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THERAPIES

Addictovigilance

Alprazolam misuse: Analysis of French Addictovigilance Network data from 2011 to 2020*

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Summary

Objectives.- Alprazolam, a high-potency and short-acting anxiolytic benzodiazepine, is one of the most misused benzodiazepines in France. In the context of various reports on alprazolam misuse during the COVID-19 pandemic, the objective of this study was to assess alprazolam abuse potential by analyzing French addictovigilance and international data. *Methods.*- Data collected from 2011 to 2020 using the following epidemiological tools of the French Addictovigilance Network were analyzed: spontaneous reports (SRs), OPPIDUM (addiction care center data), OSIAP (falsified prescriptions), DRAMES (substance-related deaths), and chemical submission surveys. Moreover, the VigiBaseTM database was analyzed to evaluate alprazolam abuse liability worldwide. *Results.*- During the study period, 675 SRs concerning alprazolam misuse were recorded (sex ratio: ~1; median age: 39 years). The desired effects were intensification of the therapeutic anxiolytic effect, euphoric effect, and management of substance withdrawal. Alprazolam was the third and first benzodiazepine listed in OPPIDUM and OSIAP surveys. Analysis of the SR and OPPIDUM data showed a recent increase in the alprazolam-opioid combination. In DRAMES data, alprazolam was directly linked to 11 deaths (associated with opioids in 10/11). VigiBaseTM data analysis highlighted that France was the third country with the most cases of alprazolam misuse. The disproportionality analysis showed that in France, alprazolam was associated with higher risk of misuse and dependence compared with other benzodiazepines: reporting odds ratio = 1.43, (95% CI: 1.04-1.95) and = 1.97 (95% CI:1.50-2.59), respectively. *Conclusions.*- This study highlighted an increase in various signals of alprazolam abuse in France, and an increased use of the alprazolam-opioid combination that was also linked to most of the recorded alprazolam-linked deaths. These signals have been reported also in the international literature, and should be thoroughly investigated.

KEYWORDS

Alprazolam; Addictovigilance; Misuse; VigiBase™

Abbreviations

ADR: adverse drug reaction

COVID-19: coronavirus disease 2019

DRAMES: *décès en relation avec l'abus de médicaments et de substances*

FAN: French Addictovigilance Network

GABA: gamma aminobutyric acid

ICSR: Individual Case Safety Reports

MedDRA: Medical Dictionary for Regulatory Activities

OPPIDUM: *observation des produits psychotropes illicites ou détournés de leur utilisation médicamenteuse*

OSIAP: *ordonnances suspectes indicateur d'abus possible*

ROR: reporting odd ratio

SRs: spontaneous reports

UK: United Kingdom

USA: United States of America

WHO: World Health Organization

Introduction

Alprazolam is an anxiolytic benzodiazepine that interacts with specific binding sites of the gamma aminobutyric acid GABA_a receptor. Upon binding, it increases the opening frequency of chlorine channels, leading to inhibition of the central nervous system [1]. Alprazolam is a triazolobenzodiazepine, with myorelaxant, anxiolytic, sedative, hypnotic, anticonvulsant and amnesic effects, and a short half-time (9-16-hours) [2].

In Europe, it is indicated for the short-term symptomatic treatment of severe and/or disabling anxiety and also for the prevention and treatment of delirium tremens and other alcohol withdrawal manifestations. In other countries, such as the United States of America (USA) and Switzerland, a delayed alprazolam formulation is available for the management of panic disorders [3]. Alprazolam is the most consumed benzodiazepine in France [4], and the most commonly prescribed psychotropic medication in the USA [5]. Like other benzodiazepines, alprazolam has a potential for abuse and dependence (i.e. high misuse risk [6] and more toxicity in overdose situations). Moreover, alprazolam causes more severe withdrawal symptoms than other benzodiazepines [7]. Recent data collected during the coronavirus disease 2019 (COVID-19) lockdown (from 17th March 2020 to 10th May 2020) highlighted an increase in benzodiazepine abuse and misuse reported to the French Addictovigilance Network (FAN), particularly alprazolam, clonazepam, and oxazepam [8].

Therefore, the aim of this study was to characterize alprazolam abuse/misuse in France, by analyzing FAN and international data.

Methods

The FAN includes 13 centers, spread throughout France. The FAN was created in 1990 under the supervision of the French health authorities. Its main objectives are i) to monitor, assess, and prevent the risks linked to the consumption of psychoactive substances with abuse potential, and ii) to provide information on the addiction risk to healthcare professionals and advice for public health decision-making [9, 10]. The FAN relies on several epidemiological tools, such as spontaneous reports (SRs) by healthcare professionals or patients and specific surveys. The present study used data from different FAN sources for the period from January 1, 2011 to December 31, 2020.

Spontaneous reports (SRs)

All 13 FAN centers were asked to provide all SRs concerning cases of alprazolam misuse, abuse or dependence received during the study period. For each case, the following data were collected when available: year of report, sex, age, effect sought (misuse, abuse, dependency, use disorder, withdrawal syndrome), way of obtention, concomitant substance use (other benzodiazepines, alcohol, other drugs), medical history. SRs were classified using the following definitions:

- misuse: situations where a medicinal product is intentionally and inappropriately used not in accordance with the marketing authorization terms;
- abuse: persistent or sporadic, intentional excessive use of medicinal products that is accompanied by harmful physical or psychological effects [11];
- dependency: a condition in which the discontinuation or dose reduction leads to a withdrawal syndrome (somatic or psychiatric symptoms), or dependency was mentioned in the case narrative of the SR.

Alprazolam use disorder: according to the DSM-5, when the information available in the SR was sufficient to conclude, or it was identified by an addiction specialist in the SR.

A case was considered as serious if it resulted in: death, life-threatening situation, hospitalization (or hospitalization prolongation), significant disability or incapacity, sequelae, malformations, or birth defects (medication taken by the mother before or during pregnancy).

OPPIDUM

OPPIDUM (survey of illegal drugs and misuse of psychotropic medications) is a cross-sectional survey performed each year since 1995. It anonymously collects information on self-reported drug abuse and dependence by patients recruited in specialized care centers dedicated to drug dependence (e.g. addiction management, support and prevention centers for outpatients, hospital addiction units, treatment units for prison inmates, and harm reduction centers for drug users nationwide) [12].

OSIAP

OSIAP (suspect prescriptions as an indicator of abuse and drug dependency) is a survey to identify drugs with abuse potential by collecting and analyzing falsified prescriptions. This survey is conducted twice per year since 2001 [13].

DRAMES

DRAMES survey (deaths related to abuse of licit and illicit psychoactive substance) collects and analyzes all cases of death related to substances use since 2005. It is based on spontaneously reported toxicology analyses to identify deaths related to the misuse of psychoactive substances and the involved psychoactive substances (drugs or illicit substances), and to assess the dangerousness of the implicated molecules. Drug-related deaths are classified as directly attributed to the drug use and as indirectly attributed to drug use when caused, for example, by falls, drowning or asphyxia following the consumption of a psychoactive substance. All deaths related to alprazolam (directly and indirectly) were analyzed [14].

Chemical submission

Chemical submission survey is a prospective and permanent monitoring system set up by the French national agency in 2003 to collect and analyze all recorded cases of chemical submission with identification and dose of the substances involved. The aim of this survey is to identify the substances involved, define the contexts of the attacks, the aggressor's *modus operandi*, and assess the clinical outcome [15].

VigiBase™

In addition, data from VigiBase™, the World Health Organization (WHO) international pharmacovigilance database, were used to compare French data on alprazolam with international data. VigiBase™ includes deduplicated Individual Case Safety Reports (ICSR) of suspected adverse events reported by the 130 countries participating in the WHO Program for International

Drug Monitoring. ICSRs are anonymized reports on individuals who experienced adverse events that may be linked to the use of one or more drugs, obtained from different sources (patients, healthcare professionals, or pharmaceutical companies). They contain several information: age, sex, country of origin, year of report, reporter's qualification, drug administration route/dose, adverse events, concomitantly used substances [16].

The VigiBaseTM database is linked to medical and drug classification systems, particularly the Medical Dictionary for Regulatory Activities (MedDRA), a standardized international medical terminology to facilitate sharing regulatory information on medical products for human use [17].

VigiBaseTM was searched for two purposes: i) to identify alprazolam use disorder worldwide, by extracting all cases from January 1, 2010 to April 7, 2021 in which “alprazolam” was associated with the MedDRA high level term “substance related and addictive disorders”; and ii) to perform a disproportionality analysis on abuse and dependency of alprazolam and the other benzodiazepines by extracting all French reports that contained at least one benzodiazepine. The presence of signals of disproportionate reporting in the VigiBaseTM data was assessed by calculating the reporting odds ratio (ROR) using a contingency table. The drug of interest (alprazolam) and the event of interest (misuse or dependency) were placed on the rows and columns of the table, and the frequency of the four possible outcomes was tabulated. The ROR is defined as the ratio between the frequency at which a specific adverse drug reaction (ADR) is reported for the drug of interest (relative to all other ADRs reported for that drug) and the frequency at which the same ADR is reported for all drugs except the drug of interest relative to all ADRs reported for all drugs except the drug of interest [18]. A ROR >1 suggests that the described ADR is more commonly reported for alprazolam, relative to the other benzodiazepines.

Other data

Open Medic

This French nationwide health insurance database was analyzed to determine alprazolam consumption in France. This database allows studying the annual prescribed drug expenditures in France starting from 2014, as well as the number of boxes delivered, according to the users' characteristics, such as age group, sex, region of residence, or prescriber's specialty [19].

Results

Alprazolam use prevalence

Open Medic

Reimbursement data extracted from the Open Medic database highlighted that alprazolam was a very consumed drug in France with a stable prevalence for the 2014-2020 period: 45.8 consumers per 1,000 inhabitants in 2014 and 48.3 in 2020.

French Addictovigilance Network data

Spontaneous reports

For the period from January 1, 2011 to December 31, 2020, 675 SRs that implicated alprazolam were obtained and analyzed. Over the analysis period, an increase in the number of SRs involving alprazolam was observed but at the same time, the total number of SRs received by the FAN also increased, which means that the annual alprazolam SRs represents between 1-2% of all SRs in function of the year, without any significant change in frequency over the years.

Among these 675 SRs, 414 (61.3%) were classified as serious, and included two fatal cases. SRs concerned mainly women (51.7%) with a median age of 39 years [IQR₂₅₋₇₅: 28-49] (min-max: 13-89), and 50.7% of all SRs concerned people in the 30-49 years group. Psychiatric disorders were specified in 420 SRs and were mainly mood disorders (46.4%), anxiety disorders (24.3%) and psychotic disorders (18.1%). The other characteristics of patients are in Table 1. Of the 365 SRs for which the method of obtaining alprazolam was specified, medical and pharmaceutical nomadism was the main method of obtaining it by diversion (42.2%). The main concomitant substances for alprazolam were benzodiazepines/Z-drugs (46.3% of all concomitant substances), prescribed opioids (15.3%), alcohol (15.25%), and cannabis (12.6%). Additional data are listed in Table 2.

Alprazolam was mainly taken orally (98%), and only in 14 cases another route was mentioned (n = 9 nasal, n = 3 sublingual, and n = 2 intravenous). The daily consumed dose and the use duration were recorded in 371 SRs (mean = 4.5 mg, maximum = 40 mg) and in 240 SRs (mean = 8 years, from 1 month to >40 years), respectively.

The main effects sought were anxiolytic and recreational (complete list in Fig. 1). A subgroup analysis in function of the effect sought (anxiolytic and recreational) showed that the mean age was higher in the anxiolytic (n = 111) than in the recreational group (n = 60), (41 years vs 28 years, p <0.01). The male/female sex ratio was 0.76 in the anxiolytic group and 1.95 in the recreational group (p <0.01). Moreover, concomitant use of alcohol was reported in 28% and 45% of cases in the anxiolytic group and recreational group, respectively (p = 0.024). There was no significant difference for other substances.

According to our SR classification, dependence was found in 55% (n = 374), misuse in 44% (n = 296), and abuse in 10% (n = 69) of SRs about alprazolam. Withdrawal syndrome was reported in 24% (n = 162) of SR, with the following main symptoms: anxiety (n=37), trembling, sweating (n = 35), sleep disorder (n = 28), and convulsions (n = 17). Two cases were fatal and concerned two men (43 and 26 years of age). Death was caused by alprazolam associated with another benzodiazepine (bromazepam and zopiclone, respectively) and one opiate (methadone in both cases).

Alprazolam was associated with at least another benzodiazepine or Z-drug in 270 SRs (40%), mainly short half-life molecules, such as zolpidem (n = 105), zopiclone (n = 71), oxazepam (n = 40) and lormetazepam (n = 25), but also medium- and long half-life molecules, such as diazepam (n = 54) and bromazepam (n = 36).

Opioids, cannabis and cocaine were associated in 179, 147 and 77 SRs, respectively (Table 2). Moreover, 46 patients consumed alprazolam with cocaine and cannabis. The evolution of consumption of cannabis, cocaine and opioids in association with alprazolam is reported in Fig. 2. SRs on the combined use of alprazolam and opioids (mostly codeine, buprenorphine, methadone and tramadol) increased by more than 10% from 2018 to 2020 (Fig. 2 and Fig. 3).

Alprazolam misuse in <18-year-old people

Thirty-three SRs concerned 13-17-year-old individuals (n = 12 girls, n = 20 boys, one unknown). Most of these cases (n = 30) occurred between 2018 and 2020 (n = 14 in 2018, n = 8 in 2019, and n = 8 in 2020).

The effects sought were recreational (n = 13 SRs) and anxiolytic (n = 6 SRs). In the six SRs that reported the sought anxiolytic effect, this was associated with help to reduce cannabis (n = 1),

replace cannabis (n = 1) and potentiate cannabis effects (n = 1). The effect sought was not specified in 14 SRs. In one case, alprazolam was consumed in the context of “purple drank” (i.e. a mixture of codeine, sedative medication, and soda). Alcohol was associated in 36.4% of these SRs (n = 12).

In the rare case where the information was available, alprazolam was bought in the street (n = 2), taken from the family (n = 2), stolen (n = 1), or obtained using a falsified prescription (n = 1).

Associated substances were cannabis (n = 17 SRs), opioids (n = 9 SRs; n = 4 codeine, n = 4 tramadol, n = 1 morphine), another benzodiazepine (n = 5 SRs), cocaine (n = 3 SRs), ketamine (n = 1 SR) and ecstasy (n = 1 SR). In 12% of these SRs (n = 4), intake was through the nasal route.

Data from FAN surveys

OPPIDUM surveys

The OPPIDUM surveys for the 2011-2020 period included 50,371 patients (Table 3). Among them, 1,071 (2.1%) used alprazolam. They were mostly men (66.6%) with a mean age of 38.9 ± 9.4 years. Moreover, 640 alprazolam users (59.75%) were in a precarious situation.

Alprazolam was the third most cited benzodiazepine in the OPPIDUM surveys, after diazepam and oxazepam, and its use has been increasing since 2016.

Polydrug use was reported by 96.5% of alprazolam users, tobacco consumption by 91.3%, and alcohol dependence by 25.1%.

Alprazolam was mainly obtained with medical prescriptions (89% of alprazolam users), from multiple prescribers (4.3%). It was illegally obtained by 11% of alprazolam users.

In 2020, 45.9% of patients were alprazolam-dependent and 85.6% reported a daily intake.

The use of opioids in alprazolam users increased from 6.7% in 2019 to 9% in 2020.

OSIAP surveys

During the study period (2011-2020), among the 12,902 falsified prescriptions collected by the FAN, 1,066 (8.3%) concerned alprazolam. This rate remained stable over the years. The mean age of individuals who used false prescriptions was 37.2 ± 13.3 years [15-82] and their male/female sex ratio was 1. Their age has been becoming younger in the last few years (Fig. 4).

Alprazolam was the first benzodiazepine cited in the OSIAP surveys (before bromazepam, diazepam and oxazepam) for the whole study period. In 2020, alprazolam was the fifth most cited drug in the OSIAP survey (seventh in 2019) after pregabalin, codeine, acetaminophen, and tramadol.

The main concomitantly used drugs were zolpidem (20.5%), zopiclone (14.4%), and tramadol (5.4%).

DRAMES survey

Over the 2011-2018 period, alprazolam was implicated in 13 deaths ($n = 11$ direct and $n = 2$ indirect deaths) in DRAMES. Direct deaths ($n = 11$) concerned 8 men and 3 women, and their mean age was 35 years [20-57]. In one case, direct death was caused by alprazolam alone (consumption of 2 wafers of 0.5 mg). In the other ten cases, death was related to consumption of alprazolam in combination with opioids: methadone ($n = 3$), buprenorphine ($n = 2$), oxycodone ($n = 1$), morphine ($n = 1$) buprenorphine and tramadol ($n = 1$), methadone and morphine ($n = 1$), dihydrocodeine,

methadone and tramadol (n = 1). In addition, other psychotropic drugs (antidepressants, antipsychotics, other benzodiazepines), or cocaine or tetrahydrocannabinol were reported.

Alprazolam concentrations were considered toxic (>75 µg/L) in seven cases (range: 80-209 µg/L).

Chemical Submission surveys

Between 2011 and 2019, 33 cases of chemical submission involving alprazolam were collected. They concerned 21 women and 12 men among whom ten were <15-year-old children. In the >15-year-old group, the median age was 25 years for women [range: 16-86 years] and 24 years for men [range: 17-59 years].

In 14 cases, alprazolam was the only substance found. In 8 cases, alprazolam was combined with alcohol (n = 1), an opioid (n = 2) (buprenorphine, codeine), and with at least another benzodiazepine (n = 5) (n = 3 lorazepam, n = 1 diazepam, and n = 1 bromazepam).

In 2019, alprazolam was the first benzodiazepine cited and represented 28% of cases in which a benzodiazepine was implicated in chemical submission.

International data

VigiBaseTM

From the VigiBase™ database, 8,114 ICSRs related to alprazolam misuse worldwide were identified. They concerned 44 countries among which the most represented were the USA (6,288/8,114 reports; 77.5%), followed by Italy (686/8,114; 8.5%) and France (556/8,114; 6.8%).

The most represented age group was the 20-30 years group in the USA (28% of ICSRs), the 30-40 years group in France (25%), and the 40-50 years group in Italy (27%). The male/female sex ratio was 1.6 for the USA, 1.1 for France, and 0.4 for Italy.

Cannabis and alcohol were the substances more often concomitantly used with alprazolam in France (11.9% and 12.1% versus 2.7% and 9.1% in the USA). The combination with at least one opioid drug was recorded in 78.8% of ICSRs in the USA, 36% in France, and 2.5% in Italy.

Fatal cases represented 56.3% (n = 4,564) of all ICSRs worldwide and at least one opioid was associated in 90% (n = 4,119). Among other fatal cases, 75 concerned alprazolam alone, 91 concerned alprazolam associated with another benzodiazepine or Z-drug, and 56 cases concerned alprazolam associated with cocaine.

In France, 4.1% of cases were fatal (n = 23/556) and concerned mostly alprazolam associated with opioids (n = 21) (mainly methadone, buprenorphine and tramadol). Two cases concerned alprazolam associated with another benzodiazepine (or z-drug). Conversely, in the USA, 71.5% of the cases were fatal (n = 4497/6288), and in 90% of them (n = 4066) alprazolam was combined with opioids (mostly oxycodone, hydrocodone, fentanyl and heroin). In addition, 67 fatal cases involved alprazolam alone, and 110 alprazolam associated with another benzodiazepine (or Z-drug).

The analysis of disproportionality performed using the VigiBase™ data for alprazolam versus all the other benzodiazepines in France gave a ROR of 1.43 (95% CI: 1.04-1.95) for misuse/abuse, and a ROR of 1.97 (95% CI:1.50-2.59) for dependency.

Discussion

Our analysis of data from different FAN tools showed that alprazolam misuse/abuse is widely reported in France and that it mainly concerns young adults. It also confirmed its high abuse potential, which is worrying because alprazolam is the most frequently prescribed benzodiazepine in France. To our knowledge, this is the first study that evaluated alprazolam misuse using multiple (French and international) data sources over a very long period (2011 to 2020).

Sociodemographic characteristics

FAN tools allowed characterizing the age and sex of alprazolam users. Men and women appeared to be equally concerned by alprazolam misuse, particularly in the 30-50 years group. This is not the case in the USA where a younger population (20-30 years) is the most affected according to VigiBaseTM data and a 2015-2016 USA study showing the highest prevalence of past-year benzodiazepine misuse in 18-25-year-old adults [20].

Our analysis also suggests that the misusers' profile differed according to the sought effects. Users seeking an anxiolytic effect were mainly older women and those seeking a recreational effect were younger men, as previously reported [20]. These two user groups require different care approaches and are generally followed in different structures (general practitioner for people looking for an anxiolytic effect and care structures for individuals with addictive behaviors for the second group).

Analysis of SR, OPPIDUM and OSIAP data showed that alprazolam users are becoming younger. In the United Kingdom (UK), a 2017 survey found that alprazolam non-medical use is becoming more common among young adults [21]. Moreover, a 2017-2018 UK statistic summary

on <18-year-old people treated for substance abuse revealed that the number of young people with benzodiazepine use problems nearly doubled from the previous year. Alprazolam was the benzodiazepine with the largest increase [22]. In our SR analysis, the percentage of <18-year-old alprazolam users started to increase from 2018, often in a context of polydrug use. A study in the USA on benzodiazepine exposure found that the percentage of concerned young people increased 54% between 2000 and 2015. The prevalence of co-ingestion of multiple drugs also increased, especially in children ages 12 to 18 years. Again, alprazolam was one of the main identified benzodiazepines [23].

More research is needed to fully understand the motivations for alprazolam misuse, particularly in <18-year-old people and to monitor changes in their behavior. The increase in alprazolam consumption among <18-year-old people is a signal that should not be overlooked.

Psychiatric disorder and substance abuse history

A large proportion of alprazolam users reported psychiatric disorders. It has been suggested that patients with psychiatric disorders might be more vulnerable to the risk of psychoactive substance misuse [24]. The frequent association of alprazolam misuse/abuse with psychiatric disorders could also be explained by an indication bias because this drug is indicated for the treatment of anxiety disorders that were frequently reported by our study population. In SRs, the anxiolytic effect was the main effect sought by alprazolam misusers.

History of psychoactive substance use (particularly alcohol, opiates, or other benzodiazepines) was reported by 40% of patients. Alprazolam was used alone in only 26% of cases, and the most associated substances were alcohol, other benzodiazepines (or Z-drugs), opioids, cannabis, and cocaine. Although the first desired effect of alprazolam misuse was anxiety

reduction, the search for a “high” effect in recreational users also was common. It has been reported that alprazolam potentiates the effect of opiates [25, 26]. Some authors suggested that individuals with history of alcohol or opiate abuse prefer alprazolam to other benzodiazepines because they find it more rewarding [27, 28]. Alprazolam was also used to manage withdrawal symptoms from other psychoactive substances (e.g. opiates) [29], and also the negative effects associated with the “comedown” after cocaine intake [30].

The links between anxiety disorders, substance use disorders, and benzodiazepine abuse could be better assessed in the context of a comprehensive and integrated care pathway.

Misuse criteria

Unusual routes of administration (mainly via the nasal route) were reported in <2% of cases in our study, particularly by young individuals (<30 years of age). In a study on drug misuse in young people, 43% of patients reported having already sniffed an anxiolytic drug [31].

Alprazolam was the most frequently reported benzodiazepine acquired using a false prescription. Medical nomadism also was frequent. These findings highlight the urgent need of increasing the healthcare providers’ awareness of the misuse risks through multiple prescriptions (“*doctor shopping*”). This practice has been evaluated in France for psychoactive drugs as part of the MEGADOSE study. Alprazolam was the fifth most obtained psychoactive drug by *doctor shopping* and was the second benzodiazepine, after oxazepam [32]. Similarly, analysis of the OSIAP data indicated that alprazolam was the first benzodiazepine cited. Medical nomadism is common worldwide; *doctor shopping* is identified as one of the primary means of prescription medication diversion in many countries. This allows obtaining higher doses and has been linked to substance disorder-related deaths [33-35]. It could also be a significant factor in the supply of prescription drugs on the black market.

Therefore, the surveillance systems to monitor this practice and raise the healthcare professionals' awareness must be improved because prescription drug abuse is almost surpassing the use of illicit drugs in the USA and other countries [36], as predicted by The International Narcotics Control Board [33].

Alprazolam use disorder and dependence

Our results underline the significant risk of alprazolam dependence and abuse. Indeed, alprazolam dependence was identified for 55% of the individuals included in the SRs and 45.9% of the individuals included in the OPPIDUM surveys. Moreover, the disproportionality analysis showed that in France, alprazolam was associated with a risk of dependence twice as high compared with other benzodiazepines. Alprazolam pharmacokinetic and pharmacodynamic properties can partly explain this misuse potential. Its rapid absorption, low lipophilicity, and short elimination half-life induce a rapid, but brief effect, leading the user to re-consume alprazolam. Moreover, alprazolam displays high potency and more severe withdrawal symptoms, even after a short period of use [37]. Alprazolam also induces a significant increase in extracellular dopamine concentration in the striatum, and also in serotonin levels [37, 38].

Association of alprazolam with opioids

Many FAN tools highlighted an increase in the concomitant use of opioids and alprazolam, with frequent serious and lethal cases. Analysis of the VigibaseTM, SR and DRAMES data showed that in France, most cases involved an opioid/alprazolam combination, although few were fatal. This

risk excess has been reviewed in many studies, and could be explained by the fact that both benzodiazepines and opioids cause central nervous system depression [39-40]. In addition, an Australian study found that intoxication with alprazolam was specifically associated with more frequent invasive ventilation use and coma [7].

In VigiBaseTM, the majority of alprazolam misuse cases from the USA was fatal and mostly involved also an opioid. Co-prescription of an opioid with a benzodiazepine increased by 41% from 2002 to 2014, and this association contributed significantly to the overall risk of opioid overdose in the population [41-42]. This high rate of fatal cases in the USA could be explained by the more frequent association with opiates, in a country in the middle of an opioid crisis [43-44]. In France, SR analysis revealed the increase in the use of opioids associated with alprazolam from 2018 to 2020. Extreme caution is warranted due to the high risk of this concomitant use.

A cohort study based on French and UK healthcare data showed an excess risk of death associated with benzodiazepines over a 12-month period. These results stress the benzodiazepine dangerousness linked to their pharmacological mechanism, and suggest a higher mortality risk in case of benzodiazepine abuse [45]. More than half of patients in the French cohort were exposed to alprazolam (55%).

Strengths and limitations

The major strength of this study is the use of different tools to thoroughly assess alprazolam misuse in France for a very long period (2011 to 2020): all relevant FAN tools and the worldwide pharmacovigilance database VigiBaseTM.

It has also some limitations. Like for all studies relying on spontaneous notifications, underreporting and limited information are the main limitations of the analysis of SR and

VigiBase™ data. The OPPIDUM survey is based on the willingness of healthcare facilities to perform them and concern a specific user population. Therefore, they cannot provide an exhaustive description of alprazolam consumption in France. Similarly, the OSIAP survey is based on the dispensing pharmacists' willingness and is done only twice per year; therefore, it is not exhaustive. The main limitation of the DRAMES survey is that it is based on the expert toxicologist's willingness to report the cases and therefore, it does not provide an complete description of all alprazolam-related deaths in France. Furthermore, only the judicial authorities can decide to carry out toxicological investigations.

Given the many different data sources, the collected data were heterogeneous in terms of information collected, completeness, and information fidelity among tools.

Conclusion

Alprazolam is a widely misused benzodiazepine, with serious adverse effects and a significant risk of dependence. The real incidence of alprazolam misuse is probably underestimated. Healthcare providers must be aware of the risk of its association with opiates, potentially leading to lethal overdoses. Its prescription and dispensing must be properly regulated because alprazolam is frequently obtained using falsified prescriptions and medical and pharmaceutical nomadism.

Preventive actions also must be put in place, particularly specific training of healthcare professionals to make them aware of the risks of dependence and misuse linked to benzodiazepines, and to allow them to direct the patient towards the most appropriate treatment center.

Disclosure of interest

The authors report no conflict of interests.

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Table 1. Characteristics of the patients with alprazolam misuse in spontaneous reports (n = 675)

Characteristic	N (%)
Male to female sex ratio (n = 673)	0.93
Age	
<20 years	66 (10.2%)
20-29 years	112 (17.3%)
30-39 years	154 (23.8%)
40-49 years	174 (26.9%)
50-59 years	87 (13.4%)
≥60 years	54 (8.3%)
Alprazolam indication (n = 82)	
Anxiety	62 (75.6%)
Depression	10 (12.2%)
Sleep disorder	4 (4.9%)
Alcohol dependence treatment	2 (2.4%)
Agoraphobia	2 (2.4%)
Restless legs syndrome	1 (1.2%)
Sadness	1 (1.2%)
History of substance use (n = 435)	
Alcohol	136 (30.3%)
Opioids	120 (26.7%)
Benzodiazepines	90 (20.0%)
Stimulant substances	61 (13.6%)
Z-drugs	28 (6.2%)

Psychiatric disorders (n = 420)

Mood disorder	195 (46.4%)
Anxiety disorder	102 (24.3%)
Psychotic disorder	76 (18.1%)
Eating disorder	22 (5.2%)
Sleep disorder	8 (1.9%)
Obsessive-compulsive disorder	5 (1.2%)
Other (agoraphobia, acute delusions, behavioral disorder, social phobia, cognitive disorders)	12 (2.9%)

Table 2. Characteristics of alprazolam misuse in spontaneous reports.

Characteristic	N
Method to obtain alprazolam (n = 365)	
Medical nomadism	134
Associated with pharmaceutical nomadism	83
Pharmaceutical nomadism	109
Prescription theft	44
Trafficking	32
Prescription forgery	17
Non-prescription	18
Taking from family	4
Internet purchase	1
Self-medication	1
Self-prescription	1
Medical nomadism with aggression of the prescriber	1
Illegal procurement without specifying	3
Theft	6
Street purchase	1
Overlapping prescriptions	11
Concomitant substances	
None	160
1 benzodiazepine	270
Opioids*	179
Alcohol	178
Z-drugs	176

Zolpidem	105
Zopiclone	71
Cannabis	147
Cocaine	77
2 benzodiazepines	76
Antidepressants**	34
3 benzodiazepines	18
Antihistamines***	12
Ecstasy/MDMA	12

**opioids are listed in Figure 3*

***antidepressants: escitalopram (n = 9 SRs), venlafaxine (n = 8 SRs), amitriptyline (n = 6 SRs), mianserin, mirtazapine, sertraline, tianeptine (n = 2 SRs/each), agomelatine, milnacipran, fluoxetine (n = 1 SR/each)*

****antihistamines: hydroxyzine (n = 5 SRs), doxylamine (n = 3 SRs), alimemazine (n = 2 SRs), oxememazine (n = 1 SR), promethazine (n = 1 SR)*

Table 3. OPPIDUM survey data on alprazolam for the 2011 to 2020 period

	Period 2011-2020	Survey 2020
Number of patients included in the survey	51442	4723
Number of patient using alprazolam, n (%)	1071 (2.1 %)	111 (2.4 %)
Polydrug users, %	1029 (96.1%)	103 (92.8%)
Patients consuming > 3 substances, %	41.2 %	39.6 %
Injecting drug users	89 (8.3%)	16 (14.4%)
Nasal drug users	188 (17.6%)	27 (24.3%)
Alprazolam route of administration, %		
Oral	1026 (99.2 %)	110 (100 %)
Intranasal	17 (1.6 %)	3 (2.7 %)
Intravenous	2 (0.2 %)	0 (0 %)
Dose higher than recommended in the SmPC n (%)	87 (11%)	13 (15.9%)
Illegal obtaining, %	177 (17.2 %)	34 (31.2 %)
Main mode of obtaining, n (%)		
Medical order	935 (90.8%)	97 (89.0 %)
Gift	28 (2.7%)	5 (4.6 %)
Doctor shopping	28 (2.7%)	2 (1.8 %)
Deal	20 (1.9%)	3 (2.8 %)
False prescription	2 (0.2%)	1 (0.9 %)
Consumption modalities, %		
Daily consumption	911 (87.2%)	96 (86.5%)
Dose increase since 6 months	213 (20.9%)	31 (27.9%)
Withdrawal symptoms	487 (48.1%)	48 (44%)
>1 year consumption	688 (70.2%)	80 (75.5%)
Concomitant use of alcohol	215 (21.0%)	32 (29.1%)
Effect, %		
Reinforcing effect	498 (48.9 %)	54 (48.6 %)
Substitutive effect	520 (51.1 %)	57 (51.4 %)
Dependence		

Alprazolam dependence, n (%)	409 (40.5 %)	50 (45.9 %)
Alcohol dependence, n (%)	266 (25.1 %)	28 (25.5%)
Concomitant substances		
Cocaine users	141 (13.2 %)	25 (22.5%)
Cannabis users	310 (28.9%)	37 (33.3%)
Heroin users	94 (8.8%)	8 (7.2%)
Buprenorphine users	299 (27.9%)	19 (17.1%)
Methadone users	488 (45.6%)	53 (47.7%)
Codeine users	21 (2%)	0 (0.0%)
Other prescribed opioids users*	52 (4.9%)	10 (9%)

*Others than codeine

OPPIDUM:survey of illegal drugs and misuse of psychotropic medications; SmPC: summary of product characteristics

Figure 1. Main effects sought by alprazolam misusers.

* To manage cocaine comedown (n = 12), opiate withdrawal (n = 2) alcohol withdrawal (n = 2), cannabis reduction (n = 1), cocaine craving (n = 1), withdrawal (without further information) (n = 10).

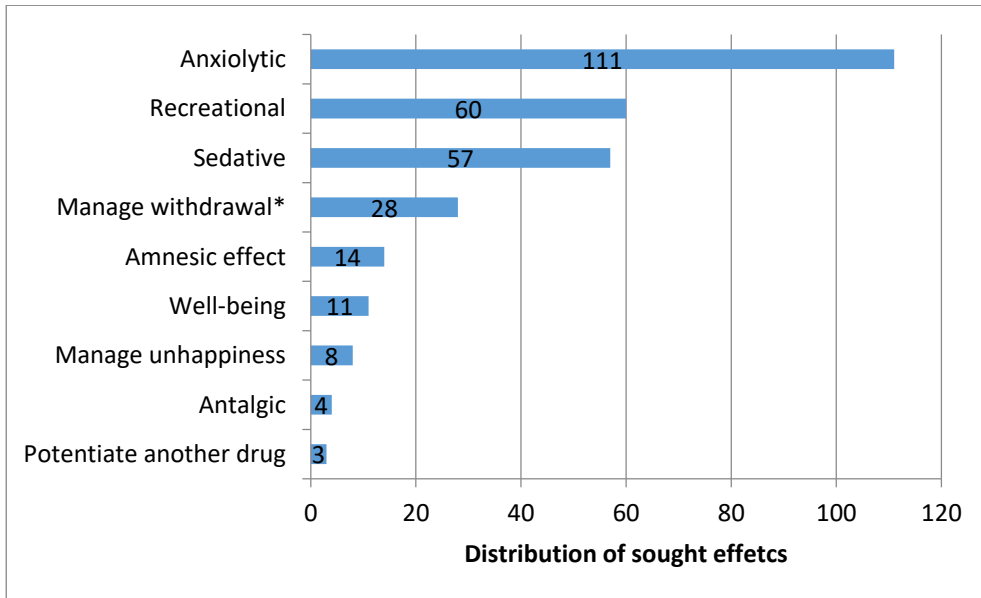


Figure 2. Percentage of spontaneous reports (SRs) per year in which alprazolam was combined with opioids, cocaine and cannabis.

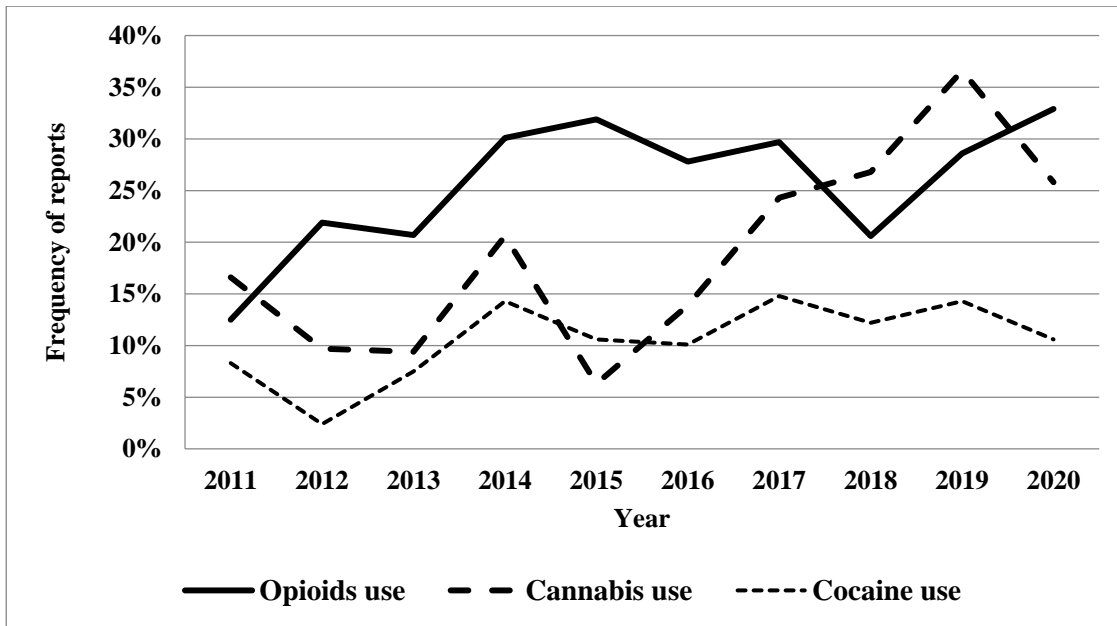


Figure 3. Main opioids associated with alprazolam use in spontaneous reports (SRs).

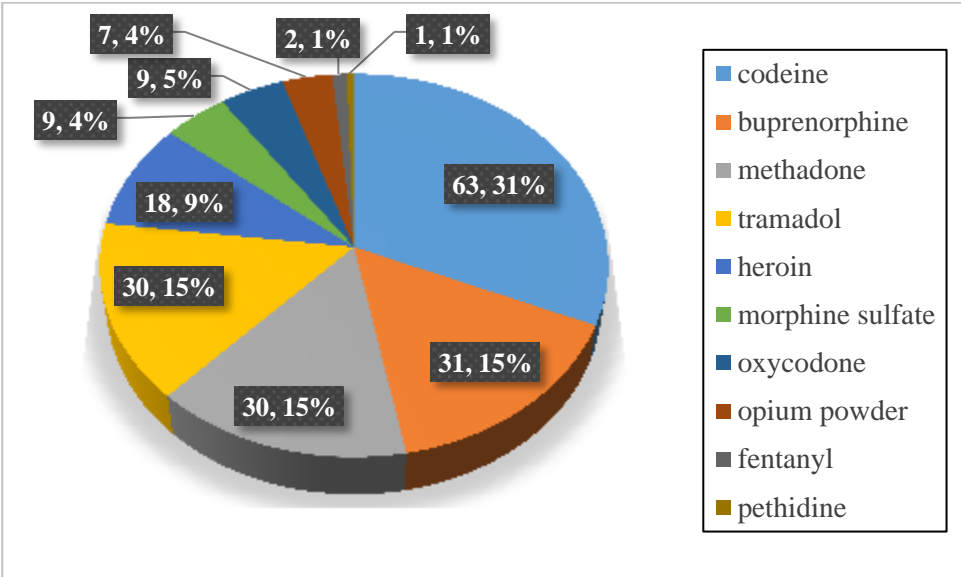
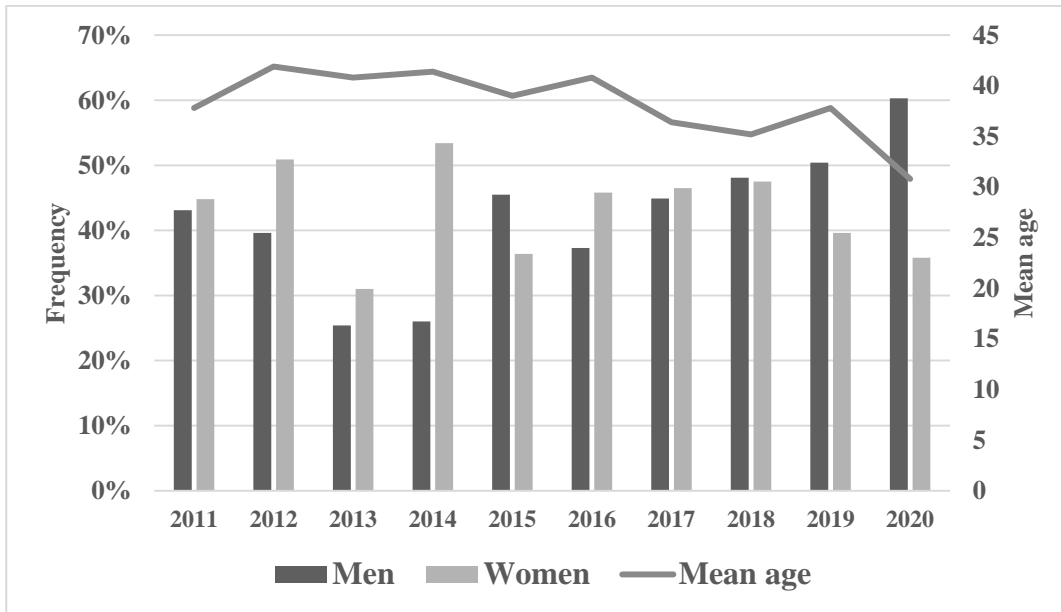


Figure 4. Age and sex changes of alprazolam users from 2011 to 2020 (OSIAP survey data).



OSIAP: suspect prescriptions as an indicator of abuse and drug dependency