related dependence and withdrawal, which is a more appropriate term than 'discontinuation'[141,145], some issues may, however, need to be considered. Dependence is characterised per se by tolerance and/or withdrawal symptoms, with 'withdrawal', however, not necessarily including the occurrence of physical signs and symptoms. Finally, 'addiction' is characterised by a further range of issues, e.g., compulsive substance use; craving; and continued use despite its adverse consequences[146]. Hence, withdrawal symptoms that occur upon discontinuation of medications prescribed for valid medical reasons, such as SSRIs, do not suggest per se either a substance-related[147] or an addiction disorder[141,148]. Withdrawal occurring with most recreational substances and a range of prescribed drugs may include the following features: i) rebound, e.g., the re-occurrence of the original symptoms for which the index medication was prescribed; ii) withdrawal properly called, including both rebound and new (unrelated) symptoms; and iii) persistent post-withdrawal disorder, characterised by a return of the original illness at higher severity, often associated with additional features[149]. Other related issues of clinical relevance include *relapse*, considered as the re-emergence of the same disease episode due to loss of pharmacological effects, and *recurrence* meaning a new episode of a recurring primary disorder following previous recovery (e.g., a remission over 6–9 months) due to loss of pharmacological effect [137,139,141]. Hence, although SSRIs are considered non-addictive pharmacological agents, a range of proper withdrawal symptoms can occur well after discontinuation. Indeed, when tapering down a therapeutic-dosage of SSRIs, symptoms most typically are both mild/go untreated, and resolve spontaneously[149]. A number of these symptoms may resemble the primary disease (e.g., depression/anxiety/agitation/irritability), whereas others can be clearly differentiated from the disorder, with most common symptoms including: flu-like symptoms, e.g., fatigue, weakness, and dizziness; disturbed sleep and vivid dreams/nightmares; imbalance/dizziness/light-headedness; nausea; sensory disturbances, e.g., electric shock-like sensations and dysesthesia [139,140]. Indeed, most of these signs and symptoms were described here as paroxetine withdrawal-related PTs.. Finally, other researchers [139] have also suggested that a range of 'withdrawal symptoms' may indeed

relate to the occurrence of a serotonin syndrome; SSRIs can in fact facilitate not only the blockade of serotonin transporters, but also their reduction/down-regulation after long-term use, resulting in a serotonin hyperfunction after the SSRI has been discontinued.

4.1.1.4 Abuse of antipsychotics

Regarding antipsychotics, quetiapine was confirmed here to be the most documented abused second-generation antipsychotic drug[15,150]; anecdotally known as “Susie Q,” “Quell,” and “baby heroin”, crushed quetiapine tablets can be self-administered through nasal insufflation, although both oral and intravenous routes of administration have been reported. Consistent with these anecdotal clinical observations, post-marketing surveillance reports indicate an increase in quetiapine availability on the black market[15]. Furthermore, quetiapine, either on its own or in combination with substances, such as alcohol, cocaine, heroin and/or marijuana, is consistently associated with high rates of ambulance attendances, indicating rising community-level harms and greater harm relative to other atypical antipsychotics. There may be no straightforward pharmacological explanations for nonmedicinal quetiapine abuse, which can appear quite atypical [151]. In fact, the ‘high’ related to commonly used recreational drugs has been associated with increased levels of dopamine in the nucleus accumbens shell/mesolimbic areas, while, like other antipsychotics, quetiapine blocks dopamine D2 receptors. However, quetiapine may increase dopamine levels, preferentially in the nucleus accumbens shell, with some data suggesting a quetiapine-associated enhancement of cocaine as well as reinforcing potency[15,130]. Conversely, mechanisms, such as fast dissociation from dopamine receptors and prefrontal dopamine release mediated by 5-HT1A receptor activation and 5-HT2A inhibition, putatively explaining some recreational effects, are shared by other non-misused second-generation antipsychotics. Hence, there may be other factors or pharmacological effects that may be behind the molecule’s misusing potential. These effects may include norquetiapine-related norepinephrine reuptake blockade, 5-HT7 antagonist properties, and sigma receptors activation. Some pharmacokinetics issues have been suggested to represent important issues as well in facilitating quetiapine misuse. In fact, as quetiapine metabolism is mediated by the human cytochrome CYP3A4, a pharmacokinetic interaction may occur with a variety of drugs, including

analgesics, antiarrhythmic drugs, antibiotics, anticonvulsants, antihistamines, antiparkinsonian, pump inhibitors, steroids, and triptans. Furthermore, the high plasma concentrations of free testosterone in male subjects may contribute to higher CYP3A4 activity, which may be associated with a faster biotransformation of quetiapine, and hence a possible tendency to increase its dosage, in males. Both quetiapine extended-release (XR) and immediate-release (IR) formulations are generally well tolerated. However, with respect to the IR one, the XR formulation presents with a delayed (i.e., by approximately 3 hours) and blunted (i.e., by approximately 67%) serum peak, features that may contrast the occurrence of the drug-related 'rush', hence making it less attractive to abusers. Furthermore, the XR formulation coating may make the crushed tablets' snorting quite problematic. Conversely, olanzapine ('Lilly') has been anecdotally advised, at daily dosages of up to 50 mg, as the 'ideal trip terminator/modulator' after a psychedelic drug binge to treat unwanted 'comedown' symptoms (depression, dysphoria, anxiety, and insomnia) from drug/alcohol intake[152]. The neuropharmacological issues behind olanzapine misuse/ self-medication potential may be associated, per se, with its anxiolytic/antipsychotic activity, a 'reshuffling' in GABA(A) receptor subtypes over time, and the rewarding glutamatergic stimulation of the VTA dopaminergic neurons. It is of further interest that both quetiapine and olanzapine present with different degrees of 5-HT2C and histamine (H1) antagonist properties. Finally, quetiapine, clozapine, and olanzapine are unique among second-generation antipsychotics because they possess levels of anticholinergic activity, a pharmacological element that has been associated with a misusing potential. However, olanzapine and clozapine are much more potent than quetiapine at inhibiting the muscarinic M1 receptors. One could tentatively hypothesise that quetiapine and olanzapine are being misused in different ways and/or for different reasons. Both drugs may indeed be self-administered to cope with anxiety/sleep disturbances and/or with remaining recreational drug withdrawal symptoms. However, while olanzapine may be ingested/misused to self-medicate the psychopathological issues associated with remaining recreational drug intake, quetiapine might possess peculiar levels of recreational value as well, which may increase its addictive liability levels. According to the clozapine EV dataset[88], withdrawal/discontinuation ADRs were the most frequently reported and, as such, current findings confirmed and expanded on previous anecdotal data, and are likely to be related to clozapine multi-

receptor agonism/antagonism. Indeed, the clozapine pharmacodynamic profile may well include: i) a dopaminergic super-sensitivity, with the risk of a dopaminergic psychosis and symptoms such as dystonias, dyskinesias, and catatonia; ii) a cholinergic rebound, inducing in vulnerable patients a rapid worsening of psychosis, agitation, confusion, insomnia, and symptoms including nausea, vomiting, diarrhoea, headache, diaphoresis, and abnormal movements, such as dystonias and dyskinesias; iii) a serotonergic syndrome due to long-term clozapine 5-HT2A antagonism and receptor downregulation; iv) a sudden decrease in GABA activity, with the development of catatonic symptoms which may include mutism, waxy flexibility, staring, posturing, mannerisms, negativism, and also restless, irrelevant speech, and psychomotor agitation. Specifically, discontinuation should be seen here as distinct from the withdrawal scenario associated with alcohol and other addictive substances, a scenario which commonly presents together with craving, drug-seeking behaviour, and the inability to stop drug use. Thus, if a discontinuation of clozapine is needed, the molecule should be gradually tapered off over several weeks rather than abruptly discontinued, except in cases of emergency (e.g., agranulocytosis), and only with close clinical monitoring. Considering the current misuse/abuse issues, the number of clozapine-related ADRs (e.g., 326 ADRs; referring to: 'drug abuse', 'drug abuser', 'drug diversion', 'intentional product misuse', 'product use issue', and 'substance abuse') identified might be difficult to interpret, and possibly associated with instances of severe central effects, including lethargy/drowsiness/slurred speech; agitation/irritability; confusion and hallucinations, involving subjects suffering from both schizophrenia and a co-occurring substance use disorder. Furthermore, our findings did not identify any idiosyncratic intake modalities (e.g., intravenous use) that are typical of substance misuse behaviour. Hypothetically, putative levels of clozapine misuse liability might be tentatively explained considering the range of its pharmacodynamics activities, and the occurrence of rewarding and pleasurable effects due to the agonism at both delta-opioid and cannabinoid CB1 receptors, and the antagonism at muscarinic receptors[153]. Additionally, polypharmacy ingestion may have facilitated the occurrence of synergistic reactions, and hence the EMA ADRs' reporting, due to possible increase in clozapine plasma concentrations associated with metabolism inhibition. Regarding the ADRs' outcomes, figures seemed to be a reason for concern, since most cases (298/559 = 53.3%) required a prolonged

hospitalisation; fatalities were reported, mostly occurred in the context of: high dosage clozapine intake; suicidal behaviour; and/or polydrug abuse.

4.1.1.5 Characteristics of over-the-counter medicines most abused

Relating to OTCs, loperamide abuse and diversion showed increasing levels over time in both the EV and the FAERS datasets, especially with supratherapeutic doses (>16mg) and in the context of polydrug abuse[92], and, consistent with the previous literature available, was associated here with several fatalities. Loperamide is a common OTC anti-diarrhoeal compound, considered safe in the 2±16 mg daily dosage range, due to a rapid metabolism and a poor blood brain barrier penetration. Loperamide is a potent mu opioid receptor agonist with predominantly peripheral activity on the myenteric plexus, primarily decreasing intestinal propulsive activity. Secondary peripheral effects are seen at kappa-opioid and delta-opioid receptors. These receptor activities initially prompted, in 1977, the US FDA to place loperamide in Schedule V of the Controlled Substance Act. Later studies, however, supported its safety and low physical dependence risk, and by 1988 loperamide was made available for OTC use in the USA. Ingestion of higher, e.g., > 50 mg, loperamide dosages has however been associated with euphoria, CNS depression, and cardiotoxicity, recently prompting the FDA to release a safety warning commenting on the safety risks of ingesting high dosages of loperamide and approved changes to the packaging for tablet and capsule forms of loperamide limiting each carton to no more than 48 mg of loperamide and requiring the tablets and capsules to be packaged in individual doses [154,155]. Promethazine diversion has been increasingly recorded since the early 2000s. In our study[96], out of the total of 557 ‘suspect’ abuse/misuse/dependence-related cases, most recorded reactions were abuse-related ADRs, and specifically ‘drug abuse’ and ‘intentional product misuse’, with high-intake promethazine modalities (up to 8,000mg). Finally, benzydamine abuse issues, were limited by data availability. However, despite the small number of cases identified, the results confirmed the abuse and recreational use of benzydamine in young adults (16-24 years) to achieve psychotic-like effects by insufflation or ingestion of macro-doses[97].

4.1.2 Vulnerable categories of misusers

As previously described, referring to the intrinsic features of pharmacovigilance studies, issues reported here might have depended on the type of molecule, its indications and prescription.

However, some other factors, including gender, age, a physical or mental health problem, or a previous addiction, may have determined an increased risk or constituted a vulnerability factor for the abuse or the diversion of a specific pharmaceutical. Even though the WHO has not outlined a definition [156], vulnerability is defined by susceptibility, exposure, and resilience, in relation to individual factors such as sex, age, race, gender, ethnicity, displacement, disability and health status that can often overlap and can contribute to poor health outcomes [157]. On a social perspective, vulnerability is clearly contextual, dependent on social and cultural systems and political and economic trend [158]. In relation to substance use disorders, there are evidence from preclinical, clinical, and population studies that both biologic, e.g. genetic polymorphisms and personality/neurobiological traits, such as novelty seeking cue-reactivity and impulsivity, and environmental factors, e.g. acute/chronic stress, peer use, drug exposure, etc. might increase abuse and addiction vulnerability [159].

In our research, to give an example, the female gender was more represented in all gabapentinoid ADRs received by the EMA, including both abuse and dependence cases[7]. Indeed, excluding epilepsy, gabapentinoids are prescribed to treat several disorders that are more typically identified in female individuals, including chronic/neuropathic pain, generalised anxiety disorder, fibromyalgia, restless legs syndrome, migraine, and vasomotor symptoms of menopause[124]. Similarly, the study of SSRI antidepressants through both the EV and FAERS datasets showed a major involvement of female adults in comparison to males and other age-groups, due to the high prevalence of anxiety disorders and depression in women[132]. By contrast, but consistent with the literature available[122,123], our study highlighted the abuse of the NDRI bupropion in people with a history of drug addiction. Moreover, high levels of bupropion abuse have been identified in inmates, leading to bupropion removal from some US prison formularies; similarly, anecdotal reports indicated an increase in misusing levels of the antipsychotic quetiapine in prison settings possibly in relation to its anxiolytic/sedative properties[15]; unfortunately, due to data limitations, we could not access

further information from pharmacovigilance datasets concerning the employment or legal status of the cases recorded. While the female gender was more represented in all Z-drugs' and promethazine ADRs received by the EMA, males were prevalent among fentanyl and clozapine cases, consistent with substance and opioids abuse prevalence in the general population, and the use of clozapine in subjects suffering from both schizophrenia and a co-occurring substance use disorders[95]. A vulnerable population detected in almost all studies performed included people with current or previous history of substance abuse/dependence, e.g., both quetiapine and olanzapine misuse was putatively carried out to enhance and/or counteract psychotropics' effects[150]; similarly, gabapentinoid abuse ADRs appeared to be recorded in concomitance with the use of opioids[4,160,161], enhancing their effects[7]; also, interestingly, the non-medical use of SSRIs might have occurred in people using medicines without medical reasons either for recreational purposes, or for reducing withdrawal/ adverse symptoms occurring after having ingested other recreational psychotropics[29]. Unfortunately, those data may be only of partial help; in fact, in the citalopram, escitalopram, and fluoxetine EV cases 'drug abuse' was mentioned as a clinical indication, consistent with previous literature suggestions[162,163]. In consideration of the literature available, hypothetically, three main categories of opioid users have been identified by this study: i) chronic users of prescription opioids who then substituted them with other opioids or decided to experiment with new opioids for recreational purposes; ii) users of different types of opioids consecutively to self-medicate or manage withdrawal, including during opioid agonist or antagonist therapy; and iii) opioid users inadvertently exposed to other opioids [29].

4.1.3 Idiosyncratic reactions, dosages, and routes of administrations

Since the first study, including gabapentinoids, supratherapeutic dosages have been described throughout the ADRs recorded, especially when reporting abuse/misuse issues. Thus, by using mega doses, drug-related pharmacodynamic properties might be modified, and putatively explain the abuse liability of a specific molecule, or interactions between molecules which could lead to unpredictable consequences in terms of psychotropic effects that might have justified their use. For example, the antidiarrhoeic drug loperamide has been recorded as being abused at very high

dosages (>40mg) to achieve opioid-central effects such as euphoria ('lope dope') and/or avoid opioid withdrawal[92]; similarly, high doses of tramadol (e.g., 400mg) have been found to induce effects of 'drug liking'[164]; finally, bupropion[10,122] was recorded here above the therapeutic range (>300mg/day), with a maximum recorded dosage of 3,000mg, and venlafaxine dosage was higher than the maximum typically recommended (e.g., 375mg), with the highest dosage recorded being 6,300mg. Supporting drug recreational use, bupropion, but also venlafaxine, injecting and snorting intake practices were reported here, typically in combination with alcohol, illicit drugs and/or prescription opiates/opioids. With reference to dosages and routes of administrations, another interesting finding was described in the study of quetiapine and olanzapine pharmacovigilance datasets[150]. To give an example, in 106 out of 259 cases reporting drug dosage, quetiapine was found to have been prescribed in the dosage range of 25 to 200 mg, whereas in 43 cases dosages ingested exceeded the daily maximum therapeutic amount of 800 mg, with 19,000 mg being the highest level being reported. Although information on the formulations of quetiapine (i.e., XR versus IR) associated with the above ADRs was available for only a minority of reports (i.e., n = 2,265), the IR preparations were involved in most cases (n = 2,122 [93.7%]). Finally, 22 cases of quetiapine nasal insufflation and 18 cases of parenteral/intravenous intake were described. Conversely, despite the limitations in data availability, in 19 out of 115 cases (16.5%), olanzapine had been prescribed at a dosage below 5mg. Conversely, in 37 cases (32.2%), the dosage ingested exceeded the daily maximum therapeutic amount of 20mg, with 11,000mg being the highest level reported. Finally, one case of olanzapine nasal insufflation and seven cases of parenteral/intravenous intake were described.

Unfortunately, due to limitations intrinsic to the type of data available, the EV database did not provide further details of clinical interest, including: i) possible concurrence of psychopathological conditions; ii) medication dosage prescribed prior to discontinuation; iii) range/intensity of withdrawal symptoms; and iv) timeframe of the clinical presentation of withdrawal. Moreover, in both the MHRA and FAERS datasets, doses and routes of administration were unavailable.

4.1.4 Concomitantly abused licit/illicit drugs

4.1.4.1 A synergistic effect

As previously described, data available to this study did not always allow the evaluation of the concomitant use of prescription/OTC drugs, nor illicit substances, nor organic diagnoses which might have influenced the clinical presentation recorded. However, some interesting points can be highlighted: consistent with the literature available, opioids were implicated in most cases of gabapentinoid abuse/dependence recorded[7], and, vice versa, in a high number of opioid abuse/dependence cases retrieved here, gabapentinoids were recorded as concomitant drugs used. This might be related to an increasing prescribing of gabapentinoids and, therefore, availability, possibly solicited by a change in the attitude of society and the medical profession towards pain, resulting in more intensive management of pain syndromes, and on the other hand from a reputation for low risk of abuse, contrasting with the context of the health crisis linked to opioid abuse[165]. In fact, opioids might potentiate gabapentinoid analgesic effects, or have been prescribed for anxiolytic effects or for reducing opioid withdrawal symptoms[160]. However, co-prescription of gabapentin or pregabalin with opioids might increase the risk of opioid-related death by 50%, due to additive respiratory depression, as well as increased gabapentinoid bioavailability due to slowed gastrointestinal transit time[161]. Interestingly, in both the EV and FAERS datasets concomitant drugs prescribed with the selected opioids were benzodiazepines, antidepressants, other from the index drug opioids, and OTC antihistamines. These data support the literature describing those misusing prescription opioids were more likely to misuse prescription sedatives, tranquilisers, and stimulants, alcohol, and also illicit drugs, e.g., cocaine, [166–168] presenting unique problems in assessment and treatment. Reasons for adding other substances to opioids include enhancement of the 'high', compensation for undesired effects of one drug by taking another, compensation for negative internal states, or a common predisposition that is related to all substance consumption. While toxicity can be increased through pharmacokinetic or pharmacodynamic interactions and drug combinations involving opioids, specific recreational effects might be obtained through additive or synergistic rewarding effects, such as increasing dopamine release in the nucleus accumbens. In fact, preclinical studies have shown that activation of mu opioid receptors on GABA-VTA cells disinhibits dopamine neurons and increases their activity and dopamine function in the nucleus accumbens; thus, even if opioid receptors are maximally occupied, a stimulant, e.g., cocaine, might increase

synaptic levels of dopamine or enhance dopamine terminal release results, increasing ratings of high and 'liking'. Conversely, benzodiazepines often co-administered with opioids, binding GABA-A receptors resulting in the inhibition of VTA-GABA neurons, would be additive to the acute action of opioids, and possibly enhancing the subjective effects of opioids, including the high, but also increasing the risk for overdose and inhibition of respiration [169]. Consistent with the opioid epidemic[36,170,171], promethazine[96] concomitantly used drugs recorded among all cases and related fatal cases were opioids, putatively due to synergic effects on sedation and analgesia. In fact, the use of promethazine with opioids was typically reported with cough syrup containing codeine and promethazine outside of acceptable medical practice or guidelines for recreational reasons, e.g., to get 'high'. Benzodiazepines (e.g., diazepam, alprazolam, and lorazepam), were also recorded, and potentially related to the sedative synergic effect of benzodiazepines if consumed together with promethazine. Other prescription drug categories recorded included antidepressants: citalopram and amitriptyline were the most reported antidepressants, which is consistent with the most recorded diagnoses, such as Depression/Depressed Mood/Major Depression; Bipolar Disorder; and Anxiety/ Anxiety Disorders. Moreover, even though belonging to different antidepressants groups, citalopram being a SSRI, and amitriptyline a tricyclic antidepressant, both might have hypothetically been prescribed despite the fact that they have a potential sedative effect, which is common with promethazine, and therefore conjointly with promethazine might have been prescribed/diverted with the aim of helping sleep induction. Finally, it is worth mentioning the presence of some NPS in the opioid study. The stimulant cathinones were the most represented NPS, including mephedrone, 4-methylethcathinone, and methylenedioxypyrovalerone (MDPV). They are stimulants inducing euphoria, improved psychomotor speed, alertness, and talkativeness. Acute psychiatric effects may also include dysphoria, loss of appetite, difficulty in sleeping, paranoid ideation and delusions, cognitive impairment, changes in perception, agitation, hallucinations, confusion, violence, and suicidal thoughts [172]. Interestingly, out of 20 cases involving cathinones, 10 (50.0%) had a fatal outcome, consistent with the literature available highlighting the medical toxicity issues of cathinones, especially if used together with other molecules, e.g., they might be implicated in serotonin syndrome occurrence together with serotoninergic drugs, such as antidepressants,

tramadol, etc. [13,173,174]. Moreover, another NPS detected was mitragynine, which has been recorded in tramadol- and oxycodone-related cases in combination with other prescription drugs (other opioids, e.g., hydromorphone and buprenorphine; benzodiazepines, e.g., alprazolam, clonazepam, and diazepam; antidepressants, e.g., mirtazapine, venlafaxine, and fluoxetine; etc.), the OTC loperamide, alcohol and amphetamines. Mitragynine, found in 15 cases, is a vegetal alkaloid commonly known as kratom. Its effects are dose-dependent, inducing at low doses a mild stimulating effect, while producing at larger doses sedation and antinociception typical of opioids. Regular use may lead to dependence and opioid-like withdrawal symptoms upon discontinuation, and many related fatalities have been reported [101]. Interestingly, one fatal case was reported involving the abuse/overdose of tramadol, together with mitragynine, and loperamide, which presumably induced a condition of cardiotoxicity resulting in cardiac arrest. Other NPS recorded included an unspecified phenethylamine, reported in an accidental overdose, and the designer benzodiazepine flubromazolam[24], used together with the dissociative molecules 4-Methoxyphencyclidine and 3-Methoxyphencyclidine [172], causing a fatal outcome.

4.1.4.2 Pharmacokinetic interactions

Drug-drug interactions might be related to the synergistic effects of two drugs, for example when mixing a sedative and an antihistamine, as above recorded, but also to pharmacokinetic interactions between drugs, where reciprocal influencing of absorption, distribution in the various compartments, metabolization, and elimination can affect the effective concentrations at their sites of action [175]. To give an example, P-glycoprotein (P-gp) is a multidrug efflux transporter expressed in many tissue barriers such as intestine, liver, kidney, and blood–brain barrier, and in the placenta, testis, lymphocytes, and tumour cells, and extrudes predominantly lipophilic connections/bindings from inside the cell via the apical membranes of epithelial or endothelial cells. Substrates, inhibitors, and inducers might affect its activity, e.g., inducers accelerating efflux transport and reducing the bioavailability of drugs.

During the study of loperamide data, benzodiazepines, opiates/opioids, and antidepressants (mostly SSRIs) were most frequently identified in combination with loperamide. With regard to

antidepressants, whilst this may suggest the comorbid presence of depression/anxiety in these patients, in being SSRIs P-gp inhibitors, they might hence increase loperamide bioavailability levels. In fact, loperamide is a substrate for the P-glycoprotein (P-gp), which is an ATP-binding efflux transporter acting as a cell membrane extruder, hence increasing the elimination of xenobiotics from the CNS whilst protecting the body from potentially harmful substances. Oral loperamide ingestion is characterised by less than 2% bioavailability levels, and, when loperamide is taken as advised, any potential P-gp inhibition involvement is unlikely to become problematic for the user. Conversely, large loperamide dosages or its combination with a molecule that will slow down the effectiveness of P-gp will produce a `great high'. Moreover, misusers' perceived different euphoric effects may be related as well to differences in P-gp expression and activity. Finally, consistent with previous reports, a further range of molecules was identified here, including dextromethorphan, diphenhydramine, cimetidine, quinidine-quinine, and omeprazole. Once again, it is possible that the identification of these molecules in loperamide cases was the result of comorbid medical conditions. These idiosyncratic combinations may however `boost' loperamide effects and hence increase the likelihood of adverse events, including overdose or death. Similarly, the OTC cough and cold medication dextromethorphan is an opiate/opioid drug, hence arguably synergistically interacting with loperamide. Dextromethorphan presents with sedative, dissociative, and stimulant properties which can be, at high dosages, of recreational value. The antihistamine diphenhydramine intake may have occurred here for its sedative properties, often useful to cope with possible opiate/opioid withdrawal. Both cimetidine and omeprazole are frequently mentioned in pro-drug web fora as being able to impact on P-gp activities and hence facilitating the occurrence of the above-mentioned `lope `highs'. Moreover, since loperamide metabolism is related to cytochrome P450 (CYP450), CYP2C8 and CYP3A4 isozyme, its concomitant use with CYP3A4 (e.g., cimetidine, omeprazole, grapefruit juice, tonic water, itraconazole); and CYP2C8 (e.g., gemfibrozil) inhibitors can increase loperamide plasma levels. Finally, the loperamide/quinine-quinidine combination inhibits P-gp activities, hence increasing loperamide bioavailability levels. However, quinidine intake is also associated, per se, with QTc prolongation, further increasing the cardiotoxicity risk. Interestingly, a dextromethorphan/quinidine compound has recently been approved by the US FDA, with quinidine

serving to inhibit the CYP2D6 enzymatic degradation of dextromethorphan and thereby increase its circulating concentrations [176]. Other CYP2D6 recorded are: bupropion, cimetidine, quinidine, chlorphenamine, clomipramine, etc. Conversely, in being SSRIs potent inhibitors of CYP2D6 (fluoxetine, paroxetine) and CYP1A2 (fluvoxamine), consequences in the coadministration of other drugs may occur, e.g., in everyday practice, interactions between antidepressants and common medical drugs, such as certain beta- blockers. Fluoxetine and paroxetine also inhibit the metabolism of the beta-blocker metoprolol and can thus causing lowering of blood pressure, bradycardia, and other undesired effects. Fluvoxamine, on the other hand, inhibits CYP1A2 and can thus increase the toxicity of theophylline or clozapine. A fatal interaction between fluoxetine and clozapine has also been reported. The inhibition of CYP2D6 can also reduce the formation of active metabolites of codeine into morphine or tramadol into O-desmethyltramadol. Apart from the pharmacokinetic interactions, another aspect to consider with SSRIs is potentiation of the serotonergic effects, e.g. tramadol or triptans, simultaneously administered together with SSRI, can increase the risk of serotonin syndrome[175].

4.1.4.3 The role of alcohol

'Polysubstance use' is a term for the use of more than one drug or type of drug at the same time or one after another [177]. It can involve both illicit drugs and legal substances, such as alcohol and pharmaceuticals. The present research has shown alcohol to be the most used substance in conjunction with the molecules studied. This might be related to several reasons, including its wide availability, the relatively low cost and its dose-dependent psychoactive effects. Even though its harmful effects are frequently underestimated by young users, alcohol use might cause both short-term and long-term effects, including respectively accidental injuries, poisonings, risky sexual behaviours (which may result in unintended pregnancy or sexually transmitted diseases) and chronic diseases, such as hypertension, strokes, liver diseases, digestive problems, mental health problems, e.g., depression and anxiety, social/family/job-related problems, alcohol use disorders, or alcohol dependence.

Normally alcohol interacts with many drugs including medications, OTC medicines and illegal drugs, increasing or reducing their effects. In fact, mixing alcohol and medicines or illegal drugs can have various effects, depending on the type of drug, e.g. alcohol can increase the risk of drowsiness when mixed with other depressant drugs such as benzodiazepines or opioids; conversely, mixing alcohol with cocaine produces a chemical called coca ethylene, which is more toxic and is associated with seizures, liver damage, and compromised immune system [178,179]. Data from the Drug Abuse Warning Network indicate that the majority of prescription benzodiazepines, opioids, and related ED visits also involved the use of another substance, most frequently alcohol [180]. Consistently, the nonmedical use of prescription drugs has been associated with heavy drinking behaviour among adolescents and young adults in the US [181,182], with a 12-month prevalence of concurrent and simultaneous polydrug use of alcohol and any prescription drug of 12.1%. Male gender, Caucasian ethnicity and an earlier onset of drinking are the most important correlates [180,181].

4.1.5 Fatalities

4.1.5.1 Prescription pharmaceuticals involved

Due to the unavailability of the total number of patients exposed to a drug (number of people who consumed or better were prescribed with a specific drug), the present study did not allow the proper calculation of a drug-related 'fatal toxicity index'. However, it is interesting that several fatalities have been recorded in the pharmacovigilance datasets of the index molecules, e.g., in the EV database, 27 pregabalin- and 86 gabapentin-related fatality reports were identified, mostly implicating opioids, a finding consistent with the literature recording since 2006 a progressively increasing number of gabapentinoids-related death cases[5–7,120,165]**.** Studying both the FAERS and the EV datasets with regard to opioids, despite differences both datasets were consistent in recording the highest values of fatal outcomes with oxycodone and codeine. Similar data have been previously recorded in the literature available, and might possibly be influenced by several factors, including: regular use of opioids; increased opioid availability in the community or increased dosage; the use of a nervous system depressant, e.g., benzodiazepines and alcohol; injecting drug practices; and the concomitant consumption of other illicit substances, e.g., heroin, cocaine, etc.[183–185]. Other

conditions which might have influenced the outcome are: i) past suicide attempt; ii) presence of mental health disorders; iii) lack of formal education; iv) medical comorbidities; v) middle age (40 to 60 year-old); and vi) poverty [183–185]. Unfortunately, although the well-known increase in drug overdose incidence and prevalence in several countries worldwide over the past decade[36], we could not understand from the present data if the mortality related to opioid drugs was on the increase during the years here considered, and if those fatalities were accidental or intentional, the dosage and the formulations used. Also, inconsistencies between datasets might here be associated with underreporting or missing data regarding the ADR outcome(s). Interestingly, codeine and oxycodone both exist in extended-release/controlled-release formulations, which have been marketed as abuse-deterrent formulations and have already been shown to reduce prescription opioid misuse [115,186,187]. In this respect, their introduction and increased opioid pharmacovigilance activities (e.g., updated guidelines for prescription opioids, prescription drug monitoring programmes, ADR datasets such as EV and FAERS, etc.) might be considered responses to clinicians' concerns about misuse, diversion and fatalities related to prescription opioids and the opioid epidemic[188]. Fentanyl data[91] seem to confirm that non-medical prescription of high potency opioids is a major worldwide public health concern. Possibly because of its high potency, fentanyl prescribing was reported in a number of cases to be associated with iatrogenic dependence/withdrawal issues. However, as fentanyl self-administered either in idiosyncratic ways (i.e., parenteral, ingesting transdermal patches) or at high/very high dosages to achieve significant blood levels, a large proportion of EMA ADR cases (e.g., roughly two-thirds) were associated here either with a prolonged hospitalisation or resulted in death, high fentanyl dosages being associated with respiratory arrest, pulmonary oedema, chest wall rigidity and apnoea. Also, despite some 54.9% of EV ADRs fentanyl intake being reported on its own, a range of both prescription (e.g., other opiates/opioids, benzodiazepines), and recreational (e.g., cocaine and cannabis) psychotropics was identified as well; this is a reason for concern due to the possibility of polydrug intoxication or related-death, but it might also reflect the characteristics of clients prescribed with fentanyl, e.g., frequently affected by chronic pain conditions, anxiety, and depression, at times presenting as well with a history of drug misuse. Similarly, although SSRIs are thought to be relatively safe in overdose[189], consistent with previous data [190] a range of fatality reports

were recorded here with citalopram, fluoxetine and less frequently with sertraline. Apart from those cases where an intentional overdose with suicide intent occurred [191,192], SSRI-related fatalities are relatively rare. In this respect, some risk factors have been identified, including the concurrent ingestion of: i) sedatives such as alcohol, benzodiazepines, and opioids; ii) drugs that can facilitate the occurrence of serotonin toxicity, e.g., tramadol and amphetamines; iii) and other drugs involved in CYP-mediated drug-drug interactions, since fluoxetine and paroxetine are potent CYP2D6 inhibitors [121,128,193]. Interestingly, considering the study on IPEDs, three clenbuterol- and 34 salbutamol-related fatalities were identified[90]. The clenbuterol, polydrug, fatalities' issues identified are consistent with previous findings. Conversely, consistent with only a single report of salbutamol abuse-related fatality having been previously described, the molecule is usually considered safer than clenbuterol. Indeed, supra-therapeutic plasma concentrations of salbutamol could be well tolerated, without serious cardiac arrhythmias or any fatalities being reported. However, when used in combination with remaining medications, typically in asthmatic children, this is the most likely reason of the four cases of fatal overdosage ADRs, not being associated with abuse or dependence, here identified in underage subjects. Overall, overdosage and off-label use issues were identified slightly more frequently in salbutamol (typically in association with remaining medications), as opposed to clenbuterol cases (respective salbutamol versus clenbuterol PRR values: 1.32 and 1.33), with this being consistent with previous findings.

4.1.5.2 Over-the-counter drugs involved

Even though considered safe, the OTCs loperamide[92] and promethazine[96] here appeared to be associated with several fatalities. Specifically, even though loperamide was reported in the context of elevated (e.g., 195±1,600 mg) drug intake, lethal outcomes were here represented in 94/434 (21.6%) cases of patients reported to have misused/abused with loperamide, as a result of cardiac/cardiorespiratory arrest and serious arrhythmias. Occurrence of loperamide-related QT prolongation may be facilitated as well by a range of factors, including: advanced age; co-ingestion with other drugs (e.g., Class 1A and Class III antiarrhythmics; antipsychotics; antibiotics; methadone) that are known to prolong the QT interval; electrolyte abnormalities; and history of: congenital long

QT syndrome. Moreover, in about half of these fatalities, loperamide abuse had occurred in combination with a range of prescription/non-prescription/recreational psychotropics; conversely, multi-drug toxicity was reported in 39/42 (93.0%) of suicides. Similarly, the use of promethazine in combination with other prescription drugs or illicit drugs resulted in fatal (50.3%) and moderate ('recovered/resolved') outcomes (22.2%), consistent with previous data reporting adverse clinical course and high frequency of health care facility treatment.

4.2 Pharmacovigilance as a tool for drug prescription monitoring

The increasing rates in reporting ADR over time identified here may suggest a recently growing emphasis on pharmacovigilance data [62,194,195], which may well provide both real-world and affordable information on medications' use/misuse that is normally not recorded in controlled trials. Consistent with this, prescription-based methods of drug safety surveillance might represent areas of possible progress, since combining aspects of public health surveillance, voluntary reporting and epidemiological studies can improve triangulation and confidence in deriving conclusions [196].

All the molecules analysed until now by our research group are currently emerging as possibly abused or diverted by users, although their potential diversion and abuse or misuse had not been detected by pre-marketing processes, such as pre-marketing trials which normally involve the administration of carefully controlled, daily limited, therapeutic dosages and exclude patients with a current/previous history of drug misuse/addiction. The same has occurred in the past, firstly with benzodiazepines and then with Z-drugs. Also, pre-marketing processes did not consider the possibility of an interaction among (licit/illicit) drugs and, for example, opioids and alcohol. On the other hand, during the post-marketing surveillance phase, the chance to assess the abuse or diversion potential of newly released drugs should be evaluated, especially for those with activity on the CNS. Indeed, the fact that no information on the abuse or misuse potential of a new medicine's interaction with the CNS has been reported does not mean that a specific medicine does not actually produce these effects.

4.2.1 Implications of current findings for clinical practice

This research programme set out to answer a series of related questions, which are summarised in the previous sections and have implications for current and future clinical practice.: From data analysed, diversion, abuse, and dependence are issues which might present with several of the studied drugs, especially if used in large or extremely large dosages, concomitant licit/illicit drugs, and unconventional routes of administration. These findings strongly support the importance of providing the appropriate training to health professionals who work in EDs, general practice, drug treatment services, prisons, and mental health services. They should be aware of the diversion potential of both prescription and OTC drugs, recognise misuse cases, considering the possibility of polydrug misuse, and prevent it where possible. The possible diversion of pharmaceuticals for recreational purposes is a challenging issue for clinicians, due to the several toxidromes and confounding clinical issues with which patients might present. Clinicians should be careful in prescribing to vulnerable categories, e.g., patients with a history of a substance use disorder or dual diagnoses, and inmates. Informing NPS users, especially youngsters, who enter earlier the mental health services is essential. Also, suspected behaviours such as frequently requested prescription or *doctor shopping* should be monitored, developing or adopting, if there are none in the standard practice, drug monitoring plans. Finally, raising awareness among health professionals to report eventual ADRs, giving full details of a specific event, including e.g., the dosage, concomitant drug, diagnoses, etc., may provide further data for future studies. In fact, much of the work undertaken in this research programme possibly applies to other molecules and other pharmacovigilance datasets, which might in the future be studied in order to improve current findings. Overall, we believe there is a need to improve pharmacovigilance and its tools, in order to detect, understand and prevent adverse effects or drug diversion activities due to real-time comprehensive surveillance/toxicovigilance databases. Monitoring and treatment of such situations is essential, but when talking about addiction an important point is the prevention of at-risk behaviours. Like traditional drugs and alcohol, if taken inappropriately, medicines might lead to serious problems, which are not only related to substance-related disorders or addiction. Thus, preventing and reducing prescription drug misuse represents a major challenge for states and communities. For their part,

drug users/misusers can take steps to ensure that they use prescription medications appropriately by: i) following the directions as explained on the label or by the pharmacist; ii) being aware of potential interactions with other drugs as well as alcohol; iii) never stopping or changing a dosing regimen without first discussing it with the doctor; iv) never using another person's prescription and never giving their prescription medications to others; and v) storing prescription stimulants, sedatives, and opioids safely[38]. On the other side, health and social responses to problems related to the non-medical use of medicines should be planned and delivered, including education of at-risk categories such as adolescents and young people or people affected by a substance use disorder, harm reduction strategies [29,197].

4.2.2 Strengths of the study approach

Medicines safety monitoring is a continuous and dynamic process throughout all the phases of the life cycle of a drug. The post-marketing assessment of medicines plays a key role for better defining drugs' safety profile in real-world setting and filling the evidence gap of pre-marketing studies, which are normally conducted on limited numbers of patients that are selected based on strict eligibility criteria and not fully representing real-world populations, and have limited duration, thus preventing detection of rare and long-term adverse reactions. Thus, voluntary reporting in pharmacovigilance is a widely used, effective, and relatively inexpensive method of collecting information on suspected ADRs, detecting new, rare, and serious ADRs, which remained undetected in the pre-marketing clinical trials[198]. Two other advantages of spontaneous reporting are that it potentially maintains ongoing surveillance of all patients and is relatively inexpensive[199]. Further, the study of spontaneous reports allows hypothesis generation with the need to explore possible explanations for the adverse event in question. By fostering suspicions, voluntary report-based surveillance programmes perform an important function - which is to generate signals of potential problems that warrant further investigation.

In the face of a growing demand for safer drugs, our research offers a means of identifying early drug-related safety signals through large multinational datasets of ADRs. The substantial number of abuse/dependence-related events identified provides further evidence corroborating the

potential diversion of several drugs reported to be potentially misused for recreational purposes by a growing body of literature. This is important as they are prescription drugs or OTC drugs, thus not considered with a potential misuse and sold without a medical prescription. Clearly, the assessment of the medical product-adverse event relationship for a particular report or series of reports can be difficult. However, although this kind of approach should only be considered as exploratory to generate signals, disproportionality analysis in pharmacovigilance databases is a validated method in drug safety research and surveillance. Finding of a disproportionality ratio for a drug should lead to a new reinvestigation of data from experimental pharmacology and randomised clinical trials. It should also stimulate specific case–control or cohort analysis to confirm the signal. Experimental data, clinical trials, spontaneous notifications, case–control studies, cohort studies and data mining should be considered together for evaluating drug risk. Thus, given the results of the present project, it might be important for researchers to conduct additional prospective studies to characterise abuse-related events and identify risk factors for such abuse. Overall, a multicomponent approach is recommended, including monitoring drug utilisation, tracking users' posts on social media, and exploring health care databases, which enable performing proactive and effective post-marketing surveillance and pharmacovigilance, which have already been proven to be a relevant, efficient, and accurate strategy, e.g., with gabapentinoids, which have been both recently rescheduled in the UK [61,200,201].

4.2.3 Limitations of pharmacovigilance studies

Even though pharmacovigilance studies on ADRs can be considered a tool to detect hypothesis of safety issues, the analyses performed on the ADRs per se do not allow one to assess whether a causal link/association exists between a pharmaceutical product and the reaction(s) reported. In fact, as with other pharmacovigilance datasets[6,8,202], examining issues through the analysis of voluntary adverse events reporting systems might have limitations, given their reliance on self-reporting and likelihood of missing data[66]. In fact, pharmacovigilance datasets, including both EV and FAERS, do not receive reports for all adverse events related to a drug, which may result in under-reporting. Other factors, such as increased likelihood to report events with more severe

outcomes and increased publicity of the abuse of these medications may influence whether an event is reported, resulting in outcome reporting bias. Also, based on the current reporting rules in the EEA, report duplications may occur e.g., where a healthcare professional reported the same suspected ADR to the national Regulatory Authority and the Marketing Authorisation Holder and they both reported subsequently to EV. Therefore, those data were screened in order to be used to calculate the real numbers of drug-related adverse event. Clearly, case reports of suspected ADRs alone are not always sufficient to prove that a certain suspected reaction has indeed been caused by a specific medicine. This could be a symptom of another illness, or it could be associated with another medicinal product taken by the patient at the same time. Any case report should be seen considered together with all available data including case reports world-wide, clinical trials, epidemiological studies and toxicological investigations, in order to allow for robust conclusions. Finally, case reports reflect the information as provided by the reporter, and not all data fields might be provided for all reports, e.g., dosages or routes of administration of the medical products; in fact, the medical histories or histories of drug abuse or drug dependence have been rarely described. The instance of the reporting for a selected molecule may have been encouraged by a public awareness of a safety concern, but also caused by the availability of the medicinal product on the market and its extent of use, or by the nature or seriousness of the reactions.

Finally, another limitation of the study was the non-availability of reporting rates derived from sales or prescriptions. These denominators are not readily available, especially internationally. In fact, data on drug prescriptions were considered as a further area to be explored during the present doctoral programme in order to provide more comprehensive information, improve the strength of the study and support data on drug diversion, helping in defining the entity of the abuse, misuse and dependence phenomena investigated. In fact, prescription-based methods of drug safety surveillance would provide a numerator (e.g., the number of reports) and a denominator (e.g., the number of patients exposed), both being collected over a precisely known period of observation. Unfortunately, however, detailed prescription data are typically available only at a national level, whereas both the EV and the FAERS collect data at an international, cross-country, level. For example, in the United States a Public Health System Dashboard exists that contains several

indicators of health spending, quality of care, access, and health outcomes, and a prescription drug monitoring programme tracking controlled substance prescriptions is functioning, but none of them specifies the exact prescription rate of a pharmaceutical, or in the second case only opioids prescriptions have been reported; also, data are geographically limited to the USA. In some papers authors have used data from the US Medical Expenditure Panel Survey, explaining data were limited to the civilian and non-institutionalised population, excluding institutionalised patients. Lacking overall prescription data levels, a representative sample of national data was here considered, and contact has been made with the Clinical Practice Research Datalink (CPRD) - an observational and interventional research service that operates as part of the UK Department of Health, and with which the University of Hertfordshire is building connections/collaborations, which could provide information on socio-demographics, follow-ups on individuals' prescribing histories, look for specific diagnoses, abuse, etc. However, due to unavailability of funding, we needed to find alternative solutions, and the PCA, which provides details of the number of items of all prescriptions dispensed in the community in the UK, was here considered in the analysis of ADRs related to SSRI abuse/misuse/dependence issues; indeed, related data are freely available online in a legacy format. Similarly, from the US, results from the last NHANES from the National Center for Health Statistics, providing the estimate number of individuals receiving a certain type of medication in the past month, were here analysed to evaluate trends in SSRI use.

Chapter 5 - Conclusions

The work presented in this thesis has demonstrated that some drugs, including both prescription drugs, e.g., gabapentinoids, some antipsychotics and antidepressants, and some OTC drugs, such as loperamide, dextromethorphan, promethazine, etc. could be associated to misuse and abuse, especially in vulnerable individuals or in some contexts, such as polysubstance abuse, history of drug abuse or drug addiction. The use of concomitant substances or of high/supra-high doses for recreational purposes may cause unpredictable effects, such as overdoses or drug-related fatalities. Disproportionality analysis in pharmacovigilance databases can be considered a useful method in drug safety research and surveillance of abuse and dependence issues which have not previously detected in pre-marketing clinical trials.

Non-medical prescription drug use is a globally recognised problem with potential severe adverse consequences. This phenomenon is not a new one if we consider the diverted use and related dependence determined over a long time period by using opioids (including both pain relief medications and opioid substitution treatment medications), stimulants, and sedatives/hypnotics (e.g., barbiturates, benzodiazepines, and z-hypnotics). However, other drugs appeared to be diverted, with non-medical use typically encompassing taking the medication without an indication or in a manner that was not intended by the prescriber (e.g., taking higher doses or using non-approved administration routes).

Overall, the changing settings of drug abuse imposes a reflection on the reasons why a non-medical use of prescription drugs should be chosen. The complexity and the variety of the factors which may promote the occurrence of this phenomenon has been investigated, without a definitive conclusion that may suggest a solution - at the moment. Surely, a reason that may condition the use of prescription/OTC drugs for a recreational purpose is the perception that the related non-medical use is more socially acceptable, less stigmatised, and safer than the consumption of other illicit substances. Moreover, they may be extremely easy to find online through the web, avoiding the risk of legal problems linked to the illegal purchase of illicit drugs. Finally, the possibility of interactions between prescription drugs and other licit/illicit substances, emphasising the effects of the drug abuse due to NPS interactions, make them more attractive. However, the unpredictability of the

resulting clinical toxidromes makes this phenomenon a public health issue with enormous implications for clinical practice. Controlling the problem of prescription and OTC drugs misuse and abuse might be challenging due to the need for achieving high level of consumer safety, while not restricting access to medications in general for those who continue to use them safely. Prescribers, whether doctors or other specialists, need to be made more aware of prescribing certain combinations of drugs or improving their history-taking. Staff training should be evaluated for pharmacists and healthcare providers, in order to self-monitor care and use of medicines, to educate patients and promote harm reduction messages targeted towards those already using drugs or at risk of using new substances, and to intervene and support those experiencing problematic drug use [200,203–205]. In this regard, prevention and early education on substance abuse in vulnerable categories, such as young teens, are critical, but also other groups where problems have been observed. These may vary between countries, but include: recreational stimulant users, psychonauts, prisoners, men who have sex with men, people avoiding drug tests, and high-risk drug users. Record-keeping[206,207] and real time monitoring[208,209] could be methods of restricting access to some prescription/OTC drugs and prevent 'shopping' from one pharmacy to another, and where these measures result ineffective, regulatory interventions, e.g., drug re-scheduling, might be useful[4,208,210]. Early-warning and risk assessment should be developed; risk communication with authorities, professionals and users related to particularly harmful new substances[29]. Finally, appropriate and specific clinical guidelines for the management of acute toxicity caused by prescription or OTC drugs diversion and dependence might be hypothetically useful [29,211].

5.1 Recommendations for future research

Pharmacovigilance is a very interesting approach to the study of clinical phenomena during the post-marketing period, as it allows the monitoring of possible ADRs, such as the abuse and misuse of medications, including both prescription and over-the-counter drugs, through real data. In fact, ADRs are normally voluntarily reported by different actors and through specific pharmacovigilance datasets, existing at national, international, and global level, and constitute a huge pool of data to be studied. Clearly, it cannot be regarded in itself as a certain descriptive source of a specific

phenomenon, but, when added to the study of pharmacology and to clinical practice, the interpretation of the data can clearly provide a support to the confirmation of hypotheses on specific issues. It would certainly be useful to ensure that health professionals, including doctors and pharmacists, were more willing to contribute to the collection of such data as well as to their study. In this means, many of the most popular databases, e.g., the FAERS dataset or the YCS data, are freely accessible and analysable. Future research should be based on the study of molecules that may have abuse potential on the basis of their effects, chemical structures, or the anecdotally reported diversion potential, so that cases of serious toxicity, e.g., cardiovascular reactions related to loperamide abuse, or deaths related to specific substances can be prevented.

5.2 Final self-reflections

Carrying out this study has been intriguing and educating throughout its whole duration. A turning point during the PhD occurred when, as the study progressed, the methodology was improved using new and more complex disproportionality measures through the support of Dr. Rachel Vickers-Smith. She is an assistant professor of epidemiology in the University of Kentucky College of Public Health. She has provided applied statistical expertise and data analysis support, thus enabling the study to be completed more quickly than originally planned. Although I am satisfied with the outcome, the process and management of the project has been demanding, especially in consideration of my clinical practice as a psychiatrist and personal life. However, I maintained my motivation and persevered by balancing out my priorities. I benefited enormously from my academic supervisory team who reviewed any work done, supported and inspired me. Together with them, I was able to write and publish several works that are already published. For the research activities, it helped that from the beginning I was certain about the research question I wanted to address. Despite all the setbacks and challenges I faced, the experience I gained in conducting a study at this level was invaluable and puts me in a better position to manage the challenges I may encounter in my future research endeavours.

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Appendices

Appendix 1. Glossary

GLOSSARY (according to the Medical Dictionary for Regulatory Activities-MedDRA) (MedDRA 2020a; MedDRA 2020b)

ABUSE: intentional, non-therapeutic use by a patient or consumer of a product, over-the-counter or prescription, for a perceived reward or desired non-therapeutic effect including, but not limited to, getting high (euphoria).

ADVERSE (DRUG) REACTION (ADR): a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. An adverse drug reaction, contrary to an adverse event, is characterised by the suspicion of a causal relationship between the drug and the occurrence.

DEPENDENCE: overwhelming desire by a patient or consumer to take a drug for non-therapeutic purposes together with inability to control or stop its use despite harmful consequences.

DRUG ABUSE:

- Habitual use of drugs:
  - Not needed for therapeutic purposes (e.g., to alter mood).
  - To affect a body function unnecessarily (e.g., laxative).
  - Non-medical use of drugs
- Prevalence of cocaine, other psychostimulant abuse appears to be increasing in some metropolitan areas
- Initiation and persistence of drug abuse determined by complex interaction of: Pharmacologic properties and relative availability of drug, the personality and the expectation of the user, and the environmental context in which the drug is used. Personality and expectation of user, and the environmental context in which the drug is used. Environmental context of drug usage
- Polydrug abuse is increasingly common
- May be an acute or a chronic intoxication
- Symptoms vary according to pharmacologic properties, dose, and regular use of drug.

DRUG DIVERSION: drug diversion means that a drug is diverted from legal and medically necessary uses toward illegal uses.

EUROPEAN ECONOMIC AREA (EEA): Established on 1 January 1994 following an agreement between the member states of the European Free Trade Association (EFTA) and the European Community, later the European Union (EU). Specifically, it allows Iceland, Liechtenstein and Norway to participate in the EU's Internal Market without a conventional EU membership. In exchange, they are obliged to adopt all EU legislation related to the single market, except laws on agriculture and fisheries. One EFTA member, Switzerland, has not joined the EEA.

INTENTIONAL PRODUCT MISUSE: intentional product use issue known to be intentional and specifically identified as being misuse.

MISUSE: intentional use for a therapeutic purpose by a patient or consumer of a product, over-the-counter or prescription, other than as prescribed or not in accordance with the authorised product information. Misuse of a medicinal product is indicated as "a situation where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation", while the "Misuse of a medicinal product for illegal purposes is misuse with the additional connotation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault".

SPONTANEOUS REPORTING: system whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

WITHDRAWAL: a substance-specific syndrome which follows cessation or reduction in the intake of a psychoactive substance previously regularly used’.

WITHDRAWAL SYNDROME:

- Abrupt cessation of use in a habituated person
- A substance specific syndrome follows cessation or reduction in intake of a psychoactive substance previously used regularly
- Withdrawal symptoms vary according to psychoactive substance used: Generally, “opposite” the acute effects of drug. Include nonspecific symptoms e.g., nausea, diarrhoea or obstipation, profuse sweating, increase in respiratory rate, tachycardia. Common symptoms include anxiety, restlessness, irritability, insomnia, impaired attention.

Appendix 2. Achievements

PhD-related publications

1. **Chiappini S,** Schifano F. A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. CNS Drugs. 2016 Jul;30(7):647-54. Doi: 10.1007/s40263-016-0359-y.

2. **Chiappini S**, Schifano F. Is There a Potential of Misuse for Quetiapine? Literature Review and Analysis of the European Medicines Agency/European Medicines Agency Adverse Drug Reactions' Database. J Clin Psychopharmacol. 2018 Feb;38(1):72-79. Doi: 10.1097/JCP.0000000000000814.

3. Milano G, **Chiappini S**, Mattioli F, Martelli A, Schifano F. B-2 Agonists as Misusing Drugs? Assessment of both Clenbuterol- and Salbutamol-related European Medicines Agency Pharmacovigilance Database Reports. Basic Clin Pharmacol Toxicol. 2018 Aug;123(2):182-187. Doi: 10.1111/bcpt.12991.

4. Schifano F, **Chiappini S.** Is There a Potential of Misuse for Venlafaxine and Bupropion? Front Pharmacol 2018 Mar 21;9:239. Doi: 10.3389/fphar.2018.00239.

5. Schifano F, **Chiappini S**. Is there such a thing as a 'lope' dope? Analysis of loperamide-related European Medicines Agency (EMA) pharmacovigilance database reports. PLoS ONE 2018; 13(10): e0204443. Doi:10.1371/journal.pone.0204443.

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10. Schifano N, **Chiappini S**, Castiglione F, Salonia A, Schifano F. Is medicinal ketamine associated with urinary dysfunction issues? Assessment of both the European Medicines Agency (EMA) and the UK Yellow Card Scheme pharmacovigilance database-related reports. Lower Urinary Tract Symptoms. 2020; 1– 8. Doi:https//doi.org/10.1111/luts.12355.

11. **Chiappini S**, Miuli A, Mosca A, Pettorruso M, Guirguis A, Corkery JM, Martinotti G, Di Giannantnio M, Schifano F. The benzydamine experience: a systematic review of benzydamine abuse. Current Neuropharmacology 2021 Oct 18;19(10):1728-1737. Doi: 10.2174/1570159X19666210113151136.

12. Schifano F, **Chiappini S,** Miuli A, Mosca A, Santovito MC, Corkery JM, Guirguis A, Pettorruso M, Di Giannantonio M and Martinotti G. Focus on Over-the-Counter Drugs' Misuse: A Systematic Review on Antihistamines, Cough Medicines, and Decongestants. Front. Psychiatry 2021; 12:657397. Doi: 10.3389/fpsyt.2021.657397.

13. **Chiappini S**, Mosca A, Miuli A, Semeraro F, Mancusi G, Santovito MC, Di Carlo F, Pettorruso M, Guirguis A, Corkery JM; Martinotti G, Schifano F, Di Giannantonio M. Misuse of anticholinergic medications: a systematic review. Biomedicines 2022 Feb 1;10(2):355. Doi: 10.3390/biomedicines10020355.

14. **Chiappini S**, Vickers-Smith R, Guirguis A, Corkery JM, Martinotti G, Schifano F. Discontinuation issues with Selective Serotonin Reuptake Inhibitors (SSRIs)? Analysis of both the European EMA and the US FAERS pharmacovigilance databases. Pharmaceuticals (Basel) 2022 May 1;15(5):565. Doi: 10.3390/ph15050565.

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Other publications

1. Schifano F, **Chiappini S**, Corkery JM, Guirguis A. Abuse of Prescription Drugs in the Context of Novel Psychoactive Substances (NPS): A Systematic Review. Brain Sci. 2018 Apr 22;8(4). pii: E73. Doi: 10.3390/brainsci804007.

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5. Schifano F, Napoletano F, **Chiappini S,** Guirguis A, Corkery JM, Bonaccorso S, Ricciardi A, Scherbaum N, Vento A. New/emerging psychoactive substances and associated psychopathological consequences. Psychological Medicine 2019; 1–13. Doi:10.1017/S0033291719001727.

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obtain-illicit-highs-how-pharmacists-can-prevent-abuse/20208538.article?firstPass=false). Doi: 10.1211/PJ.2020.20208538.

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Chapters published

1. Cannabis: evidenze epidemiologiche, cliniche e terapeutiche. **Chiappini S**, Schifano F. Book Title: UNOSUQUATTRO. Diffusione e significati del consumo di cannabinoidi tra gli adolescenti: una questione educativa. Iori V, Gianotti F. September 2019. Franco Angeli Editore. EAN: 9788891781109. ISBN: 889178110X.

2. Substance-Use Disorders and Violence. Schifano F, Zangani C, **Chiappini S**, Guirguis A, Bonaccorso S, Corkery J. Series Title: Comprehensive Approach to Psychiatry. Book Title: Violence and Mental Disorders. October 2019. ISBN:978-3-030-33187-0.

3. [NUOVE SOSTANZE PSICOATTIVE]. Santacroce R, Martinotti G, **Chiappini S,** Schifano F. Book Title: Compendio di Psicopatologia. October 2019. ISBN: 978-8899235123.

4.Nuove frontiere nell'abuso di sostanze, psiconauti e internet. Zangani C, **Chiappini S**, Napoletano F, Orsolini L, Schifano S. In Modonutti GB (Eds), Prevenzione, giovani e… come investire nella formazione scolastica per la salute, Edizioni Goliardiche. ISBN: 978-88-8874-560-5.

5. Psychobiological; medical; and psychiatric implications of new/novel psychoactive substance (NPS) use. Chapter 11 (pp. 213-233) in Murphy, P. (ed.). Psychobiological Issues in Substance Use and Misuse. Routledge. Submitted 7 May 2020. Accepted 8 June 2020. Published 30 December 2020. Available from: https://books.google.co.uk/books?hl=en&lr=&id=-mQPEAAAQBAJ&oi=fnd&pg=PT212&ots=9x3DvDxNag&sig=jFMMvfi1BAHKIMZtjMGqjSJDPEE#v=onepage&q&f=false ISBN hardback: 978-0-367-27360-6; ISBN paperback: 978-0-367-27361-3; ISBN e-book: 978-0-429-29634-5. Schifano F, **Chiappini S**, Catalani V, Napoletano F, Arillotta D, Zangani C, Guirguis A, Vento AE, Bonaccorso S, Corkery JM (2021).

6. NPS Stimulants (Schifano F, Corkery JM, Catalani V, **Chiappini S**, Arillotta D, Vento A, Scherbaum N, Guirguis A) in New psychoactive substances. Challenges, consequences and treatment approaches edited by Kristina Adorjan, Sharon Walsh and Thomas G. Schulze. Oxford University Press (delivered on 23rd Dec 2021).

Poster presentations

1. Life and Medical Science Conference- University of Hertfordshire, Hatfield (UK) (April 2018). Analysis of European Monitoring Agency (EMA) EudraVigilance Adverse Drug Reactions database; a pharmacovigilance approach to the study of prescription drug misuse in the context of the Novel Psychoactive Substances (NPS) phenomenon. **Chiappini S**, Schifano F, Corkery JM, Guirguis A.

2. School of Health and Social Work Annual Research Conference 2018- University of Hertfordshire, Hatfield (UK) (June 2018). Prescription drug diversion and misuse. Assessment of the non-medical use of a range of molecules through pharmacovigilance databases. **Chiappini S**, Schifano F, Corkery JM, Guirguis A.

3. NPS conference- Maastricht (NL) (April 2019). Loperamide diversion and abuse: assessment of its non-medical use through the analysis of loperamide-related European Medicines Agency (EMA) pharmacovigilance database reports. **Chiappini S**, Corkery, JM, Guirguis, A, Schifano F.

4. Life and Medical School Research Conference, University of Hertfordshire, Hatfield (UK) (April 2019). The uncontrollable rise of opioids. Study of the European situation from the EudraVigilance adverse drug reactions database of fentanyl abuse/misuse/ dependence cases. **Chiappini S**, Schifano F, Corkery JM, Guirguis A.

5.Royal Pharmacology Society Annual Conference, London (UK) (November 2019). Are Z-drugs safe? study of their misuse, abuse and dependence according to the European Medicines Agency (EMA) pharmacovigilance database. **Chiappini S**, Guirguis A, Corkery J, Schifano F.

6. VII New Psychoactive Substances conference- online ed. (November 2020). Beyond the Purple Drank. Study of promethazine abuse according to the EudraVigilance dataset. **Chiappini S**, Schifano F, Corkery JM, Guirguis A.

7. Life and Medical Science Conference- University of Hertfordshire, Hatfield (UK) (June 2021). The benzydamine experience: an analysis of benzydamine related data from the European Monitoring Agency (EMA) adverse drug reactions (ADR) database. **Chiappini S**, Miuli A, Mosca A, Guirguis A, Corkery JM, Martinotti G, Schifano F.

Oral presentations

1. Conference “Unosuquattro. Cannabis use on Italian young people”. Reggio Emilia (IT). Cannabis: epidemiological, clinical and therapeutic evidences (April 2018).

2. 7th Young Psychiatric Network Meeting- Catania (IT)- The abuse of over-the-counter medications in the adolescents: the new phenomenon of ‘pharming’ (December 2018).

3. IV NPS conference- Maastricht (NL) - Prescription and over-the-counter drug misuse in the context of the NPS scenario; considering the pharmacovigilance approach to evaluate the abuse and misuse of medications (April 2019).

4. International Pathways of Psychiatry XII° Meeting - Roma (IT). NPS and abuse of psychotropic drugs (December 2019).

5. VIII NPS conference-Washington (US). Focus on over-the-counter drug abuse: a systematic review on the diversion of antihistamines, cough medicines, and decongestants (November 2021).

Other contributions

I have been an invited reviewer of: EMCDDA. Mini guide on the non-medical use of medicines: health and social responses 2021. https://www.emcdda.europa.eu/publications/mini-guides/non-medical-use-of-medicines-health-and-social-responses_en

Awards

Post Graduate Research student Conference and Training Funding - UH Trust 2020

Training

- Research Integrity – RDP Online Provision page on StudyNet/UH (2018)
- Plagiarism and How to Avoid It – RDP Online Provision page on StudyNet/UH (2018)
- RDP sessions on Technical writing, Critical reading and Qualitative research (2019)
- Uppsala Monitoring Centre- Introduction to pharmacovigilance (July 2020)
- Uppsala Monitoring Centre- Signal detection and causality assessment (July 2020)
- Uppsala Monitoring Centre- Statistical reasoning and algorithms in pharmacovigilance (July 2020)
- Medicines and Healthcare products Regulatory Agency (MHRA). E-learning: Adverse drug reactions: reporting makes medicines safer (April 2021)
- Completion of the online course on Electv: An Introduction to R (April 2021)
- Good Pharmacovigilance Practice (GPvP) online training. Available online: https://www.whitehalltraining.com/all-pharmacovigilance-courses from the Whitehall Training website, which has several partners including the NHS and numerous pharmaceutical companies. The course was divided into different modules, including a first one dedicated to Drug Safety, a second one to Global Regulations and a third one to Signalling & Risk Assessment (June 2021)
- Atomic-Addiction to medication: Improving care. Non-medical use of prescription drugs. Available online: https://addiction-to-medication.org/atomic/ (July 2021)

Appendix 3. Ethics Committee Approval

UNIVERSITY OF HERTFORDSHIRE

FORM EC1A: APPLICATION FOR ETHICS APPROVAL OF A STUDY INVOLVING HUMAN PARTICIPANTS (Individual or Group Applications)

Please complete this form if you wish to undertake a study involving human participants.

Applicants are advised to refer to the Ethics Approval StudyNet Site and read the Guidance Notes (GN) before completing this form.

http://www.studynet2.herts.ac.uk/ptl/common/ethics.nsf/Homepage?ReadForm

Use of this form is mandatory [see UPR RE01, 'Studies Involving Human Participants', SS 7.1-7.3]

Approval must be sought **and granted** before any investigation involving human participants begins [UPR RE01, S 4.4 (iii)]

If you require any further guidance, please contact either hsetecda@herts.ac.uk or ssahecda@herts.ac.uk
Abbreviations: GN = Guidance Notes UPR = University Policies and Regulations

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THE STUDY

Q1 Please give the title of the proposed study

Assessing the extent and characteristics of non-medical use of a range of prescribed drugs focussing on a range of pharmacovigilance databases, including: the European Monitoring Agency (EMA) EudraVigilance (EV) Database of Adverse Drug Reactions; the UK Yellow Card Scheme; and the UK Report on Illicit Drug Reactions (RIDR).

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THE APPLICANT

Q2 Name of applicant/(principal) investigator (person undertaking this study)

Stefania Chiappini

Student registration number/Staff number

UH PhD student ID 17021041

Email address

stefaniachiappini9@gmail.com
c.stefania@herts.ac.uk

Status:
☐Undergraduate (Foundation) ☐Undergraduate (BSc, BA)

☐Postgraduate (taught) x☐Postgraduate (research)

☐Staff ☐Other

If other, please provide details here:

Click here to enter text.

School/Department:

Life and Medical Sciences (Pharmacy, Pharmacology and Postgraduate Medicine department)

If application is from a student NOT based at University of Hertfordshire, please give the name of the partner institution: Click here to enter text.

Name of Programme (eg BSc (Hons) Computer Science):

PhD title: Assessing the extent and characteristics of non-medical use of a range of prescribed drugs; epidemiological and pharmacovigilance approaches.

Module name and module code: Click here to enter text.

Name of principal Supervisor: Prof. Fabrizio Schifano Supervisor's email: f.schifano@herts.ac.uk

Name of Module Leader if applicant is undertaking a taught programme/module:

Click here to enter text.

Names and student/staff numbers for any additional investigators involved in this study

PhD Co-Supervisor: John Corkery: j.corkery@herts.ac.uk
PhD Co-Supervisor: Amira Guirguis: a.guirguis2@herts.ac.uk

Is this study being conducted in collaboration with another university or institution and/or does it involve working with colleagues from another institution?

☐Yes x ☐No

If yes, provide details here:

Click here to enter text.

DETAILS OF THE PROPOSED STUDY

Q3 Please give a short synopsis of your proposed study, stating its aims and highlighting where these aims relate to the use of human participants (See GN 2.2.3)

Patterns of recreational drug use have changed dramatically over the last decade, with emerging New Psychoactive Substances (NPSs), attracting a new population of drug users, whilst being designed to legally mimic the effects of traditional recreational drugs. NPSs were first named by United Nations Office on Drugs and Crime (UNODC) as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat". The term "new" does not necessarily refer to new inventions — several NPSs were first synthesised 40 years ago — but to substances that have recently become available on the market. NPSs include synthetic cannabinoids, cathinone

derivatives, psychedelic phenethylamines, novel stimulants, synthetic opioids, tryptamine derivatives, phencyclidine-like dissociatives, piperazines, GABA-A/B receptor agonists, ***a range of prescribed medications,*** and psychoactive plants/herbs. Users are typically attracted by these substances due to their intense psychoactive effects and likely lack of detection in routine drug screenings. Over the last few years, a range of prescription drugs are being misused indeed as NPSs; this group includes: novel/potent opioids, designer benzodiazepines, some antidepressants, gabapentinoids, a selected number of antipsychotics, and a few image- and performance-enhancing drugs (IPED; e.g., anabolic steroids, clenbuterol and salbutamol). In misusing with prescription drugs, there are not just those risks associated with drugs per se, but also with the systematic context in which they are taken. These include side effects, but also interactions between medicines (both licensed and unlicensed) and other products (food and environmental chemicals), and individual variation in responses, due to genetic inter individual differences and possible presence of comorbidities. From this point of view, a pharmacovigilance approach may be of help. This approach includes "activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (World Health Organization WHO., 2002). In line with this general definition, and consistent with current EU legislation, the underlying objectives of pharmacovigilance include preventing harms from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorization; and promoting the safe and effective use of medicinal products. Pharmacovigilance is therefore "an activity contributing to the protection of patients' and public health" (EMA HMA Guideline on Good Pharmacovigilance Practices, Rev 4, October 2017). In Europe, these activities are coordinated by the European Medicines Agency (EMA).

The research here proposed aims at assessing the misuse, abuse and dependence of a range of prescription drugs, with particular attention to their addictive liability levels and diversion potential. As the intended and actual use of medicines differs between clinical trials and the real world use, focus will be here on the post-marketing phase. Ultimately, analysis of these data will hopefully support physicians in prescribing safely, limiting diversion activities and facilitate proper medication tapering. Taking on from previous studies of our group (gabapentinoids: Chiappini and Schifano, 2016; antipsychotics: Chiappini and Schifano, 2018; antidepressants, Schifano and Chiappini 2018 submitted) focus will be here on a number of prescription drugs previously, but anecdotally, identified as possessing a potential of misuse/abuse/dependence and withdrawal; these include clozapine; Z-drugs (e.g. zolpidem, zopiclone; zaleplon); ketamine; anti-asthmatics (e.g. salbutamol and clenbuterol); opioids (e.g. fentanyl, oxycodone, codeine, tramadol, dihydrocodeine, pentazocine); and the anti-diarrhoeal medication loperamide.

To assess the potential of misuse/abuse/dependence and withdrawal of these molecules, the EMA Adverse Drug Reactions (ADRs) EudraVigilance (EV) database will be analysed. When possible, data relating to diagnosis, concomitant drugs, route of administration and dosage of the index drug will be properly considered as well. EV is a pharmacovigilance database that collects spontaneous reports related to an individual case of a suspected side effect due to a specific drug. EMA defines an ADR as "a response to a medicinal product which is noxious and unintended". 'Response' in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated by the by healthcare professional or consumer as primary source, it meets the definition of an adverse reaction. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization. Use outside the marketing authorization includes off-label use, overdose, misuse, abuse and medication errors (EMA HMA Guideline on Good Pharmacovigilance Practices, Rev 4, October 2017). The individual case safety report (ICSR) is the format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time. ***The EMA Adverse Drug Reactions (ADRs) EudraVigilance (EV) data relating to patients affected are fully and completely de-identified,*** therefore it is not possible at all to derive from such data the names of the individuals affected by the ADR, not even their country or town. Hence, per definition, the need to obtain their informed consent is not applicable. Furthermore, only a portion of the EV data is made available to academics, and normally for academic purposes only. Data are organised in a dataset, having each individual patient a code (e.g., the EV local number) for unique identification/computation activities to occur. Specifically, data are not publicly available from the EMA website, but the single academic is given access to the database portion of interest only after a formal, motivated, request to EMA is being submitted and approved. Apart from the EMA EV database, and focussing on the UK, consideration will be given here as well to the Drug Analysis Profiles pharmacovigilance data (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/403099/Pharmacovigilance___how_the_MHRA_monitors_the_safety_of_medicines.pdf) available from the Yellow Card Scheme (https://yellowcard.mhra.gov.uk/iDAP/) of the UK-Medicines and Healthcare products Regulatory Agency (MHRA). The system collects reports of adverse drug reactions reported from within the UK, and these reports are then consistently forwarded to EMA (www.ema.europa.eu/docs/en_GB/document_library/...or.../WC500139752), hence formally contributing to the EV database implementation. Very recently, the Yellow card scheme, relating to prescribing drugs' only issues, has been enriched by an option that gives Public Health England (PHE) all of the functionality of Yellow Card but is tailored to ask a small number of additional questions around recreational psychoactives/NPS. The website is called RIDR, which stands for Report Illicit Drug Reactions (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/610260/Item_08__2017-OB-03__Vigilance_Projects_Update.pdf). Similar to what happens with the EMA EV system, also ***the Yellow Card Scheme and RIDR data are completely anonymised and fully de-identified.***

Q4 Please give a brief explanation of the design of the study and the methods and procedures used. You should clearly state the nature of the involvement the human participants will have in your proposed study and the extent of their commitment. Ensure you provide sufficient detail for the Committee to, particularly in relation to the human participants. Refer to any Standard Operating Procedures SOPs under which you are operating here. (See GN 2.2.4).

After being allowed access to the EV database, we will analyze data relating to the diversion and misuse potential of the following molecules: clozapine; Z-drugs; ketamine; salbutamol and clenbuterol; selected opioids (fentanyl, oxycodone, codeine, tramadol, dihydrocodeine, pentazocine); and loperamide. In order to assess the ADRs of interest from the database, the list of Preferred Term (PT), e.g., reactions or events categorised by EMA according to 'Medical Dictionary for Regulatory Activities' (MedDRA) definitions, will be properly considered. PT is a distinct descriptor (single medical concept) for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, but also refers to medical, social or family history characteristics. PTs are unambiguous and as specific and self-descriptive as possible in the context of international requirements. Data in the database are divided in: primary source, type of reports, severity of ADRs (hospitalization, death) and characteristics of pharmacotherapy (i.e., dose, pharmaceutical form). The number of ADRs is different from the number of individual case reports as one case report may refer to several ADRs. Each individual patient in the database has a code (EV local number) for identification. Hence, the number of individual patients is unequivocally identified counting the number of values in the EV local number column of the ADRs' database.
Being a pharmacovigilance research, focus will be here on those ADR reports spontaneously reported to EMA through ICSR/ADR reports. ADRs will be analysed considering a range of parameters, including: socio-demographic characteristic (age and sex); source/reporter country (from European Economic Area/EEA or non-EEA); reporter qualification (i.e., pharmacist, physician); outcomes (fatal, recovered, resolved); and possible concomitant drug(s) ingested. In carrying out the analysis, a selected a group of MedDRA terms from the 'drug abuse, dependence and withdrawal' section of the Standardised MedDRA Query (SMQ) system will be selected. For a further assessment of data relating to the misuse potential of the above described prescribing drugs, also the Yellow Card Scheme and RIDR data (which are completely anonymised and fully de-identified, and which contribute to the EMA EV database implementation), will be accessed and analysed.

In order to better assess the misuse potential of a given drug, the prevalence of the ADR of interest will be compared with that of another drug of the same group (e.g., within the anti-asthmatic medication group, comparison will be made between salbutamol and clenbuterol) using the proportional reporting ratio (PRR) approach. PRR is here defined as: 'the ratio between the frequency with which a specific adverse event is reported for the drug of interest (relative to all adverse events reported for the drug) and the frequency with which the same adverse event is reported for the drug(s) in the comparison group (relative to all adverse events for drugs in the comparison group'). Being a measure of disproportionality, a PRR greater than 1 suggests that the adverse event is more commonly reported for individuals taking the drug of interest relative to the comparison drug(s). The PRR is computed as follows:

$(W/W+X)/(Y/Y+Z)$

where: W=number of the first drug cases relating to the chosen adverse event(s); X=number of the first drug cases involving any other adverse events; Y=number of the second drug cases relating to the chosen adverse event(s); and Z=number of the second drug cases involving any other adverse events. The computation, finally, defines which one between the two molecules is more prone to determine the ADR studied.

Q5 Does the study involve the administration of substances?

☐Yes x☐No

PLEASE NOTE: If you have answered yes to this question you must ensure that the study would not be considered a clinical trial of an investigational medical product. To help you, please refer to the link below from the Medicines and Healthcare Products Regulatory Agency:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf

To help you determine whether NHS REC approval is required, you may wish to consult the Health Research Authority (HRA) decision tool: http://www.hra-decisiontools.org.uk/ethics/

If your study is considered a clinical trial and it is decided that ethical approval will be sought from the HRA, please stop completing this form and use Form EC1D, 'NHS Protocol Registration Request'; you should also seek guidance from Research Sponsorship.

I confirm that I have referred to the Medicines and Healthcare Products Regulatory Agency information and confirm that that my study is not considered a clinical trial of a medicinal product.

Please type your name here: STEFANIA CHIAPPINI

Date: 18TH February 2018

Q6.1 Please give the starting date for your recruitment and data collection:

Data collection and analysis will be started as soon as the Ethics permission will be available

Q6.2 Please give the finishing date for your data collection:

Possible finishing date for data collection and analysis: September 1st, 2020.

(For meaning of 'starting date' and 'finishing date', see GN 2.2.6)

Q7 Where will the study take place?

University of Hertfordshire

Please refer to the Guidance Notes (GN 2.2.7) which set out clearly what permissions are required;

Please tick all the statements below which apply to this study

☐ I confirm that I have obtained permission to access my intended group of participants and that the agreement is attached to this application

☐ I confirm that I have obtained permission to carry out my study on University premises in areas outside the Schools and that the agreement is attached to this application

☐ I confirm that I have obtained permission to carry out my study at an off-campus location and that the agreement is attached to this application

☐ I have yet to obtain permission but I understand that this will be necessary before I commence my study and that the original copies of the permission letters must be verified by my supervisor before data collection commences

☐ This study involves working with minors/vulnerable participants. I/we have obtained permission from the organisation (including UH/UH Partner Institutions when appropriate) in which the study is to take place and which is responsible for the minors/vulnerable participants. The permission states the DBS requirements of the organisation for this study and confirms I/we have satisfied their DBS requirements where necessary.
NB If your study involves minors/vulnerable participants, please refer to Q18 to ensure you comply with the University's requirement regarding Disclosure and Barring Service clearance.

x☐ Permission is not required for my study as:

Other than a UH Ethics advise/approval, the need of a specific permission is not identified here. In fact, this is a pharmacovigilance study, aiming at analysing a dataset of spontaneous reports through the EMA EV database, collecting individual case safety reports (ICSR) or Adverse (drug) reaction (ADR) reports. As already stated above, it is hereby confirmed that ***the EMA Adverse Drug Reactions (ADRs) EudraVigilance (EV) data relating to patients affected are fully and completely de-identified,*** therefore it is not possible at all to derive from such data the names of the individuals affected by the ADR, not even their country or town. Hence, per definition, the need to obtain their informed consent is not applicable. Moreover, only a portion of the EV data is made available to academics, and normally for academic purposes only. Similar to what happens with the EMA EV system, also ***the Yellow Card Scheme and RIDR data are completely anonymised and fully de-identified.***

HARMS, HAZARDS AND RISKS

Q8.1 It might be appropriate to conduct a risk assessment (in respect of the hazards/risks affecting both the participants and/or investigators). Please use Risk Assessment Form EC5 if the answer to any of the questions below is 'yes'.

If you are required to complete and submit a School specific risk assessment in addition to Form EC5, please append it to your completed Form EC5.

Will this study involve any of the following?

Invasive Procedures/administration of any substance/s?	☐YES	x☐NO
Are there potential hazards to participant/investigator(s) from the proposed study? (Physical/Emotional)	☐YES	x☐ NO
Will or could aftercare and/or support be needed by participants?	☐YES	x ☐NO

IF 'YES' TO THE ABOVE PLEASE COMPLETE EC1 APPENDIX 1 AND INCLUDE IT WITH YOUR APPLICATION

Q8.2 Is the study being conducted off-campus (i.e. not at UH/UH Partner?) ☐YES x ☐ NO

It might be appropriate to conduct a risk assessment of the proposed location for your study (in respect of the hazards/risks affecting both the participants and/or investigators) (this might be relevant for on-campus locations as well). Please use Form EC5 and, if required, a School-specific risk assessment (See GN 2.2.8 of the Guidance Notes).

If you do not consider it necessary to submit a risk assessment, please give your reasons:

Since most of the work will be carried out whilst working in front of a screen, the health and safety issues when working with computers will be taken into account (https://www.bbc.co.uk/education/guides/zkyg87h/revision/3). More precisely: tiltable screens; anti-glare screen filters; adjustable chairs; and foot supports will be provided to staff. Lighting levels will be suitable; workstations will not be cramped; and there will be frequent breaks from working in front of the screen. All rules for all electrical appliances in a computer room will apply as well, including: no trailing wires; and electrical sockets not being overloaded. Furthermore, attention will be given to prevention activities of fire risks with PCs, such as avoiding wearing any dangling accessories. Steps will also be taken towards preventing common problems, e.g., back problems; and eyestrain.

ABOUT YOUR PARTICIPANTS

Q9 Please give a brief description of the kind of people you hope/intend to have as participants, for instance, a sample of the general population, University students, people affected by a particular medical condition, children within a given age group, employees of a particular firm, people who support a particular political party, and state whether there are any upper or lower age restrictions.

Being a pharmacovigilance study with the analysis of spontaneous reports' data, subjects involved are part of the worldwide general population.

Q10 Please state here the maximum number of participants you hope will participate in your study. Please indicate the maximum numbers of participants for ***each*** method of data collection.

Being a pharmacovigilance study focusing on data collected by EMA through EV dataset of spontaneous reports, this number is difficult to be established a priori and is indeed different from each of the molecules being assessed here. However, it is anticipated that the number of adverse drug reactions being reported to the EMA EV database for each of the molecules here is in the order of thousands.

Q11 By completing this form, you are indicating that you are reasonably sure that you will be successful in obtaining the number of participants which you hope/intend to recruit. Please outline here your recruitment (sampling) method and how you will advertise your study. (See GN 2.2.9).

See Q10

CONFIDENTIALITY AND CONSENT

(For guidance on issues relating to consent, see GN 2.2.10, GN 3.1 and UPR RE01, SS 2.3 and 2.4 and the Ethics Approval StudyNet Site FAQs)

Q12 How will you obtain consent from the participants? Please explain the consent process for each method of data collection identified in Q4

☐ Informed consent using EC3 and EC6 (equivalent)

☐ Implied consent (e.g. via participant information at the start of the questionnaire/survey etc)

☐ Consent by proxy (for example, given by parent/guardian)

Use this space to describe how consent is to be obtained and recorded for each method of data collection. The information you give must be sufficient to enable the Committee to understand exactly what it is that prospective participants are being asked to agree to.

Click here to enter text.

If you do not intend to obtain consent from participants please explain why it is considered unnecessary or impossible or otherwise inappropriate to seek consent.

As already stated above, it is hereby confirmed that ***the EMA Adverse Drug Reactions (ADRs) EudraVigilance (EV) data relating to patients affected are fully and completely de-identified,*** therefore it is not possible at all to derive from such data the names of the individuals affected by the ADR, not even their country or town. Hence, per definition, the

need to obtain their informed consent is not applicable. Similar to what happens with the EMA EV system, also ***the Yellow Card Scheme and RIDR data are completely anonymised and fully de-identified.***

Q13 If the participant is a minor (under 18 years of age) or is unable for any reason to give full consent on their own, state here whose consent will be obtained and how? (See especially GN 3.6 and 3.7)

See above; Q12

Q14.1 Will anyone other than yourself and the participants be present with you when conducting this study? (See GN 2.2.10)

☐YES x☐NO

If YES, please state the relationship between anyone else who is present other than the applicant and/or participants (eg health professional, parent/guardian of the participant).

Click here to enter text.

Q14.2 Will the proposed study be conducted in private?

x☐YES ☐NO

If 'No', what steps will be taken to ensure confidentiality of the participants' information. (See GN 2.2.10):

Click here to enter text.

Q15 Are personal data of any sort (such as name, age, gender, occupation, contact details or images) to be obtained from or in respect of any participant? (See GN 2.2.11) (You will be required to adhere to the arrangements declared in this application concerning confidentiality of data and its storage. The Participant Information Sheet (Form EC6 or equivalent) must explain the arrangements clearly.)

☐YES x☐NO

If YES, give details of personal data to be gathered and indicate how it will be stored.

Click here to enter text.

Will you be making audio-visual recordings?

☐YES x ☐NO

If YES, give details of the types recording to be made and indicate how they will be stored.

Click here to enter text.

State what steps will be taken to prevent or regulate access to personal data/audio-visual recordings beyond the immediate investigative team, as indicated in the Participant Information Sheet.

Indicate what assurances will be given to participants about the security of, and access to, personal data/audio-visual recordings, as indicated in the Participant Information Sheet.

Click here to enter text.

State as far as you are able to do so how long personal data/audio-visual recordings collected/made during the study will be retained and what arrangements have been made for its/their secure storage, as indicated in the Participant Information Sheet.

Click here to enter text.

Will data be anonymised prior to

storage? x☐YES

☐NO

Q16 Is it intended (or possible) that data might be used beyond the present study? (See GN

2.2.10) ☐YES ☐NO

If YES, please indicate the kind of further use that is intended (or which may be possible).

It is possible, and indeed hopeful, that the vast amount of data collected for the pharmacovigilance studies here proposed will form the basis of a range of peer-reviewed research papers and conference presentations.

If NO, will the data be kept for a set period and then destroyed under secure

conditions? ☐YES ☐NO

If NO, please explain why not:

Click here to enter text.

Q17 Consent Forms: what arrangements have been made for the storage of Consent Forms and for how long?

As already stated above, it is hereby confirmed that ***the EMA Adverse Drug Reactions (ADRs) EudraVigilance (EV) data relating to patients affected are fully and completely de-identified,*** therefore it is not possible at all to derive from such data the names of the individuals affected by the ADR, not even their country or town. Hence, per definition, the need to obtain their informed consent is not applicable.

Q18 If the activity/activities involve work with children and/or vulnerable adults satisfactory Disclosure and Barring Service (DBS) clearance may be required by investigators. You are required to check with the organisation (including UH/UH Partners where appropriate) responsible for the minors/vulnerable participants whether or not they require DBS clearance.

Any permission from the organisation confirming their approval for you to undertake the activities
with the children/vulnerable group for which they are responsible should make specific reference to any DBS requirements they impose and their permission letter/email must be included with your application.

More information is available via the DBS website - https://www.gov.uk/government/organisations/disclosure-and-barring-service

REWARDS

Q19.1 Are you receiving any financial or other reward connected with this study? (See GN 2.2.14 and UPR RE01, S 2.3)

☐YES x☐NO

If YES, give details here:

Click here to enter text.

Q19.2 Are participants going to receive any financial or other reward connected with the study? (Please note that the University does not allow participants to be given a financial inducement.) (See UPR RE01, S 2.3)

☐YES x☐NO

If YES, provide details here:

Click here to enter text.

Q19.3 Will anybody else (including any other members of the investigative team) receive any financial or other reward connected with this study?

☐YES x ☐NO

If YES, provide details here:

Click here to enter text.

OTHER RELEVANT MATTERS

Q20 Enter here anything else you want to say in support of your application, or which you believe may assist the Committee in reaching its decision.

Click here to enter text.

DOCUMENTS TO BE ATTACHED

Please indicate below which documents are attached to this

application:

☐ Permission to access groups of participants from student body

☐Permission to use University premises beyond areas of School

☐Schools Permission from off-campus location(s) to be used to conduct this study

☐Risk Assessment(s) in respect of hazards/risks affecting participants/investigator(s)

☐Copy of Consent Form (See Form EC3/EC4) Copy of Form EC6 (Participant Info Sheet)

☐ Copy of Form EC6 (Participant Info Sheet)

☐A copy of the proposed questionnaire and/or interview schedule (if appropriate for this study). For unstructured methods, please provide details of the subject areas that will be covered and any boundaries that have been agreed with your Supervisor

☐Any other relevant documents, such as a debrief, meeting report. Please provide details here:

Three papers, either already published or in their final phase of review, and using the methodology here proposed, are here included:

1: Chiappini S, Schifano F. Is There a Potential of Misuse for Quetiapine?: Literature Review and Analysis of the European Medicines Agency/European Medicines Agency Adverse Drug Reactions' Database. J Clin Psychopharmacol. 2018 Feb;38(1):72-79. doi: 10.1097/JCP.0000000000000814. Review. PubMed PMID: 29210868 (*accepted word version and PubMed abstract being provided here; pdf of the published paper not yet available*)

2: A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. CNS Drugs. 2016 Jul;30(7):647-54. doi: 10.1007/s40263-016-0359-y. PubMed PMID: 27312320.

3: Schifano F, Chiappini S. Is There A Potential Of Misuse For Venlafaxine And Bupropion? Analysis of The European Medicines' Agency/EMA Adverse Drug Reactions Database. Revised version submitted to Frontiers in Pharmacology, February 2018 (*waiting for final acceptance; final word version submitted being made available here*)

Furthermore, a few screen shots of the EMA EV database will be included here as well.

DECLARATIONS

1 DECLARATION BY APPLICANT

I undertake, to the best of my ability, to abide by UPR RE01, 'Studies Involving the Use of Human Participants', in carrying out the study.

I undertake to explain the nature of the study and all possible risks to potential participants,

Data relating to participants will be handled with great care. No data relating to named or identifiable participants will be passed on to others without the written consent of the participants concerned, unless they have already consented to such sharing of data when they agreed to take part in the study.

All participants will be informed **(a)** that they are not obliged to take part in the study, and **(b)** that they may withdraw at any time without disadvantage or having to give a reason.

(**NOTE**: Where the participant is a minor or is otherwise unable, for any reason, to give full consent on their own, references here to participants being given an explanation or information, or being asked to give their consent, are to be understood as referring to the person giving consent on their behalf. (See Q 12; also GN Pt. 3, and especially 3.6 & 3.7))

Enter your name here: STEFANIA CHIAPPINI Date 18TH FEBRUARY 2018

GROUP APPLICATION

(If you are making this application on behalf of a group of students/staff, please complete this section as well)

I confirm that I have agreement of the other members of the group to sign this declaration on their behalf

Enter your name here: Click here to enter text. Date Click here to enter a date.

DECLARATION BY SUPERVISOR (see GN 2.1.6)

I confirm that the proposed study has been appropriately vetted within the School in respect of its aims and methods; that I have discussed this application for Ethics Committee approval with the applicant and approve its submission; that I accept responsibility for guiding the applicant so as to ensure compliance with the terms of the protocol and with any applicable ethical code(s); and that if there are conditions of the approval, they have been met.

Enter your name here: FABRIZIO SCHIFANO; Date 18TH FEBRUARY 2018

Professor Fabrizio Schifano, MD, FRCPsych
Chair in Clinical Pharmacology and Therapeutics
Consultant Psychiatrist
University of Hertfordshire
Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit
School of Life and Medical Sciences
College Lane Campus
Hatfield, Herts
AL10 9AB (UK)
telephone: +44 (0)1707-286107
fax: +44 (0)1707-284506
mobile: 0039 335 6219469
email: f.schifano@herts.ac.uk

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC2: APPLICATION FOR MODIFICATION AND/OR EXTENSION TO AN EXISTING PROTOCOL APPROVAL

Please note: this form may be used to amend a study approved after January 2013. For studies approved pre-January 2013, please complete a new EC1 form for review and approval.

1 **Title of original application**:

Protocol Number:

LMS/PGR/UH/03234

Is this the first modification/extension request for this study?

X Yes **No**

If no, please include the most recent approval notification document with your application.

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2 **Protocol holder details**

Applicant name: STEFANIA CHIAPPINI

Student/Staff number : UH PhD student ID 17021041

Applicant e-mail address: stefaniachiappini9@gmail.com
c.stefania@herts.ac.uk

Work address (if appropriate):

Supervisor's name: Prof. Fabrizio Schifano

Supervisor's School & Department:
Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit
School of Life and Medical Sciences
College Lane Campus
Hatfield, Herts
AL10 9AB (UK)

Supervisor's e-mail address: f.schifano@herts.ac.uk .

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3 **Specify the nature of the modification/extension (please tick all that apply and complete Q4 & 5).**

☐ Revised title of study.

Please state amended title here

☐ Amend/extend dates

From: Click here to enter a date. To: Click here to enter a date.

☐ Additional worker(s):

Names and student/staff numbers for any additional investigators involved in this study

Click here to enter text.

☐ Change of supervisor from: Click here to enter text. to:Click here to enter text.
Please complete declaration below and give reason in Q4

Declaration by new supervisor:
I have reviewed the ethics protocol paperwork for this study and am aware of any conditions which must be adhered to.

Signed Click here to enter text.. Date: Click here to enter a date.

☐ Location of study

Detail new location here

X☐ Other

Please specify here

Our extension request is related to the molecules we wish to analyse in our study. The current protocol specifically mentions the following ones: clozapine; Z-drugs; ketamine; salbutamol and clenbuterol; selected opioids (fentanyl, oxycodone, codeine, tramadol, dihydrocodeine, pentazocine); and loperamide. However, we wish to include other substances, such as: Antipsychotics, Antidepressants, Hormones, Neurological medications , and Supplements in general.

4 **Reason for extension/modification request**
Please explain here

We think that including other molecules may improve and implement the objectives of our study. Using broad categories of drugs may be useful in order to have the possibility to easily investigate substances that by the time become abused or misused, or at least anecdotally reported as misused, and eventually compare two molecules each other, without limitations in the selection of the molecule.

5 **Hazards**

Does the modification or extension present additional hazards to the participant/investigator?

YES ☐ NO ☐**X**

If YES, please complete a new risk assessment EC5 form. Subject specific forms may also be necessary; you should therefore contact your Supervisor or School to see whether this is the case.

If you are required to complete a School risk assessment, please append this to your EC5 form. In this case the EC5 form should be used to note any risks **not** already noted on your School risk assessment. It is acceptable to state 'Included in <School> risk assessment> in the relevant spaces of the EC5 where applicable.

Signature of Applicant : Stefania Chiappini Date: 07 th Jun 2018

Support by Supervisor : Click here to enter text. Date: Click here to enter a date.

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC2: APPLICATION FOR MODIFICATION AND/OR EXTENSION TO AN EXISTING PROTOCOL APPROVAL

Please note: this form may be used to amend a study approved after January 2013. For studies approved pre-January 2013, please complete a new EC1 form for review and approval.

1 **Title of original application**: Assessing the extent and characteristics of non-medical use of a range of prescribed drugs focussing on a range of pharmacovigilance databases, including: the European Monitoring Agency (EMA) EudraVigilance (EV) Database of Adverse Drug Reactions; the UK Yellow Card Scheme; and the UK Report on Illicit Drug Reactions (RIDR).

Protocol Number:

LMS/PGR/UH/03234

Is this the first modification/extension request for this study?

No

If no, please include the most recent approval notification document with your application.

---

2 **Protocol holder details**

Applicant name: STEFANIA CHIAPPINI

Student/Staff number : UH PhD student ID 17021041

Applicant e-mail address: stefaniachiappini9@gmail.com
c.stefania@herts.ac.uk

Work address (if appropriate):

Supervisor's name: Prof. Fabrizio Schifano

Supervisor's School & Department:
Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit
School of Life and Medical Sciences
College Lane Campus
Hatfield, Herts
AL10 9AB (UK)

Supervisor's e-mail address: f.schifano@herts.ac.uk .

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3 **Specify the nature of the modification/extension (please tick all that apply and complete Q4 & 5).**

☐ Revised title of study.

Please state amended title here

☐ Amend/extend dates

From: Click here to enter a date. To: Click here to enter a date.

☐ Additional worker(s):

Names and student/staff numbers for any additional investigators involved in this study

Click here to enter text.

☐ Change of supervisor from: Click here to enter text. to:Click here to enter text.
Please complete declaration below and give reason in Q4

Declaration by new supervisor:
I have reviewed the ethics protocol paperwork for this study and am aware of any conditions which must be adhered to.

Signed Click here to enter text.. Date: Click here to enter a date.

☐ Location of study

Detail new location here

X☐ Other

Please specify here

Our extension request is related to the molecules we wish to analyse in our study. The current protocol includes broad categories of substances, such as: Antipsychotics, Antidepressants, Hormones, Neurological medications, and Supplements in general; and specifically mentions the following ones: Clozapine; Z-drugs; Ketamine; Salbutamol and Clenbuterol; Fentanyl, Oxycodone, Codeine, Tramadol, Dihydrocodeine, Pentazocine; and loperamide. We wish to include two other molecules, Promethazine and Benzydamine, due to their recent abuse reported.

4 **Reason for extension/modification request**
Please explain here

We think that including other molecules may improve and implement the objectives of our study. However, the European Medicines Agency, which allows us the access to the pharmacovigilance data, asked us to specify in the Ethics the molecules we would like to study instead of using broad categories of drugs.

5 **Hazards**

Does the modification or extension present additional hazards to the participant/investigator?

YES ☐ NO ☐**X**

If YES, please complete a new risk assessment EC5 form. Subject specific forms may also be necessary; you should therefore contact your Supervisor or School to see whether this is the case.

If you are required to complete a School risk assessment, please append this to your EC5 form. In this case the EC5 form should be used to note any risks **not** already noted on your School risk assessment. It is acceptable to state 'Included in <School> risk assessment> in the relevant spaces of the EC5 where applicable.

Signature of Applicant : Stefania Chiappini  Date: 8th March 2019

Support by Supervisors:

Fabrizio Schifano (main supervisor)  Date 8th March 2019

John Corkery (Co-supervisor) Date: 11 March 2019.