PRESCRIBING PSYCHOTROPICS: MISUSE, ABUSE, DEPENDENCE, WITHDRAWAL AND ADDICTION

EDITED BY: Fabrizio Schifano, Giovanni Martinotti and Stefania Chiappini

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PRESCRIBING PSYCHOTROPICS: MISUSE, ABUSE, DEPENDENCE, WITHDRAWAL AND ADDICTION

Topic Editors:
Fabrizio Schifano, University of Hertfordshire, United Kingdom
Giovanni Martinotti, University of Studies G. d'Annunzio Chieti and Pescara, Italy
Stefania Chiappini, University of Hertfordshire, United Kingdom

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EDITORIAL
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Editorial: Prescribing Psychotropics: Misuse, Abuse, Dependence, Withdrawal and Addiction

Stefania Chiappini[1,2*†], *Fabrizio Schifano*[1†] *and Giovanni Martinotti*[1,2†]

[1] *Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom,* [2] *Department of Neuroscience, Imaging and Clinical Sciences, "G. D'Annunzio" University, Chieti, Italy*

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Editorial on the Research Topic

Prescribing Psychotropics: Misuse, Abuse, Dependence, Withdrawal, and Addiction

Over the last decade, the trend of drug consumption has changed dramatically. The advent of a high number of new psychoactive substances (NPS) has contributed to the appearance and growth of a new "drug scenario" (1, 2) characterized by an increasing number of molecules with unknown effects; poor safety profiles and acute drug toxicity presentations; and psychiatric consequences (3–6). In this context, medications' misuse appears to be an increasingly concerning phenomenon, specifically driven by the already recorded rise in the opioid use, benzodiazepines, and other Central Nervous System (CNS) depressants (including sedatives and hypnotics), and prescription stimulants, e.g., amphetamines, methamphetamines, methylphenidate (7, 8). However, a range of remaining molecules have been reported as being misused; diverted; and recorded by drug users' online websites suggesting new trends and experimentations specifically with medicinal compounds (9–11). An increasing awareness regarding these issues has been contributing to the development of pharmacovigilance studies regarding the possible potential of misuse/abuse/dependence and withdrawal of both prescription (e.g., quetiapine, gabapentinoids, olanzapine, bupropion, etc.) and over-the-counter (OTC) drugs (e.g., loperamide, dextromethorphan, promethazine, benzydamine etc.) (12–17). Indeed, pharmacovigilance studies have helped in identifying signals of misuse associated with these molecules (18). For instance, whilst both pregabalin and gabapentin are approved treatments for epilepsy and neuropathic pain disorders, with pregabalin being prescribed as well in some countries for the treatment of generalized anxiety disorder (19), they have increasingly been reported for their misusing potential, especially when used in combination with opioids and sedatives (12). In 2018, after safety warnings following an increase in deaths related to their use, the UK Advisory Council on the Misuse of Drugs (ACMD) recommended that both had to be controlled under the Misuse of Drugs Act 1971 as Class C substances and scheduled under the Misuse of Drugs Regulations 2001 as Schedule 3, so as not to preclude legitimate use on prescription (20). Conversely, a range of factors are thought to contribute to the non-medical use of prescription/OTC drugs, such as the perception of these molecules being more socially acceptable/less stigmatizing; likely lack of detection in standard drug screens; and safer than remaining illicit substances as well. "Pharming"; "pharm-parties"; and "doctor-shopping" attitudes, involving high-/mega-dosage prescription drugs' intake, are trends which are increasingly being reported among young adult populations (9, 21, 22). In parallel with this, increasing levels of access to the web over the past 15 years or so may have boosted the current scenario of prescribed drugs' misuse and abuse, with social networks playing

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Yasser Khazaal,
University of Lausanne, Switzerland

***Correspondence:**
Stefania Chiappini
stefaniachiappini9@gmail.com

†These authors have contributed equally to this work and share first authorship

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a role in medications' aggressive marketing/distribution from rogue "pharmacy" websites (10, 23–25). Moreover, the web has been contributing to the diffusion of new synthetic compounds, such as designer benzodiazepines and illicit fentanyl analogs, which are associated with a high abuse potential and severe adverse effects including coma and death (26–28). Finally, since the beginning of 2020, due to drug shortage issues resulting to the COVID-19 pandemic, a shift in misusing behavior relating to both prescription and OTC medicines has been recorded (10, 13, 29–33).

Consistent with these issues, the current Research Topic has focussed on the assessment of the misuse, abuse, dependence, withdrawal, diversion, and addiction potential of prescribing and OTC drugs. A range of original research papers, systematic reviews, meta-analysis, reviews, and case reports are here made available. This Research Topic will hopefully shed further light on the harms associated with medications' misuse and abuse, highlighting the importance of this field for clinicians; prescribers; and health professionals in general. Indeed, 13 original articles of excellent quality and likely broad impact are here offered to the Frontiers in Psychiatry readers. A description of prescription drugs' misuse in "clubbers" and disco goers in Ibiza showed that current trends of such phenomenon may not be limited to subjects with psychiatric disorders, as prescription drugs may be used an alternative to classic and novel psychoactive compounds and/or may be used to tamper and self-medicate the effects determined by the use of substances. Considering prescription drugs misused, the diversion of the benzodiazepine etizolam was here recorded, being characterized by high-dosage intake and resulting dependence issues; also, the misuse and diversion of several OTCs, including antihistamines (e.g., diphenhydramine, promethazine, chlorpheniramine, and dimenhydrinate); dextromethorphan- and codeine-based cough medicines; and the nasal decongestant pseudoephedrine have here been reported. Furthermore, a few surveys are here being collected; the first one is a European survey investigating psychiatry trainees' attitudes, knowledge and training in addiction psychiatry, while a second paper evaluated the German addiction medicine physicians' knowledge of both health and psychosocial harms of 33 psychoactive substances, including opioids and non-opioid prescription analgesics, e.g., gabapentinoids. Finally, using data from the RADARS® survey on the non-medical use of prescription drugs conducted in five European countries, the non-medical use of gabapentinoids resulted to have the highest prevalence in Germany and UK compared with Spain, Italy, and France. Data related to gabapentinoids as recorded by the French Addictovigilance Network confirmed the importance of pharmacovigilance monitoring for gabapentinoids due to their abuse potential and their related health harms, including hospitalization for serious neurologic, psychiatric or cardiac effects; requests for specific support; and deaths. Similarly, the analysis of the FDA Adverse Event Reporting System (FAERS) database, using big data search analytics as a supplementary tool to detect drug abuse-related safety signals, supported these issues. In parallel, within a multidimensional monitoring of prescription drug abuse, the early detection and quantification of "doctor shopping" practices may well need to be considered essential. Moreover, the identification of specific personality traits (e.g., hopelessness, anxiety sensitivity, sensation seeking, and impulsivity) and psychometric indicators (e.g., the Severity of Dependence Scale-SDS) might be useful in providing drug abusers with personalized interventions and strategies. Finally, the treatment of drug intoxication, as in a case of kratom use disorder, and of drug withdrawal through the continuous infusion of flumazenil in the management of benzodiazepines detoxification were here described.

In conclusion, the abuse of prescription and OTC drugs has become an issue of increasing public concern across the globe (34). Whilst health services are already under unprecedented levels of strain, the current drug scenarios have further modified, in parallel with the current pandemic-related goods' and people local; national; and international restrictions of movements. At these challenging times, healthcare professionals are recommended to both be vigilant and develop strategies to ensure continuity of care for people who use drugs and people with drug use disorders, whilst preventing as well possible medicines' misuse and diversion issues (9).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Ranking the Harm of Psychoactive Drugs Including Prescription Analgesics to Users and Others–A Perspective of German Addiction Medicine Experts

Udo Bonnet[1,2], Michael Specka[2], Michael Soyka[3], Thomas Alberti[4], Stefan Bender[5], Torsten Grigoleit[6], Leopold Hermle[7], Jörg Hilger[8], Thomas Hillemacher[9,10], Thomas Kuhlmann[11], Jens Kuhn[4,12], Christian Luckhaus[13], Christel Lüdecke[14], Jens Reimer[15,16], Udo Schneider[17], Welf Schroeder[18], Markus Stuppe[19], Gerhard A. Wiesbeck[20], Norbert Wodarz[21], Heath McAnally[22,23] and Norbert Scherbaum[2]*

[1] Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, Evangelisches Krankenhaus Castrop-Rauxel, Academic Teaching Hospital of the University of Duisburg/Essen, Castrop-Rauxel, Germany, [2] Department of Psychiatry and Psychotherapy, Faculty of Medicine, Landschaftsverband Rheinland-Hospital Essen, University of Duisburg-Essen, Essen, Germany, [3] Department of Psychiatry and Psychotherapy University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany, [4] Department of Psychiatry, Psychotherapy and Psychosomatic, Johanniter Hospital Oberhausen, Oberhausen, Germany, [5] Psychiatry, Psychotherapy and Psychosomatics, Landschaftsverband Westfalen-Lippe-Hospital Marsberg, Marsberg, Germany, [6] Psychiatry and Psychotherapy, Landschaftsverband Rheinland-Hospital Langenfeld, Langenfeld, Germany, [7] Clinic for Psychiatry and Psychotherapy, Christophsbad, Göppingen, Germany, [8] Clinic for Psychiatry, Psychotherapy, Psychosomatics and Neurology, Evangelische Stiftung Tannenhof, Remscheid, Germany, [9] Department of Psychiatry, Socialpsychiatry and Psychotherapy, Hannover Medical School, Hanover, Germany, [10] Department of Psychiatry and Psychotherapy, Paracelsus Medical University, Nuremberg, Germany, [11] Clinic for Psychosomatics Bergisch-Gladbach, Bergisch Gladbach, Germany, [12] Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, [13] Division of Cognitive Neuropsychiatry and Psychiatric Preventive Medicine, Department of Psychiatry, Landschaftsverband Westfalen-Lippe University Hospital Bochum, Ruhr University Bochum, Bochum, Germany, [14] Lower Saxonian Psychiatric Hospital, Asklepios Hospital, Göttingen, Germany, [15] Center for Interdisciplinary Addiction Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [16] Health North Hospital Group Bemen, Bremen, Germany, [17] Department of Psychiatry and Psychotherapy, Ruhr-University Bochum, Campus Ostwestfalen-Lippe, Luebbecke, Germany, [18] MEDIAN Clinics Wied, Wied, Germany, [19] Department of Addiction Medicine, Helios Medical Center Schwerin, Carl-Friedrich-Flemming-Clinic, Schwerin, Germany, [20] Psychiatric Hospital, University of Basel, Basel, Switzerland, [21] Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany, [22] Northern Anesthesia & Pain Medicine, Limited Liability Company, Eagle River, AK, United States, [23] Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, WA, United States

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Edited by:
Giovanni Martinotti, University of Studies G. D'Annunzio Chieti and Pescara, Italy

Reviewed by:
Fabrizio Schifano, University of Hertfordshire, United Kingdom
Mariangela Corbo, Università Degli Studi G. D'Annunzio Chieti e Pescara, Italy
Fabio De Giorgio, Catholic University of the Sacred Heart, Piacenza, Italy

***Correspondence:**
Udo Bonnet
udo.bonnet@uni-due.de

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Background: Over the past 15 years, comparative assessments of psychoactive substance harms to both users and others have been compiled by addiction experts. None of these rankings however have included synthetic cannabinoids or non-opioid prescription analgesics (NOAs, e.g., gabapentinoids) despite evidence of increasing recreational use. We present here an updated assessment by German addiction medicine experts, considering changing Western consumption trends–including those of NOAs.

Methods: In an initial survey, 101 German addiction medicine physicians evaluated both physical and psychosocial harms (in 5 dimensions) of 33 psychoactive substances including opioids and NOAs, to both users and others. In a second survey, 36 addiction medicine physicians estimated the relative weight of each health and social harm

dimension to determine the overall harm rank of an individual substance. We compared our ranking with the most recent European assessment from 2014.

Results: Illicit drugs such as methamphetamine, heroin, cocaine and also alcohol were judged particularly harmful, and new psychoactive drugs (cathinones, synthetic cannabinoids) were ranked among the most harmful substances. Cannabis was ranked in the midrange, on par with benzodiazepines and ketamine—somewhat more favorable compared to the last European survey. Prescribed drugs including opioids (in contrast to the USA, Canada, and Australia) were judged less harmful. NOAs were at the bottom end of the ranking.

Conclusion: In Germany, alcohol and illicit drugs (including new psychoactive substances) continue to rank among the most harmful addictive substances in contrast to prescribed agents including opioid analgesics and NOAs. Current laws are incongruent with these harm rankings. This study is the first of its kind to include comparative harm rankings of several novel abused substances, both licit/prescribed and illicit.

Keywords: gabapentinoids, psychoropic drugs use, alcohol, illicit abused substance, new psychoactive drugs

KEY POINTS

Illicit drugs such as methamphetamine, heroin, and cocaine, and also alcohol were judged particularly harmful.
Prescribed drugs including opioids (in contrast to the USA, Canada and Australia) and non-opioid analgesics including gabapentinoids were judged less harmful.
Current laws are somewhat incongruent with these harm rankings.

INTRODUCTION

Abuse of addictive psychoactive substances is characterized by negative health and social consequences not only for the user, but also for non-users in the community or society (1, 2). The DSM-5 has defined various specific substance-related dependence and addiction conditions (3), and ICD-10 coding reflects distinct mental and behavioral disorders related to alcohol, tobacco, opiates, cocaine, stimulants, hallucinogens, sedatives and hypnotics, cannabis and cannabinoids, and volatile solvents (4).

Over the past 15 years, the relative health and social harms potential of various addictive substances has been determined in England (5), the Netherlands (6), Scotland (7), France (8), and most recently in Australia (9) by medical and non-medical addiction experts. The average overall harm of various substances is usually reported in relative rankings, based upon multi-decision analyses (5, 9) or relying on "*ad-hoc*" assessments (6–8) using validated health and social dimensions (5). These rankings do not necessarily display congruence with legislative and law enforcement priorities in terms of relative regulation and control of substances, with alcohol being a prime example of dissonance between overall harms and control efforts (5–9). Nutt et al. were the first to demonstrate this incongruity (5).

In 2014, a group of 40 medical and non-medical addiction experts from 21 EU countries came to the same conclusion (10). This survey included 20 substances (10). In the interim, as in other Western countries, there have been shifting patterns of substance abuse trends as well as political framework conditions in Germany, especially

- Increasing abuse of methamphetamine mainly in regions bordering the Czech Republic (11–13).
- Increasing occurrence of new psychoactive substances (NPS), in particular a plethora of synthetic cannabinoids and stimulants (mostly cathinones) (12–14).
- Increasing fatal overdoses with heroin/morphine, opioid-containing, and non-opioid analgesics, synthetic opioids, narcotics, amphetamine, amphetamine derivatives, methamphetamine, and NPS, accompanied by a decrease in overdose deaths through opioid dependence treatment drugs such as methadone and buprenorphine (11, 15).
- Increasing availability of highly potent cannabis products with increased risk for psychosis and addiction (11, 13, 16, 17).
- Legalization of medicinal marijuana and cannabinoids for medical prescription (18).

Given these developments, we sought to update the assessment of the health and social harms from substances that are commonly misused in Germany and elsewhere and also of substances less frequently abused in our country, but already emerging (11, 12). In this context, synthetic cannabinoids (14) were included into harms rankings for the first time. We also included index surveys of harms rankings for propofol, an intravenous anesthetic (19), and some non-opioid analgesics (NOA), i.e., gabapentinoids, non-steroidal anti-inflammatory drugs (NSAIDs), flupirtine, and triptans (20–24). We decided to include NOAs together with opioid analgesics into our ratings because gabapentin and pregabalin (gabapentinoids) have recently entered the focus of addiction medicine. In the last

decade, several pharmacovigilance databases, population-based studies and case reports have warned of their potential abuse liabilities and putative contribution to fatal overdoses especially in combination with opioids (22, 23). Even though NSAIDs are commonly thought to be non-addictive, there are recent case reports (25, 26) and epidemiologic (27, 28) as well as clinical data (24) that are raising some safety concerns about this traditional view. Other NOAs have also shown potential abuse and dependence liability e.g., flurpirtine (21) or triptans (20). Therefore, we felt it prudent to include the aforementioned NOAs for the first time in a study of this kind, too. This study is the first of its kind to include comparative harm rankings of several novel abused substances, both licit/prescribed and illicit.

TABLE 1 | Participants' characteristics.

Surveys		**Cohort 1 (*n* = 101)**	**Cohort 2 (*n* = 36)**
Age (years old)	Mean (SD)	49.8 (9.6)	52.9 (6.9)
	Median	50	55
Gender	Female (*n*, %)	26 (25.7%)	10 (27.8%)
	Male (*n*, %)	75 (74.3%)	26 (72.2%)
Years of professional experience	Mean (SD)	21.6 (9.5)	24.9 (8.2)
	Median	20	26
Years of tertiary care of SUD	Mean (SD)	16.3 (8.4)	17.6 (7.4)
	Median	15	16,5
Main focus of professional work	Acute care hospital (*n*, %)	76 (75.2%)	26 (72.2%)
	Rehabilitation hospital (*n*, %)	25 (24.8%)	10 (27.8%)

METHODS

This cross-sectional questionnaire-study comprised two consecutive steps (survey 1 and survey 2, see below), in which quantitative questionnaires were distributed in written form among German addiction medicine experts. These experts were recruited at German addiction congresses and conferences. Additionally, the questionnaires were sent via email to 40 heads of German drug addiction treatment centers who were asked to distribute them in their zone of influence among other addiction medicine experts. Only those questionnaires which had been filled out by physicians who (i) were specialists, i.e., had extra expertise in at least one medical specialty and (ii) had been working longer than 5 years in tertiary care hospitals in the field of substance use disorders (SUD) treatment were included in the analysis. The experts' identity was kept anonymous with the exception of information about their age, gender, specialties, years of professional experience, years of work in tertiary care of SUD, and main focus of professional work (acute care or rehabilitation hospital) (**Table 1**).

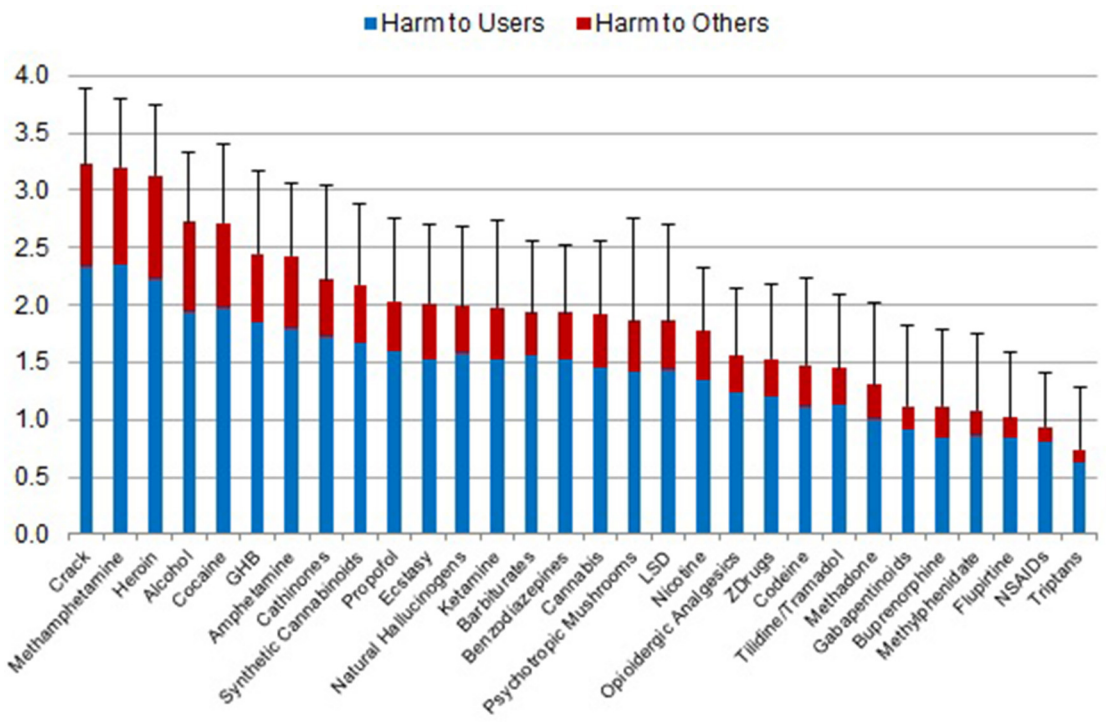

FIGURE 1 | Average overall harm of 30 substances (mean values and standard deviations) as assessed by cohort 1 on a scale from 0 ('not harmful') to 4 ('extremely harmful'), shown as harmful to users and harmful to others. The relative contribution of the 5 dimensions (**Supplemental Figure 1**, **Supplemental Table 1**) had been weighted by cohort 2.

The first survey was conducted from March 2016 to September 2017 and assessed the average harm of 33 substances in in 5 dimensions (physical harm to users, psychological harm to users, social harm to users, physical and psychological harm to others, and social harm to others). As shown in **Supplementary Figure 1**, these dimensions were defined by 16 criteria, which have been validated in several studies of this type (5, 9, 10) (see **Supplementary Materials—Methods Section**). Overall harm to users and overall harm to others comprised 3 (physical, psychological, social) dimensions and 2 (physical & psychological, social) dimensions, respectively (for details see **Supplementary Figure 1**). The assessments were carried out using 5-point scales (from "not harmful" to "extremely harmful").

The questionnaire was returned by 122 physicians and from those 101 were evaluated since 21 experts did not meet the inclusion criteria. The physicians were allowed to decide for themselves whether to rate a substance or not, and they were instructed to estimate their professional experience ("no/little" or "moderate" or "a lot") with each substance they had rated. This information was needed to assess the validity of the ratings and to verify defined exclusion criteria, i.e., a substance with <60% ratings or more than 60% "no/little experience" ratings was excluded from further analysis. Consequently, the substances ayahuasca, khat, and kratom had to be excluded from the harm-evaluation (**Supplementary Figures 2** and **3**).

The second survey (weighting of the dimensions to determine the overall harm in **Figure 1**) was conducted from September 2017 to May 2018 by cohort 2, which were recruited only from the emails to the aforementioned 40 heads of German drug addiction treatment centers. This follow-up survey was administered subsequently because the first survey was quite comprehensive, and combining the two surveys was deemed likely to overburden cohort 1 respondents, reducing the return quota. The second survey asked participants to estimate the relative weight (as a proportion between 0 and 1) of each of the 5 dimensions

TABLE 2 | Plausibility check of the overall harm ranks.

Substances/Rank in dimension	PHU	PSHU	SHU	PPHO	SHO	OH	LD−	LD+
Crack	2	2	2	1	2	1	0	1
Methamphetamine	1	1	3	3	3	2	1	1
Heroin	5	4	1	2	1	3	2	2
Alcohol	4	8	5	4	4	4	0	4
Cocaine	7	3	4	5	5	5	2	2
GHB	6	5	7	7	7	6	1	1
Amphetamines	11	6	6	6	6	7	1	4
Cathinones	9	10	10	9	8	8	0	2
Synthetic cannabinoids	13	7	9	8	11	9	−2	3
Propofol	10	18	11	13	14	10	0	8
Ecstasy	15	16	12	10	9	11	−2	5
Natural hallucinogens	8	14	18	15	17	12	−4	5
Ketamine	14	15	13	11	12	13	−2	2
Barbiturates	12	12	17	19	20	14	−2	6
Benzodiazepines	16	9	15	18	16	15	−6	3
Cannabis	21	13	8	17	10	16	−8	5
Psychotropic mushrooms	18	17	16	14	13	17	−3	5
LSD	20	11	14	16	15	18	−7	2
Nicotine	3	25	24	12	18	19	−16	6
Opioidergic Analgesics	19	19	19	23	22	20	−1	3
ZDrugs	22	20	22	22	23	21	−1	2
Codeine	23	22	20	20	19	22	−3	1
Tilidine/Tramadol	24	21	21	21	24	23	−2	1
Methadone	26	24	23	24	21	24	−3	2
Gabapentinoids	27	23	27	27	27	25	−2	2
Buprenorphine	30	27	25	25	25	26	−1	4
Methylphenidate	28	26	26	26	26	27	−1	1
Flupirtine	26	28	28	28	28	28	−2	0
NSAIDs	17	29	29	29	29	29	−12	0
Triptans	29	30	30	30	30	30	−1	0

The lower the largest difference (LD)-value the lower the variability of the 5 dimension-ranks with reference to the (individual) overall harm (OH)-rank of any substance. Discrepancies of ≥8 ranks are marked with grey horizontal background indicating considerable variability of the single dimension-ranks with reference to the individual OH-rank requiring plausible explanations. Abbreviations of the single dimensions: PHU – physical harm to users, PSHU – psychological harm to users, SHU – social harm to users, PPHO – physical & psychological harm to others, SHO – social harm to others, OH – overall harm, LD− – largest difference between OH-rank and any lower dimension-rank, LD+ – largest difference between OH-rank and any higher dimension-rank.

used in the first survey for the constitution of overall harm of psychotropic substances. All of the 36 returned questionnaires were included. We used the mean relative weight given by the 36 experts to each dimension for calculating the overall harm of each substance (**Figure 1**). Further details of the overall harm calculation of the remaining 30 substances and related data analyses including the comparison with the previous EU-ranking (**Figure 3**) are presented in the **Supplementary Materials.**

Validation of rankings was performed first by evaluating the magnitude of variability between the overall harm rating and any of the five component dimensions. A difference between the overall harm rating and any of the 5 separate ratings in the dimensions ≥8 ranks was considered significant and requires plausibility explanation (**Table 2**). An additional validation/sensitivity test was performed by substituting our survey-derived mean weights with the consensus-based weights of the previous EU-study (**Supplementary Table 1**) and comparing the resulting substance-ranks of **Supplementary Figure 9** with those of **Figure 1** (**Supplementary Table 2**).

RESULTS

Sample and Participants' Experience

The specialist physicians had worked for a median of 15 years (cohort 1) and 16.5 years (cohort 2) in the tertiary care of patients with SUD. Approximately three out of four participants worked in acute care hospitals, with the remainder working in rehabilitation clinics (**Table 1**).

Average Overall Harm

Experts' ratings in the 5 separate dimensions are shown in the (**Supplementary Figures 4–8**). Regarding overall harm, traditional drugs of abuse, i.e., cocaine (including "crack"), methamphetamine, heroin, and alcohol were ranked as being most harmful. The NPS, i.e., cathinones and synthetic cannabinoids, had subordinate positions in the top harm-level group. Ketamine, benzodiazepines, cannabis, psychotropic mushrooms, LSD, nicotine, and opioid analgesics were in the midrange. Methadone and buprenorphine (both preferred in Germany for maintenance therapy of opioid dependence) fell into the lower ranges, while methylphenidate (in Germany the preferred medication for ADHD-treatment), and NOAs were at the lowest ranges of the harm-ranking. Among the NOAs, gabapentin and pregabalin (gabapentinoids) were regarded as more harmful than flupirtine, NSAIDs and triptans (**Figure 1**).

Difference Between Acute and Rehabilitation Hospital Raters?

The assessments of the specialists from acute and rehabilitation hospitals were very similar as shown in **Figure 2**.

Comparison With the Last European Analysis

This updated German survey assessed methadone, nicotine, cannabis and alcohol as less harmful than did the EU-raters in 2014 (10), while psychotropic mushrooms, cathinones, ecstasy, GHB, methamphetamine, and crack were judged to be more harmful—see **Figure 3**.

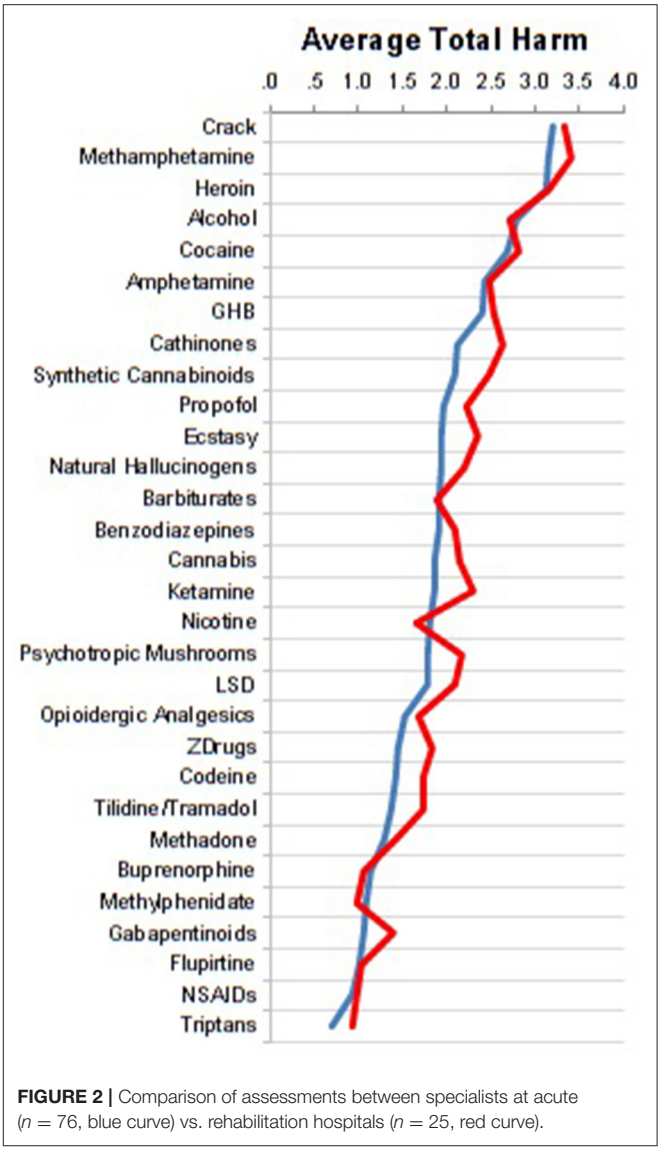

FIGURE 2 | Comparison of assessments between specialists at acute ($n = 76$, blue curve) vs. rehabilitation hospitals ($n = 25$, red curve).

Plausibility Check and Sensitivity Test

The lowest discrepancies between the average overall harm-rank and the 5 health and social dimension-ranks were found for the traditional illegal drugs crack (and other cocaine), heroin, methamphetamine, and also for alcohol, which were also ranked at the top positions in terms of harms. The same applied to GHB and NPS ranking near the top, ketamine in the midrange, opioids at lower ranges, and most NOAs (gabapentinoids, flupirtine, triptans) at the lowest ranks. Striking discrepancies were seen for propofol, cannabis, nicotine and NSAIDs (**Table 2**). In case of nicotine and NSAIDs disproportionate physical harm concerns (e.g., cancer, stroke, coronary disease, COPD for the former, and GI bleeds, renal and cardiovascular disease for the latter) likely account for most of the discrepancy for those substances.

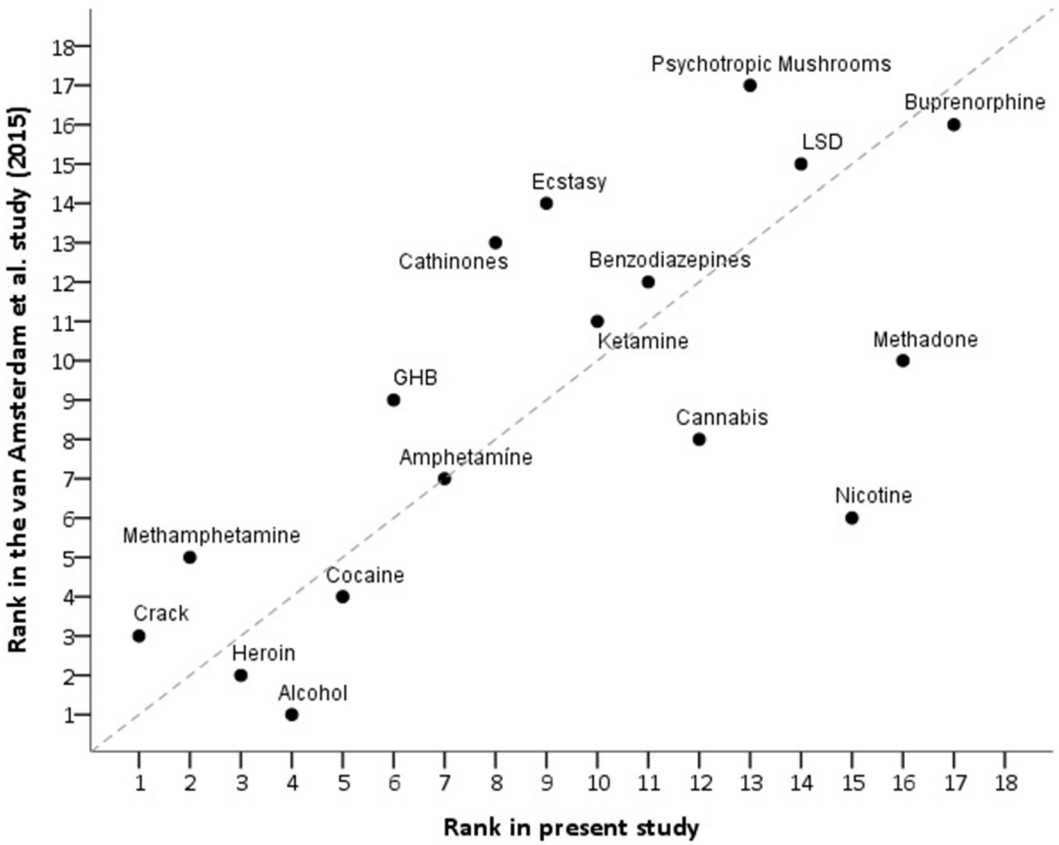

FIGURE 3 | Correlation of the present assessment and the last EU-assessment (10) of the overall harm of drugs of abuse (rs = 0.73). For better orientation, the bisector indicates perfect correlation (rs = 1).

In the case of cannabis, the German literature currently reflects a general perception of relatively low physical harms and conversely a perception of elevated psychosocial harms to users, which dichotomy serves to corroborate the discrepancy here (29–31). The discrepancy for nicotine (and perhaps also for propofol to some extent) may be owing in part to an unexpectedly low ranking of psychological harm to users which diverges from empiric evidence. This potential underestimation may therefore threaten the validity of the overall harm-ranks of these specific substances.

When alternatively, we used the consensus-based weights of the EU-rating study (10) as a comparison sensitivity test, we found that the resulting ranking of overall harms (**Supplementary Figure 9**) was very similar to our survey-derived weighted rankings shown in **Figure 1** (see **Supplementary Table 2** for comparison). This suggests that the outlier/skewed weightings of individual dimensions (**Supplementary Table 1**) do not critically influence the resulting overall harm rankings in our study.

DISCUSSION

Our data corroborate the situation in many other countries (5–10) of discordance between expert harm rankings of popular drugs of abuse and their regulation by narcotic laws, as evidenced most strikingly by the assessment of alcohol—judged to be among the most harmful substances abused in our country. The relatively high prevalence of alcohol use/abuse (compared to that of less-frequently abused but perhaps more dangerous substances) likely contributes to its dimension-specific ratings, e.g., harm to others, as well as to its overall position. Similarly, the decreasing prevalence of nicotine use in Germany (as tobacco smoking has been banned from many public areas such as hospitals, educational establishments, public transport, restaurants, pubs, and discos during the last 10 years or so) may contribute to a lower-than-expected harm ranking. In addition it should be mentioned that nicotine use, despite its ability to produce considerable behavioral dependence is hardly associated with dramatic psychiatric effects, e.g., in contrast to alcohol or hallucinogen use. This study was the first to compare the harms of various NOAs with harms of well-characterized substances of abuse, and as expected identifies the harms of NOAs to be considerably lower than those of the traditional substances of abuse. The present study was also the first to include synthetic cannabinoids and propofol in an overall-harm ranking schema, which may be beneficial for the psychoeducation of users, for regulatory considerations, or for defining fields of political action for health promotion.

NPS (cathinones and synthetic cannabinoids) have been assigned to the top harm-level group here. Policy-makers and clinicians would benefit from further data about the NPS-phenomenon, e.g., associated morbidity (32, 33) and mortality which are on the rise (33).

Compared with the EU-rating from 2014 (10), cannabis, methadone and nicotine were assessed as less harmful, while crack, methamphetamine, GHB, cathinones, ecstasy, and psychotropic mushrooms were seen as more harmful (**Figure 3**). Cannabis and hallucinogens (i.e., ketamine, psychotropic mushrooms and LSD) were considered to be on the harm level of benzodiazepines or barbiturates. It should be mentioned that psilocybin (in **Figure 1** listed as psychotropic mushrooms) and LSD have both enjoyed re-emerging therapeutic potential in psychiatric diseases and appear to show low abuse potential in that context (34).

It is interesting to note that opioid analgesics were not within the top ranks of harmful drugs. This could perhaps be related to the fact that an "opioid epidemic" (such as that in the USA, Canada and Australia), is yet not apparent in Germany or in Western Europe (35–38). The relatively low harm rankings of prescription opioids in our study stand in stark contrast to the high level of stigmatization of illicit opioids. These findings are congruent with the multi-decision analysis of nine experts (8 from the United Kingdom and 1 from the Netherlands) suggesting that the overall harms of non-medically used prescription opioids are less than half that of injected street heroin (39).

Methadone was assessed as less harmful than standard opioid analgesics, which viewpoint might be biased by addiction medicine physicians' conception of methadone primarily as a standard opioid dependence maintenance treatment, which in this context has been repeatedly shown to reduce morbidity and mortality (15). In the context of illicit use and abuse, methadone's harms (e.g., apneic and torsades-de-pointe deaths, addiction, and diversion) are obviously considerably higher than those of several other drugs ranked above it. This exposes a major limitation of drug harm-ranking studies based upon subjective assessments as they may not allow for clear differentiation between the harms of a drug with therapeutic indication in a medical context vs. illicit use/misuse outside of that context. These discrepancies in ranking of analgesics among other agents suggest that perhaps raters' experience in pain medicine should have been surveyed as well.

It cannot be excluded that our ratings may be biased toward metropolitan rather than rural perception of substance use harms; clarifying this would require further study in larger samples. Also, a possible gender influence on drug harm perceptions was not explicitly investigated here (40, 41). As we had sent out the questionnaires without tracking all recipients, requesting forwarding to other German addiction medicine experts, we are unable to provide information about the exact number of experts who finally received our questionnaires. However, such modus operandi is not unusual for studies of this kind (5). Other limitations, similar to previous studies (5–10) include the fact that the present work cannot claim to meet strict requirements for representativeness. We aimed to reduce subjectivity biases by recruiting a large and homogeneous study group (all physicians specializing in addiction medicine). However, no official statistic exists for how many specialists with more than 5 years of experience in tertiary care of SUD were working in Germany at the time of the study. We estimate that number to be somewhere between 250 and 500 physicians, thus our sample may yield a minority viewpoint. In Germany, addiction medicine experts usually are psychiatrists or general practitioners. Unlike the English (5), EU (10) and Australian (9) studies, we used no consensus–feedbacks. While this additional step may have increased the likelihood of survey participants' agreement (42), we decided against this course, because consensus-based decisions *per se* do not eliminate subjectivity (43) and there exists no "one-size-fits-all-method" for benefit-risk assessment (44). Furthermore, prior consensus-based studies utilized smaller samples comprising addiction experts from different professions (5, 9, 10), whose heterogeneity of experiences in the treatment of SUD more likely needed a consensus-based decision strategy than did our homogeneous group. Similar to the Netherlands (6), the Scottish (7), and the French research groups (8) we performed an "*ad-hoc*" assessment, using validated health and social dimensions, which have been utilized in previous (5, 10) and recent (9) empirical studies. This decision to use an "*ad-hoc*" format maximized the return of completed questionnaires.

Apart from the novel inclusion of NOAs, synthetic cannabinoids and propofol, there are a few strengths of the present study: (i) the utilization of one of the largest samples in this type of study; (ii) the considerable multidimensional addiction medicine experience of the participants, including that of rehabilitation clinic specialists (**Figure 2**), which in Germany focuses heavily upon psychosocial dimensions and outcomes; (iii) comparison with the previous EU-rating (**Figure 3**); and (iv) the addition of comparisons of illicit and licit drug rankings to the current literature.

The results of this cross-sectional questionnaire-study update the average overall harm (with component harms from various health and social dimensions) arising from use/misuse of various psychoactive substances (including prescription analgesics) from the perspective of German addiction medicine specialists. It should be emphasized however that these relative overall rankings apply to population-level risks, and depending on the individual and situational context as well as on the intensity of the individual misuse, nearly every psychoactive substance can be used in a very dangerous and harmful way.

CONCLUSION

This study provides an updated German addiction medicine expert ranking of the average overall harms as well as harms in specific health and social dimensions of various psychoactive substances, including analgesics. Alcohol was estimated to be among the most harmful addictive substances, along with heroin, cocaine, methamphetamine, GHB, and NPS (i.e., synthetic cannabinoids, cathinones). The elevated risks of alcohol are

somewhat discordant with the German narcotic law, similar to most countries. Cannabis and ketamine were ranked in midrange on par with benzodiazepines. Therapeutically used drugs such as non-opioid analgesics, methylphenidate, and opioids were estimated to be on the whole to be the least harmful at present. Such relative safety perception however is certainly subject to change should misuse and abuse patterns change over time (45).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

UB: conception and design. MSp: analysis of the data. UB and MSp: collection and interpretation of data. UB: drafting the article. All authors: revising it critically for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.592199/full#supplementary-material

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Conflict of Interest: NS has received honoraria for several activities (e.g., advisory board membership, lectures, manuscripts) from AbbVie, Camurus, Hexal, Janssen-Cilag, MSD, Medice, Mundipharma, Reckitt-Benckiser/Indivior, and Sanofi-Aventis. During the last 3 years he has participated in clinical trials financed by the pharmaceutical industry. TA has received honoraria (e.g., advisory board membership) and/or educational grants from Janssen-Cilag, Medice, and Otsuka-Lundbeck NW has received honoraria for (not product-related) lectures (Janssen-Cilag, mundipharma, and Reckitt-Benckiser/Indivior), During the last 3 years he has participated in clinical trials financed by the pharmaceutical industry and received public funding (BayStMGP) for the evaluation of Take-Home Naloxone. TH has received honoraria for several activities (e.g., advisory board membership, lectures) from Janssen-Cilag, Amomed, Shire, Takeda, Servier MSo has been working as a consultant or has Received speakers freut from Ammomed, Indivior, Camurus for the past 3 years. JR has received honoraria for participation in advisory boards, consulting and lectures from AbbVie, Camurus, Gilead, Hexal, Indivior, and Sanofi-Aventis. JK has received honoraria from Bayer, Janssen, Lundbeck, Neuraxpharm, Otsuka Pharma, Schwabe, and Servier for lecturing at conferences and financial support to travel. He has received financial support for Investigator initiated trials from Medtronic GmbH. HM is also affiliated with a private praxis (Northern Anesthesia; Pain Medicine, LLC, Eagle River, AK, USA), which has no bearing on this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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High-Dose Dependence and Cognitive Side Effects to Medical Prescription of Etizolam

Stefano Tamburin[1]*, *Elisa Mantovani*[1], *Anna Bertoldi*[2], *Angela Federico*[1], *Rebecca Casari*[2] and *Fabio Lugoboni*[2]

[1] Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, [2] Addiction Medicine Unit, Department of Medicine, Verona University Hospital, Verona, Italy

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Centre, China

***Correspondence:**
Stefano Tamburin
stefano.tamburin@univr.it
orcid.org/0000-0002-1561-2187

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Introduction: The use of novel designer drugs has increased worldwide over the years. Etizolam is a designer benzodiazepine (BZD) that has raised concern because of its growing non-medical use, liability to tolerance and dependence, and related harms. Studies exploring the abuse liability and cognitive effects of etizolam outside the therapeutic doses are lacking.

Aims: To explore the abuse liability of etizolam and the characteristics of patients affected by etizolam high-dose dependence in a nationwide tertiary referral addiction unit. To document the cognitive changes to etizolam high-dose use.

Design and Methods: Sociodemographic and clinical data on subjects with etizolam high-dose use were retrospectively collected from a database of 1,293 patients consecutively admitted to the Addiction Medicine Unit, Verona University Hospital, Italy for detoxification from high-dose BZDs or Z-drugs dependence. Thorough neuropsychological testing explored the cognitive side effects of high-dose etizolam use.

Results: We found eleven etizolam high-dose users, of which eight used etizolam only, and three used etizolam with other BZDs/zolpidem. All the patients were prescribed etizolam for medical reasons, i.e., anxiety and/or insomnia. Neuropsychological evaluation showed deficits of working memory, visuospatial memory and executive function in a 27-year-old woman who used etizolam 15 mg daily.

Discussion: Our findings suggest that abuse and dependence liability of etizolam should be considered a public health and social problem. They offer preliminary evidence on the cognitive side effects of etizolam high-dose use.

Conclusions: This report offers new information on the potential harms of etizolam in patients who are prescribed this drug for medical reasons.

Keywords: benzodiazepine, BZD, cognition, dependence, etizolam, substance use disorder (SUD), neuropsychology

INTRODUCTION

Benzodiazepines (BDZs) are gamma-amino-butyric acid type A (GABA-A) receptor positive allosteric modulators widely prescribed for anxiety, insomnia and other conditions (1).

The increasing use of novel designer BZD derivatives has been recently reported in countries, where these chemical compounds do not have marketing authorization as medicinal products (2).

Etizolam is a short-acting (half-life 5–7 h) thienodiazepine designer BZD with high affinity for the GABA-A receptor and anxiolytic and sedative properties (3). Etizolam is currently approved for therapeutic use and marketed in three countries, namely India, Italy and Japan, but available from the Internet for research purposes worldwide (4). The few available comparative studies reported that etizolam may induce less tolerance than lorazepam and may have lesser sedative effects than alprazolam and diazepam (4). The lower allosteric potency at the α1 subunit of the GABA-A receptor has been proposed as one reason for the reduced liability of etizolam to tolerance and dependence (5).

A consistent increase in the non-medical use and the illicit drug market of etizolam has been reported since 2014, being this drug implicated in several deaths in Scotland, United Kingdom, and to a lesser extent in the United States and Sweden (4, 6). A recent review concluded that few harms are documented with the therapeutic use of etizolam, being predominantly related to its non-medical use in illicitly manufactured pills and in the context of mixed-drug toxicity, in particular in combination with opioids (7). The World Health Organization Expert Committee on Drug Dependence (WHO-ECDD) considered etizolam abuse or dependence liability as an effectively public health and social problem (4). Some questions on etizolam side-effects profile are still unanswered. Evidence on etizolam safety is based on preclinical studies and case reports. Common adverse effects of etizolam include drowsiness, sedation and slurred speech, but this drug is considered generally well-tolerated in terms of cognitive side effects (4). The auditory P300 was found to be prolonged with etizolam, but this slowed brain response showed habituation, while attention and memory appeared to be unaffected by etizolam (8). Therapeutic etizolam doses (0.25–1 mg) had no effect on cognition in patients with anxiety (9) and on psychomotor performance and vigilance (10). Cognitive effects to higher doses of etizolam are still unexplored.

High-dose dependence of BZDs or related Z-drugs (e.g., zolpidem, zopiclone, eszopiclone, zaleplon), i.e., daily intake ≥5 times the recommended maximum daily dosage (1) is an emerging substance use disorder estimated to affect 0.16% of the adult population in Switzerland (11), associated to poor quality of life (12), and cognitive dysfunction (13). Data on etizolam high-dose dependence are lacking.

This report is aimed to (a) explore the liability of etizolam to abuse and the characteristics of patients affected by etizolam high-dose dependence in a nationwide tertiary referral addiction unit; (b) document the cognitive changes to etizolam in a high-dose user who underwent thorough neuropsychological evaluation.

METHODS

Subjects with high-dose etizolam were retrospectively collected from a database of 1,293 patients (650 men, 643 women) aged >18 years and admitted (January 2003–December 2019) to the Addiction Medicine Unit, Verona University Hospital, Italy, a nationwide tertiary referral center for detoxification from high-dose BZD/Z-drug dependence with slow flumazenil infusion (14).

High-dose BZD/Z-drug dependence was defined according to DSM-IV-TR criteria (15) with use lasting >6 months, daily dosage exceeding at least 5 times the recommended maximum intake (i.e., >50 mg of daily diazepam dose equivalent, DDDE), otherwise problematic use of BZD/Z-drug, such as mixing different molecules, escalating dosage, obtaining them by illegal means, and using them to enhance the effect of other substances (14).

We collected socio-demographic and clinical variables of the patients. The dosage of BZD/Z-drugs was based on self-report. DDDE (mg) was calculated according to conversion tables (14).

TABLE 1 | Sociodemographic and clinical characteristics of the patients.

Characteristics	
Sociodemographic variables	
Gender (men/women)	4/7
Age[a]	41.4 ± 7.7; 41; 27–52
Education (grade school/high school/university)	4/3/4
Employment (unemployed/employed)	3/8
Marital status (single/engaged or married)	6/5
Clinical variables	
Etizolam daily dosage	27.3 ± 29.3; 15; 5–100
Etizolam formulation (tablet/drops/both)	3/7/1
Concomitant abuse of other BZD/Z-drugs (yes/no)	3/8
DDDE (mg)[a]	272.7 ± 263.5; 150; 70–1,000
BZD/Z-drug use duration (mos)[a]	36.6 ± 26.0; 24; 10–84
Age of first BZD/Z-drug intake[a]	24.6 ± 8.3; 21; 14–37
Reason for prescription (anxiety/sleep disorders/both)	5/1/5
Poly-drug use (yes/no)	7/4
Alcohol (yes/no)	5/6
Opioids (yes/no)	1/10
Cocaine (yes/no)	2/9
Cannabinoids (yes/no)	2/9
Tobacco	5/6
Psychiatric disorders (yes/no)	9/2
Anxiety disorders (yes/no)	6/5
Major depression (yes/no)	4/7
Other psychoses (yes/no)	1/10
Personality disorders (yes/no)	2/9

[a]*Mean ± SD; median; range. BZD, benzodiazepine; DDDE, daily diazepam dose equivalent (sum of DDDEs for all BZDs and Z drugs in case of concomitant abuse of other BZD/Z-drugs); Mos, months.*

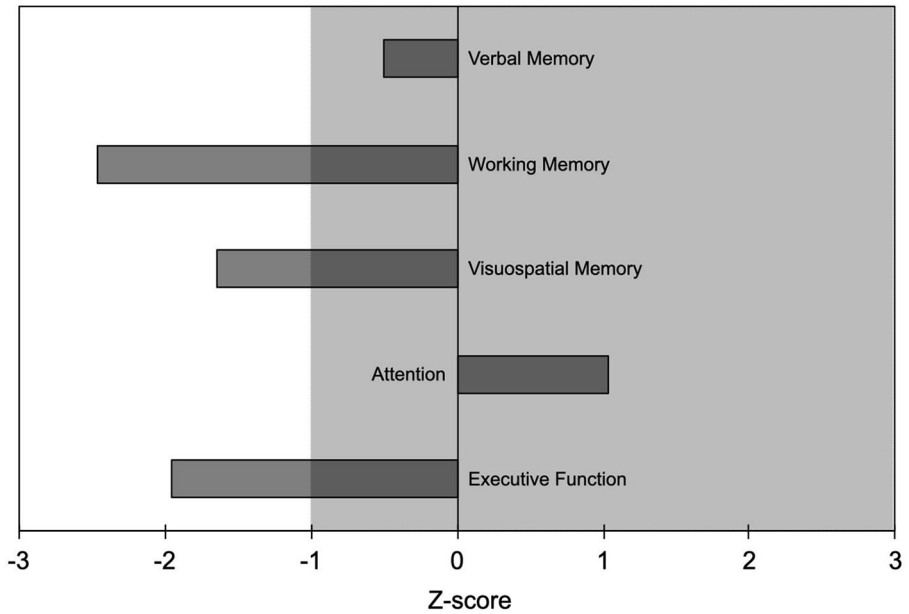

FIGURE 1 | Results of the neuropsychological evaluation from one patient (woman, age 27 years, education 8 years) who took etizolam 15 mg daily. Neuropsychological findings are reported as *Z*-scores with negative values indicating worse performance and positive values indicating better performance than the average value of the normal population. Abnormal values are worse than mean−1 SD; i.e., Z-scores <-1 indicate abnormal values. Shaded area indicates normal range of values.

The diagnosis of psychiatric disorders was based on screening tests, diagnostic interviews, and previous psychiatric assessments or evaluations, when available.

Neuropsychological evaluation explored verbal memory, working memory, visuospatial memory, attention and executive function. Verbal memory was assessed by means of the Italian versions of the Verbal Paired Association (VPA) (16) and the Digit Span Forward Test (DSFT) (17). Working memory was evaluated with the Digit Span Backward Test (DSBT) (17) and Paced Auditory Serial Addition Test (PASAT-3) (18). Visuospatial memory was explored with the 10/36 Spatial Recall Test (SPART) (18). Attention was measured with the Trail Making Test Part A (TMT-A) and the Symbol Digit Modalities Test (SDMT) (18). Executive function was evaluated by means of Trail Making Test Part B (TMT-B) (18) and the Stroop test (19). Results were standardized as Z-scores. Cognitive testing was performed 1 month before detoxification treatment.

All patients underwent a detoxification protocol with slow subcutaneous flumazenil infusion (40.5 μg/h for 24 h/day for 7 days) with a prophylactic antiepileptic treatment (14).

The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of the Verona University Hospital. All the patients gave written informed consent to the study.

RESULTS

Among the patients admitted from January 2003 to December 2019, we found 11 patients (4 men, 7 women) who used high-dose etizolam either as the only BZD (8 patients) or with other BZDs or Z-drugs (3 patients; bromazepam: 1; lorazepam and zolpidem: 1, clonazepam and triazolam: 1). All the patients were prescribed etizolam for medical use (anxiety: 5 patients; sleep disorders: 1; both reasons: 5) and obtained the drug through a prescription and a pharmacy. The number of patients was stable across years (2003–2007: 2 patients; 2008–2011: 3; 2012–2015: 4; 2016–2019: 2). Sociodemographic and clinical features of patients are reported in **Table 1**.

The remaining 1,282 patients used other BZD/Z-drugs high-doses [for further details see (12, 13)].

One patient (woman, 27 years, education 8 years; 15 mg of etizolam daily) underwent neuropsychological evaluation that showed working memory, visuospatial memory, and executive function to be outside normal values (i.e., >1 SD worse than normal controls; **Figure 1**). No medical conditions or other substance use disorder that could have contributed to the cognitive deficits were reported.

DISCUSSION

To the best of our knowledge, this is the first report of etizolam high-dose dependence in 11 patients who received etizolam for medical reasons (anxiety and/or sleep disorders). Our patients received on average 27.3 ± 29.3 mg etizolam daily, which is nearly ten times the maximum recommended daily dosage (i.e., 3 mg), with one patient taking 100 mg daily, i.e., >30 times the maximum daily dosage. These findings support the conclusion of the recent WHO-ECDD report that abuse/dependence liability of etizolam should be considered as a public health and social problem (4). They are also in keeping with individual users

reports on forums like Bluelight.org (20) and Erowid.org (21) that describe tolerance, craving and withdrawal to etizolam (7).

Etizolam high-dose users represented 0.9% of our whole sample and did not increase during the nearly 20 years covered by our large database, suggesting some concern, but stable figures across time. The big size difference between etizolam and other BZDs/Z-drugs high-dose users hampered a reasonable statistical comparison. However, when compared to high-dose users of lormetazepam, i.e., the most common BZD of high-dose use in Italy (22), etizolam high-dose users appear to be more frequently women, younger, more frequently employed, with lower DDDE, shorter BZD/Z-drug use duration, smaller age of first BZD/Z-drug intake and more frequent poly-drug use. These findings suggest that some populations of patients might be more prone to non-medical use and dependence of etizolam. In particular, they confirm the risk of etizolam harms in patients with other substance use disorders (4).

The small number of etizolam high-dose users in our large sample is likely related to the number of prescriptions in the general population. Etizolam does not stand among the ten most prescribed BZD active principles in Italy, in that its defined daily dose (DDD) in 2018 was <0.5/1,000, while that of the most commonly ones ranged from 13.2 for lormetazepam to 0.7 for flurazepam (23). The absence of data on etizolam prescription in Italian population, however, hampers the estimation of the conversion-rate from etizolam prescription to addiction.

Etizolam negatively influenced most of the cognitive domains in the patient who underwent neuropsychological testing, in particular working memory, visuospatial memory, and executive function, some of them being <2 SDs worse than normal values. This finding, despite being preliminary since stemming from a single patient, extends the notion that high doses of BZDs have an impact on cognition, even in younger patients (13, 24). BZDs cognitive side effects have been suggested to be related to the function of the GABA-A receptor α1 (responsible for anterograde amnesia) and the α5 subunits, which are involved in cognition, learning and memory (25). Based on animal studies showing etizolam lower affinity for the GABA-A receptor α1 subunit than the α5 one (5), we speculate that the cognitive effects of etizolam high-dose intake in our patient might be mainly mediated by the interaction with the α5 subunit.

The strengths of this study are that it represents the first series of etizolam high-dose users, and offers new information on the harms of this BZD derivative from a nationwide referral center in one of the few countries where it is marketed. The limitations are the retrospective design, the absence of systematic quantitative BZD measures to verify self-reported data, and neuropsychological data from a single patient that suggest caution in generalizing our findings on cognitive side effects of etizolam.

In conclusion, a small number of patients who use etizolam for therapeutic reasons appear to transition to high-dose use requiring specialist care. This report offers new information on the potential harms related to etizolam and extends them to patients who are prescribed this drug for medical reasons. Future studies should confirm our findings in larger populations and in other countries where etizolam is marketed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Verona University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ST, EM, AB, AF, RC, and FL designed the study and gathered the data. ST analyzed the data. ST, EM, AB, AF, and RC drafted the manuscript. FL and ST revised the manuscript. All authors approved the final version of the manuscript.

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Prescription Drug Misuse in "Clubbers" and Disco Goers in Ibiza

Massimo di Giannantonio[1†], Attilio Negri[2,3†], Stefania Schiavone[4], Chiara Vannini[1], Mauro Pettorruso[1], Fabio De-Giorgio[5,6], Valeria Verrastro[7], Luigia Trabace[4], Mariangela Corbo[1], Rossella Gottardo[8], Cristian Camuto[5,9], Monica Mazzarino[9], Andrea Barra[10], Domenico De Berardis[11], Juan Iglesias Lopez[12], Cristina Merino Del Villar[12], Fabrizio Schifano[13] and Giovanni Martinotti[1,13]*

[1] Department of Neuroscience, Imaging, Clinical Sciences, University G.d'Annunzio, Chieti-Pescara, Italy, [2] Department of Clinical, Pharmaceutical and Biological Sciences, School of Life & Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom, [3] Postgraduate School of Clinical Pharmacology and Toxicology, University of Milan, Milan, Italy, [4] Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy, [5] Department of Health Care Surveillance and Bioethics, Section of Legal Medicine, University Cattolica del Sacro Cuore, Rome, Italy, [6] Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [7] Department of Medical and Surgical Sciences, Magna Graecia University of Catanzaro, Catanzaro, Italy, [8] Unit of Forensic Medicine, Department of Diagnostics and Public Health, University of Verona, Verona, Italy, [9] Laboratorio Antidoping FMSI, Rome, Italy, [10] Azienda Sanitaria Locale Potenza, Potenza, Italy, [11] NHS, Department of Mental Health, Psychiatric Service for Diagnosis and Treatment, Hospital "G. Mazzini," ASL 4, Teramo, Italy, [12] Can Misses Hospital, Ibiza, Spain, [13] Psychopharmacology, Drug Misuse & Novel Psychoactive Substances Research Unit, School of Life & Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom

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***Correspondence:**
Attilio Negri
ngrttl@gmail.com

†These authors have contributed equally to this work and share first authorship

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Background: Prescription drug misuse and its related risks are considered a worldwide public health issue. Current trends show that the extent of such phenomenon may not be limited to subjects with psychiatric disorders, as it also spreads to dance party and nightclub attendees, who often consume prescription drugs in combination with alcohol and psychoactive substances. This study aims to report the sociodemographic data and the psychiatric and clinical features of a sample of clubbers reporting prescription drugs use.

Methods: Patients admitted to the psychiatry ward of the Can Misses Hospital in Ibiza were recruited for the study during a span of four consecutive years (2015–2018). The inclusion criteria were age 18–75 years old and the intake of psychoactive substances or more than five alcohol units during the previous 24 h. Substance use habits, psychopathological features, and use of unprescribed pharmaceuticals were investigated. Urine samples were collected and analyzed using gas chromatography/mass spectrometry.

Results: A total of 110 subjects with psychoactive substance intoxication were recruited for the study. Among these, 37 (40%) disclosed the use of prescription drugs without medical supervision. The most common compounds were benzodiazepines (66%), antiepileptic drugs (8%), antidepressants (6%), opioids (6%), antipsychotics (6%), stimulants (6%), and non-steroidal anti-inflammatory drugs (NSAIDs, 2%). Prescription drug misuse was negatively associated with the use of psychodysleptics (two-tailed Fisher's exact test $p = 0.018$, $\rho = -0.262$).

Conclusions: The use of prescription drugs is also common among clubbers, usually characterized by low propensity to be prescribed benzodiazepines, antipsychotics, or antidepressants. Prescription drugs may be an alternative to classic and novel

psychoactive compounds or may be used to tamper and self-medicate the effects determined by the use of substances. Party goers should be adequately informed about possible risks of co-intake of psychoactive substances and prescription drugs to prevent serious medical and psychiatric consequences.

Keywords: prescription drugs, novel psychoactive substance (NPS), club drugs, psychopathology, substance usage disorders (SUDs)

BACKGROUND

Prescription drug misuse and related risks, including co-ingestion with recreational drugs, have recently risen as a worldwide public health phenomenon. They may involve a variety of medical and social consequences that require effective public health policies to counteract such habit, as well as continuous updates for health professionals to promote education and harm reduction (1, 2). Prescription medicine misuse or non-medical use is commonly defined as the use of medications without a prescription or in a manner other than prescribed (3). This includes a number of conditions, such as using these compounds for purposes other than the medical condition they were prescribed for (i.e., recreational use or self-harm), consuming at larger doses or higher frequencies than intended, using an alternative route of administration (e.g., intravenous), or co-using with alcohol or recreational drugs (4). Studies report that the prevalence of misuse of any prescription drug in the United States increased by 67% from 1991–1992 to 2001–2002, while treatment-seeking for prescription drug use disorders increased by 53% (2). In 2017, 14 countries in EU reported on the non-medical use of such compounds (5). Among the 10,956 drug-related acute toxicity emergency room (ER) presentations in the Euro-DEN Plus dataset, approximately 29% involved at least one prescription medicine (most commonly benzodiazepines and opioids), and 45% of these involved only prescription drugs, with no illicit compounds involved (6).

Current trends show that the extent of prescription drug misuse is not limited to subjects with psychiatric disorders or co-occurring substance use disorders (SUDs). Admissions to ER and psychiatric intensive care units due to psychotropic pharmaceutical intoxications involve a heterogeneous cohort of users, including traditional drug users, "psychonauts" [from the Ancient Greek ψυχή (soul) and ναύτης (sailor), i.e., subjects who define themselves as explorers of the human soul through the use of psychoactive substances], clubbers, students, marginalized populations, and individuals with patterns of non-habitual recreational drug consumption (7). In this context, the phenomenon of co-ingesting prescription drugs in order to imitate, potentiate, modulate, or counteract the effects of prohibited psychoactive substances has been increasingly reported (8). This trend involves not only novel highly potent opioid, such as fentanyl and its derivatives, or designer benzodiazepines but also antipsychotics, antidepressants, stimulants, performance-enhancing drugs (PEDs), hormones, vitamins, beta-blockers, gabapentinoids and over-the-counter (OTC) drugs (8).

For example, students and workers may consume attention deficit hyperactivity disorder (ADHD) medications such as methylphenidate to improve their academic performance or working tasks (1). Gamma hydroxybutyrate (GHB), a drug used for many conditions, has been increasingly associated with practices such as "chemsex" (9). Furthermore, compounds such as benzodiazepines (e.g., diazepam and alprazolam) or atypical antipsychotics (e.g., quetiapine and risperidone) are often used by club goers to counteract the effects of psychostimulant drugs, such as cocaine or methylenedioxymethamphetamine (MDMA) (10, 11). Venlafaxine, a selective noradrenaline reuptake inhibitor, has been associated with recreational use at high dosages, earning for itself the name of "baby ecstasy" (i.e., MDMA) (8). With regard to the nightlife and clubbing scene, the situation shows peculiar characteristics. The growing offer of novel and traditional prescription drugs has found a fertile ground in this scenario. Summer holiday periods in popular resorts have historically represented an opportunity for excesses and experimentation, especially among young people who find an environment in which hedonistic partying is socially accepted and drugs are typically easily available (12). Alcohol use, particularly during binge drinking, and psychoactive substance use are commonly reported among festival-goers and clubbers in holiday resorts; practices such as poly-substance abuse and prescription drug misuse have also been reported (13–16). The use of a variety of pharmaceuticals including benzodiazepines (17, 18), stimulants (19, 20), opioids (21), antidepressants (8), and sedatives such as GHB (22) has been associated to dance music party attendees. Such heterogeneous cohort of compounds, presented in different forms and with various ways of intake (e.g., ingested, snorted, or intravenous), may lead to potential negative medical outcomes, including acute intoxications, SUD, and other psychiatric disorders. Nevertheless, pharmaceuticals are often perceived as less harmful and less stigmatizing than illicit drugs, particularly among young people, partly due to these substances' legitimate medical purposes (23, 24). Moreover, information on the actions of these drugs is widely available in package inserts, advertisements, and on the internet; therefore, their effects (including adverse reactions) and dosages are considered more predictable (25).

Such phenomenon is further complicated by the rise on the nightlife market of novel psychoactive substances (NPS). A number of these substances were originally developed as research chemicals and diverted for recreational purposes, as they often mimic the pharmacological effect of traditional drugs of abuse or popular prescription drugs (4). Their effects and related risks are often unknown to both users and health professionals,

due to the scarcity of evidence-based information regarding their toxicological profiles and to the ever-changing nature of this market (7, 26–28). Nevertheless, growing evidence reported potential acute and chronic psychiatric risks associated to NPS consumption, including confusion; paranoid thoughts; auditory and visual hallucinations; dissociation; delusions of reference, persecution, grandeur, and jealousy; cognitive impairment; hypomanic states; aggressiveness and irritability; violence; and suicidal thoughts (8, 29–31).

The current dynamic of recreational substance use is a serious matter of concern for public health institutions worldwide. In particular, the threats posed by psychoactive compounds and concomitant prescription drug misuse require updated policies provided by local and supranational regulatory agencies, as well as appropriate approaches by health professional, to prevent negative outcomes and reduce associated harms (32), including deaths (33). In such context, Ibiza and the Balearic Islands, two of the most popular destinations with nightlife resorts for summer holidays in Europe, may be considered as an interesting real-life scenario to explore such phenomenon. Previous studies confirmed a higher prevalence of risky behaviors for both residents and tourists in Ibiza, including problematic alcohol use, substance use, and sexual disinhibition (34–36). Moreover, it has been reported that traffickers and dealers have introduced NPS and pharmaceuticals into the Ibiza drug market to test new compounds and drug combinations on unaware customers (36).

This study aimed to assess patients admitted to the psychiatric ward of the Can Misses Hospital in Ibiza for psychoactive substance intoxication, in order to (1) identify which psychotropic prescription drugs are mostly involved in cases of concomitant psychoactive substance use and (2) report the psychopathological features and patterns of consumption associated to prescription drug use in a nightlife resort setting.

MATERIALS AND METHODS

Patients admitted to the psychiatry ward of the Can Misses Hospital in Ibiza during summer when nightclubs are open (May–October) were recruited for the study during a span of four consecutive years (2015–2018). The subjects were evaluated according to the DSM-5 diagnostic classification. The inclusion criteria were age 18–75 years old and the intake of psychoactive substances or more than five alcohol units (i.e., 10 ml or 8 g of pure alcohol) during the previous 24 h. Clinical conditions such as *delirium tremens*, epilepsy, liver encephalopathy, dementia, and other neurological diseases, severe cardiac failure, diabetes mellitus, severe liver impairment, kidney failure, or neoplastic diseases were among the exclusion criteria, as the presence of such conditions could present a confounding factor. Demographic (age, gender, family, and nationality) and socioeconomic data (living status, job status, and level of education) were collected, as well as recent and past medical and psychiatric history, current pharmacological treatment, and alcohol and substance use habits (including NPS), with a specific focus on prescription drugs misuse. Among these, recent and lifetime use of benzodiazepines (e.g., diazepam, alprazolam, and lorazepam), ADHD medications (e.g., amphetamine/dextroamphetamine and methylphenidate), and opioid painkillers (e.g., morphine, methadone, oxycodone, and fentanyl), as well as other popular prescription drugs (e.g., GHB and gabapentinoids) was investigated.

To explore the different psychopathological aspects related to substance use, such as depressive or manic symptoms, anxiety, psychosis negative and positive symptoms, somatic disorders, aggressiveness, and suicidality, the following psychodiagnostic tests were administered to patients during their hospitalization: Timeline Follow-Back (TLFB) for psychoactive substances and alcohol; Brief Psychiatric Rating Scale (BPRS); Positive and Negative Symptoms Scale (PANSS); Mania Rating Scale (MRS); Hamilton Depression Scale (HAM-D); Hamilton Anxiety Scale (HAM-A); and Modified Overt Aggression Scale (MOAS). TLFB was used to identify the main substance of abuse for each patient. The subjects were divided in three macro-groups according to the TLFB and the results of the urinalysis: psychostimulants (e.g., cocaine, amphetamines, and synthetic cathinones), depressors (e.g., opioids, alcohol, and benzodiazepines), and psychodysleptics (e.g., cannabinoids, psychedelics, and dissociatives). This classification was derived from our previous reports on the topic (7, 36).

Data collection was carried out in an anonymous and confidential way; all participants received a detailed explanation of the design of the study and a written informed consent was systematically obtained from every subject, according to the Declaration of Helsinki. Ethics approval was granted by the University of Hertfordshire Health and Human Sciences ECDA, protocol no. aPHAEC1042(03); by the CEI Illes Balears, protocol no. IB 2561/15 PI; and by the University "G. d'Annunzio" of Chieti-Pescara, no. 7/09-04-2015. Majorcan local ethics committee also gave approval to the study.

Urine Sample Analysis

A urine sample was collected at admission, stored at −30°C, and subsequently analyzed at the laboratory of the Department of Forensic Toxicology of the Università Politecnica delle Marche, at the FMSI Antidoping of Rome, and at the University of Verona, Italy. The urine samples were analyzed at the FMSI Antidoping of Rome using a routine screening test for drugs of abuse. The urine samples were extracted with a solid-phase cartridge (Oasis MCX), and the obtained solution was evaporated until dry and reconstituted with mobile phase. An Agilent 1290 Infinity II UHPLC with a binary gradient system and an automatic injector (Agilent Technologies, Cernusco sul Naviglio, Milano, Italy) was used for the chromatographic separation. The instrument was equipped with an Agilent ZORBAX Eclipse Plus C18 column (100 × 2.1 mm i.d., particle size 1.8 μm) (37). The detector was an Orbitrap Q Exactive (Thermo Fisher Scientific) with an ESI source. The method was validated according to WADA guidelines and for a screening method in antidoping test defining selectivity, limit of detection (LOD), recovery, carry over, and repeatability (38). The method showed no interference or carry over, LOD < 1 ng/ml, recovery >70%, and repeatability estimated as CV% < 1% for all the analytes.

A comprehensive screening of urine samples was performed at both the Unit of Forensic Medicine of the University of Verona and at the Politecnico of Ancona, by using a Toxtyper™ LC/IT-MS platform (Bruker Daltonics, Bremen, Germany) consisting of an ultra high performance liquid chromatography (UHPLC) coupled to a high-speed ion trap mass analyzer (IT-MS). The instrument applied the analytical protocols provided by the manufacturer, and compound identification was provided by using the Maurer/Wissenbach/Weber (MWW) library containing as many as 4,500 therapeutic, toxic/illicit drugs and their metabolites (including NPS) (39). Prior to injection, urine sample were diluted 1/10 (v/v) with water (40).

Data Analysis

Statistical analysis was performed by using IBM SPSS® Statistics software, version 20 and GraphPad 5.0 software for Windows (La Jolla, CA, USA). Fisher's exact test was used to determine whether or not there was a significant association between the categorical variables "abuse of prescription drugs" and "use of distinct categories of psychoactive substances." Spearman's correlation value (ρ) was calculated to determine if variables (abuse of prescription drugs and categories of substances) were positively or negatively correlated. Independent samples *t*-test was used to determine whether or not there was a significant difference in scale scores between subjects who abused and subjects who did not abuse prescription drugs. One-way analysis of variance (ANOVA) followed by Tukey's *post-hoc* test was used to assess whether or not there was a significant difference in scale scores among subjects who abused different classes of prescription drugs. For all tests, a two-tailed p-value <0.05 was considered statistically significant.

TABLE 1 | The most common substances used by patients who declared prescription drug misuse.

Prescription Drug	*N*	%
Benzodiazepines (e.g., diazepam and alprazolam)	32	66
NSAIDs (e.g., paracetamol)	1	2
Antidepressants (e.g., paroxetine and clomipramine)	3	6
Antipsychotics (e.g., risperidone and clotiapine)	3	6
Anticonvulsants (e.g., valproate and pregabalin)	4	8
Opioid derivatives and synthetic opioids (e.g., methadone and fentanyl)	3	6
Stimulants (e.g., methylphenidate)	3	6

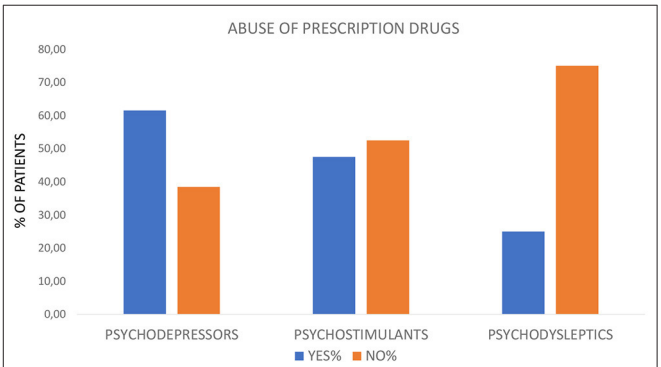

FIGURE 1 | Percentage of patients abusing (Yes%) or not abusing (No%) prescription drugs stratified for the following substance categories: psychodepressors, psychostimulants, or psychodysleptics.

RESULTS

A total of 110 subjects were recruited for the study, with most of them being of European nationality ($n = 76$, 71.8%). Age ranged from 19 to 63 years old, with the majority of patients ($n = 57$, 51.8%) under 30 years old. The median age of the 110 patients was 32.57 years. A higher percentage of males ($n = 76$, 69.1%) was reported in our sample. Nine patients were full-time or part-time students (8.1%), 52 (47.3%) were employees, and 40 (36.4%) were unemployed.

All the subjects of the sample were diagnosed with substance intoxication at admission. Although the majority of patients declared multiple substance use ($n = 77$, 70.0%) and 33% of them reported the use of more than two substance, the participants were divided in three macro-groups according to their responses to the TLFB test and their urinalysis results to identify a category of substances "of choice" for each patient. Thus, 17 (15%) depressors users, 44 (40%) stimulant users, and 49 (45%) psychodysleptics users were identified.

When asked about lifetime use of specific groups of substances, stimulant use was disclosed by 74 patients (32%) and cannabinoid use by 68 patients (29%). These were followed by depressors ($n = 32$, 14%), empathogens–entactogens ($n = 28$, 12%), dissociatives ($n = 15$, 6%), opioids ($n = 9$, 4%), and psychedelic drugs ($n = 7$, 3%). Almost half of the participants (46%) declared to have used a substance without knowing what it was at least once in their life. These results will be described in a separate manuscript (31).

In our sample, 37 patients (40%) disclosed a lifetime misuse of prescription drugs. The most commonly reported compounds were benzodiazepines, which were used by 32 subjects. **Table 1** presents the complete information on the type of pharmaceuticals reported by users.

Prescription drug misuse was reported for 8 psychodepressor (e.g., non-prescription opioids and alcohol) users, 19 psychostimulant (e.g., cocaine and amphetamines) users, and 10 psychodysleptic (e.g., cannabis and dissociatives) users. The percentage for each group of substance users is reported in **Figure 1**. Abuse of unprescribed pharmaceuticals was negatively associated with the use of psychodysleptics (two-tailed Fisher's exact test $p = 0.018$, $\rho = -0.262$).

According to their lifetime use of specific compounds, prescription drug consumption without medical supervision was reported by 31 stimulant users, 21 cannabinoid users, 10 depressor users, 7 opioid users, 7 empathogen–entactogen users, 5 dissociative users, and 1 psychedelic user.

The severity of psychiatric symptoms according to HAM-A Psychotic Anxiety scale, PANNS BPRS, and MRS was comparable among users and non-users of unprescribed pharmaceuticals. Patients who disclosed prescription drug misuse tended to report

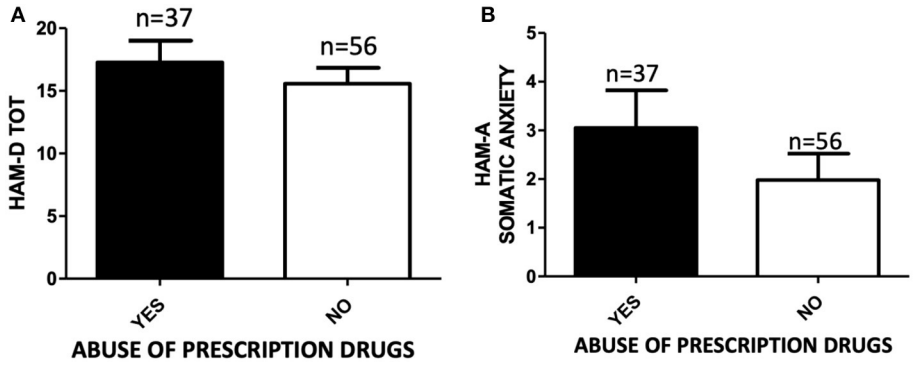

FIGURE 2 | (A) HAM-D total score of subjects abusing (YES, $n = 37$) or not abusing (NO, $n = 56$) prescription drugs. Independent samples t-test, $p > 0.05$; **(B)** HAM-A Somatic Anxiety scale score of subjects abusing (YES, $n = 37$) or not abusing (NO, $n = 56$) prescription drugs. Student's t-test, $p > 0.05$.

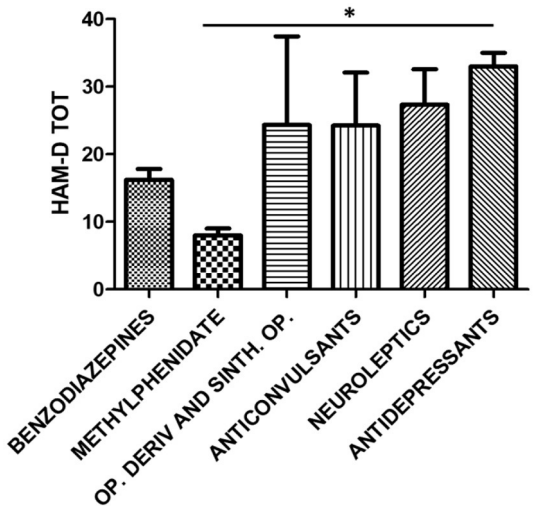

FIGURE 3 | HAM-D total score stratified for the following classes of abused prescription drugs: benzodiazepines ($n = 32$), methylphenidate ($n = 3$), opioid derivatives and synthetic opioids ($n = 3$), anticonvulsants ($n = 4$), neuroleptics ($n = 3$), and antidepressants ($n = 3$). One-way ANOVA, followed by Tukey's *post-hoc* test, $F = 3.032$, $^*p < 0.05$ methylphenidate vs antidepressants.

higher scores in HAM-D and HAM-A Somatic Anxiety, although this tendency did not reach the statistical significance (**Figure 2**).

One-way ANOVA for HAM-A total score ($F = 0.6808$, $p > 0.05$), PANNS ($F = 1.487$, $p > 0.05$), MRS ($F = 0.4402$, $p > 0.05$), and BPRS ($F = 3.094$, $p > 0.05$) did not report any statistically significant difference among users of benzodiazepines, methylphenidate, prescription opioids, anticonvulsants, antipsychotics, and antidepressants. A statistical difference was found for HAM-D scores between methylphenidate and antidepressant users (one-way ANOVA, followed by Tukey's *post-hoc* test, $F = 3.032$, $^*p < 0.05$ methylphenidate vs. antidepressants) (**Figure 3**), with higher scores of depression in the group of patients taking antidepressants.

The most common diagnosis at discharge among the patients who disclosed prescription drug use was substance or alcohol use disorder ($n = 26$, 48%), followed by schizophrenia spectrum disorders ($n = 10$, 18%) (**Figure 4**).

DISCUSSION

Our study evaluated the use of prescription drugs among a sample of clubbers, who were mainly composed of young subjects (more than 50% of the participants being aged under 30) with a medium-high socioeconomic status. Many subjects (40%) reported the use of prescription drugs. Therefore, our results show that such use is not only limited to subjects with psychiatric disorders and co-occurring SUD but can also involve subjects who are usually not considered as typical psychoactive substance users. This data pave the way for serious considerations on the possible pharmacological interactions with alcohol and other substances, as well as on other short- and long-term consequences, both physical and psychiatric. As users may concomitantly consume various prescription drugs and substances of abuse, an increased risk of drug–drug interactions may be observed, both pharmacokinetic (e.g., between prescription opioids and heroin) and pharmacodynamic (e.g., between opioids of abuse and benzodiazepines or other CNS sedative drugs) (41). This involves not only depressors, such as benzodiazepines, opioids, and alcohol, but also stimulant drugs commonly used by clubbers. For example, metabolic pathways of synthetic cathinones, antidepressants, and ADHD medications have been shown to overlap, including metabolism via cytochrome P450 enzymes and their inhibition (42).

Benzodiazepines were the most prevalent class of prescription drugs reported in our sample. This result may be explained by the use of benzodiazepines as a "trip terminator" to calm down the strong experience caused by the use of multiple substances. This confirms the data from Messina et al. (10), who showed that benzodiazepines and atypical antipsychotics are often used by club goers to counteract the effects of psychostimulant drugs, such as cocaine or MDMA. In terms of preventive strategies, the use of benzodiazepines in the context of a multiple substance use

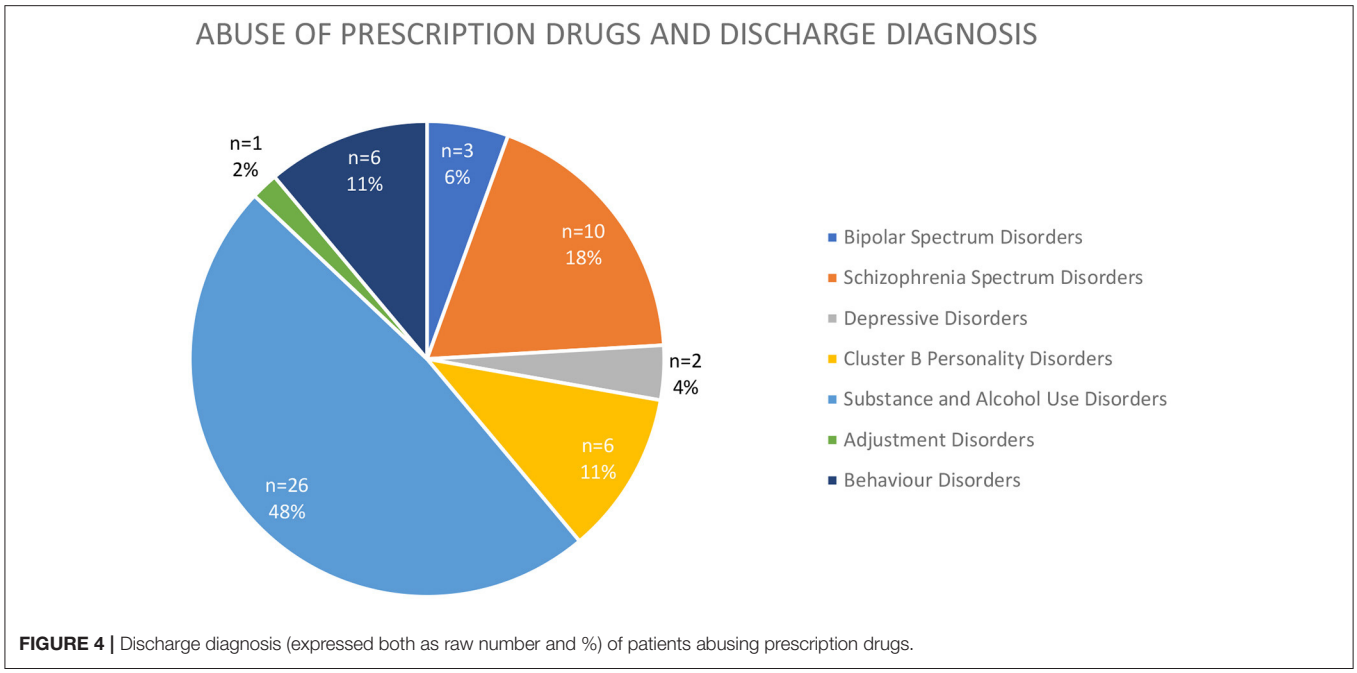

FIGURE 4 | Discharge diagnosis (expressed both as raw number and %) of patients abusing prescription drugs.

could be dangerous as it causes respiratory depression and risk of overdoses, specifically in combination with opiates, alcohol, ketamine and derivatives, and inhalants (18, 43, 44). Specific policies and harm-reduction approaches should be advised for these potentially lethal combinations, particularly with the intake of large amounts of long half-life compounds, such as diazepam. Furthermore, a number of novel designer benzodiazepines, with undisclosed toxicological profiles and variable potencies, have recently been made available in the drug market. They are developed in order to mimic prescription benzodiazepines and Z-drugs, but they may lead users to adverse events of various severities, particularly if used in combination with other substances (4, 45, 46).

Among the different categories of substances, psychodepressors were the most commonly associated with the use of prescription drugs, whereas only a small percentage of psychodysleptic users reported such habit. The typology of subject using psychodysleptics such as LSD, psilocybin, MDMA, ayahuasca, and other plants, is characterized by the search for a strong inner experience, spirituality, and high level of emotionality (47, 48). The use of benzodiazepines and antipsychotics can inhibit or temper the perception of these experiences and therefore may not be chosen by users. With regard to antidepressants, which can determine affective blunting and enhance the distance from emotional experiences, the same consideration can be reported.

Interestingly, patients who disclosed prescription drug misuse tended to report higher scores in HAM-D and HAM-A Somatic Anxiety. This finding emphasizes how those patients are the most vulnerable in terms of psychopathological load. In this regard, those who report taking prescription drugs may actually be the subjects with a psychiatric history. A prescription drug may have already been tested for therapeutic purposes and therefore may have made the patient more accustomed to its use out of indication. Moreover, the high level of depression is an issue that needs to be considered and can represent a significant suicidal risk factor in people who misuse alcohol and psychoactive substances. In fact, the use of psychotropics can represent an additional risk factor, given the possibility of a consistent increase in the levels of impulsivity, violence, and self-directed aggression due to such drugs. Therefore, it is very relevant to evaluate these patients and to put specific strategies in place to manage these psychopathological manifestations, with a specific focus on the prevention of anti-conservative behaviors.

A further point of interest, although expected, is the presence of high levels of depressive symptoms on the Hamilton scale in relation to the use of antidepressants without a specific medical prescription. This fact suggests how sometimes the use of prescription drugs may be related not only to the goal to "get high" or to the management of an intoxication but also to the self-medication need of patients who perceive a sub-leveling of their mood. For this reason, a shared strategy could be justified, even more than in other types of patients with dual disorders. Conversely, methylphenidate use was associated with lower scores at the Hamilton depression scale. This prescription drug with stimulant properties (49, 50), usually indicated for attention deficit hyperactivity disorder, can probably be chosen by users of psychostimulants as a cheaper alternative to cocaine and amphetamine. In the short run, it could also show some antidepressant properties, thus explaining the data observed at the HAM-D. The detection of methylphenidate among the prescription drugs reported in our sample may indicate some level of comorbidity between adult ADHD and SUD, as recently reported (51).

In terms of the role of the discharge psychiatric diagnosis, alcohol or substance use disorder showed a high prevalence,

although the diagnoses of schizophrenia and bipolar spectrum disorder were also significantly reported. In some cases, the presence of a psychiatric comorbidity could justify the use of prescription drugs such as antidepressants, mood stabilizers, and benzodiazepines. However, the presence of a relevant percentage of addiction diagnoses (alcohol use disorder and/or substance use disorder) further confirms that these patients do not typically represent pure psychiatric patients who increase their dosages of prescribed drugs but are instead classical party-goers who use prescription drugs for other purposes.

Limitations of this study are represented by a low and heterogeneous sample size, with a high prevalence of benzodiazepine as the main prescription drug. Moreover, although the target of the study is that of young clubbers, a significant subgroup of participants were middle-aged adults.

In conclusion, in this study, we have highlighted how the use of prescription drugs is common also among clubbers and disco-goers. These subjects usually do not have a previous psychiatric history and share a low propensity to be prescribed with benzodiazepines, antipsychotics, and antidepressants by a mental health professional. These data confirm that prescription drugs may be an alternative for classic and novel psychoactive compounds, may be used to modulate and temper the experience, and, in some cases, may be used to reduce the negative effects determined by the use of substances. From the treatment prospective and as a useful preventive strategy, a specific psycho-education process should be indicated for subjects at risk. Party-goers should be adequately informed about the possible risks of co-intake of NPS, classical substances, and prescription drugs to prevent serious medical and psychiatric consequences.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Hertfordshire CEI Illes Balears University G. d'Annunzio of Chieti-Pescara. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MdG and AN wrote the manuscript. CV, JL, MC, CD, AN, and GM recruited patients inside the Can Misses Hospital of Ibiza. SS and LT performed the statistical analysis. MP, VV, FS, and GM elaborated the study protocol and performed the translation for scales and questionnaire. FD-G, RG, CC, and MM executed the urine analysis in the different centers. AB and DD performed literature search about the topic and elaborated all the ethical procedures required for the study approval in both countries. GM coordinated all the study processes. All authors contributed to the article and approved the submitted version.

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Psychiatry Trainees' Attitudes, Knowledge, and Training in Addiction Psychiatry—A European Survey

Laura Orsolini[1,2], Irena Rojnić Palavra[3], Gabriele Duccio Papanti[4], Matej Potočan[5], Diego Quattrone[6], Matis Martens[7], Sandra Sklenářová[8,9], Jonna Levola[10], Leslie Grichy[11], Sean Naughton[12], Indre Kotryna Grinevičiene[13], Jelly Petra Kuiters[14], Tomasz M. Gondek[15], Anca-Livia Panfil[16], Milica M. Borovcanin[17], Alberto San Roman Uria[18], Ewelina Biskup[19,20], Ekin Sönmez Güngör[21], Marisa Casanova Dias[22,23], Sonila Tomori[24], Visnja Banjac[25], Petra Marinova-Djambazova[26] and Mariana Pinto da Costa[27,28,29]*

[1] Unit of Clinical Psychiatry, Department of Clinical Neurosciences/DIMSC, School of Medicine, Polytechnic University of Marche, Ancona, Italy, [2] Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom, [3] Psychiatric Hospital Sveti Ivan, Zagreb, Croatia, [4] Mental Health Department, Friuli Venezia Giulia, Italy, [5] Psychiatric Hospital Begunje, Begunje na Gorenjskem, Slovenia, [6] Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [7] Vaasa Central Hospital, Psychiatry Outpatient Clinic, Vaasa, Finland, [8] Department of Child Psychiatry, Charles University Second Faculty of Medicine, Motol University Hospital, Prague, Czechia, [9] Institute of Neuropsychiatric Care, Prague, Czechia, [10] Psychiatry, Hospital District of Helsinki and Uusimaa, Helsinki, Finland, [11] Adult Partial Hospitalization Program, Department of Psychiatry, Universitary Hospital Louis Mourier, Colombes, France, [12] Health Service Executive, Dublin, Ireland, [13] Vilnius City Mental Health Center, Vilnius, Lithuania, [14] Lentis, Zuidlaren, Netherlands, [15] European Psychiatric Association—Early Career Psychiatrists Committee, Wroclaw, Poland, [16] County Emergency Clinical Hospital, Pius Brînzeu, Liaison Psychiatry, Timisoara, Romania, [17] Department of Psychiatry, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia, [18] Psychiatric Inpatient Unit, Department of Psychiatry, Hospital Universitario Nuestra Señora de Valme, Seville, Spain, [19] Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy, [20] School of Clinical Medicine, Shanghai University of Medicine and Health Sciences, Shanghai, China, [21] University of Health Sciences, Erenköy Mental Health and Neurological Diseases Training and Research Hospital, Istanbul, Turkey, [22] National Centre for Mental Health, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, United Kingdom, [23] Section of Women's Mental Health, King's College, Institute of Psychiatry, Psychology and Neuroscience, London, United Kingdom, [24] University Hospital Center "Mother Theresa", Tirana, Albania, [25] Clinic of Psychiatry, University Clinical Center of the Republic of Srpska, Banjaluka, Bosnia and Herzegovina, [26] Department of Psychiatry in Medical University, University Hospital "Aleksandrovska", Sofia, Bulgaria, [27] Unit for Social and Community Psychiatry, World Health Organization (WHO) Collaborating Centre for Mental Health Services Development, Queen Mary University of London, London, United Kingdom, [28] Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal, [29] Hospital de Magalhães Lemos, Porto, Portugal

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Edited by:
Fabrizio Schifano,
University of Hertfordshire,
United Kingdom

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Swansea University, United Kingdom
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***Correspondence:**
Laura Orsolini
laura.orsolini01@gmail.com

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Background: Although psychoactive substance use disorders (PSUDs) are a domain of mental health, addiction psychiatry is only formally recognized as a subspecialty in a few European countries, and there is no standardized training curriculum.

Methods: A 76-item questionnaire was developed and disseminated through an online anonymous data-collecting system and hand-to-hand amongst psychiatric trainees from the 47 European countries of the Council of Europe plus Israel and Belarus.

Results: 1,049/1,118 psychiatric trainees from 30 European countries completed the questionnaire. Fifty-nine-point nine percent of trainees stated to have training in addictions. Amongst the trainees who described having training in addictions, 43% documented a not well-structured training and 37% an unsatisfactory training, mainly due to poor acquired knowledge. Overall, 97% of trainees stated that addiction represents a

core curriculum for their training. Overall, general adult psychiatric trainees reported a better knowledge in addictions, compared to trainees in child and adolescent psychiatry.

Conclusion: Despite a growing spread of PSUDs in European countries, addiction psychiatry is a relatively poorly trained field within psychiatry training programs. Further research should investigate reasons for poor training and timings of the educational activities to optimize experiential education training in addiction psychiatry.

Keywords: addiction psychiatry, addiction, EFPT, psychiatry trainees, psychiatry training

INTRODUCTION

According to the Global Burden Disease study (1), alcohol, tobacco, and illicit substance use significantly determine the global burden of disability, morbidity and mortality, being considered amongst the top four health burdens across many upper-middle and high-income countries. Mental and behavioral disorders due to psychoactive substance use include different conditions caused by the intake of medically or not medically prescribed psychoactive substances (2). Psychoactive substance use disorder (PSUD) was firstly coded as a discrete diagnostic category both in the American Psychiatric Association (APA) Diagnostic and Statistical Manual (DSM)-3rd edition (DSM-III) and in the World Health Organization (WHO) International Classification of Diseases and Related Health Problems (ICD)-9th edition of the (2–4). The current Diagnostic and Statistical Manual-5th edition (DSM-5) (5) amalgamated the abuse and dependence under a single category named "Substance Use Disorder" whilst the ICD-11 beta draft (6) described substance dependence (not substance use) (ICD: F10.xx to F19.xx) as a "*disorder of regulation of the use of a psychoactive substance arising from repeated or continuous use of the substance* [. . .]" (5, 6). Overall, PSUD may largely differ in severity and intensity in their psychopathological and clinical manifestation, i.e., ranging from an uncomplicated intoxication to the development of clinically significant psychotic disorders or other psychopathological and/or clinical manifestations) (2).

People with PSUD, including those classified as affected with a dual disorder, have been considered, compared to the general population, at higher risk of developing a range of medical and psychiatric disorders in comorbidity (7–9). Overall, PSUD subjects, particularly those with concurrent mental disorders, are overall associated with poorest outcomes, higher psychopathological severity and an increased rate of risky behaviors (i.e., hypersexuality, syringes/needles sharing, etc.) which can predispose them to an increased occurrence of serious infection diseases like Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) and Hepatitis C Virus (HCV), compared to the general population (10). Moreover, people with PSUD display a worsen psychosocial impairment (e.g., unemployment and homelessness) and they can more likely be involved in criminal and antisocial behaviors, compared to people affected by other mental disorders with a concurrent substance and/or alcohol use disorder (8, 11, 12).

However, although the PSUDs are fully considered among the mental and behavioral disorders, the contribution of psychiatrists, early career psychiatrists (ECPs) and psychiatry trainees into this clinical and research field, should be better developed. For instance, addiction psychiatry (sometimes named as addiction medicine) appears not to be adequately and homogeneously incorporated within the psychiatric training, across all European countries. Furthermore, psychiatry trainees' levels of knowledge and experiences in addiction psychiatry may greatly vary across European countries and cultures. As already documented by the 2014 WHO Global Survey on Resources for Prevention and Treatment of Substance Use Disorders, around 37% of the 155 responding countries do not provide adequate access to the post-graduate training programme for professionals working in PSUD treatment (13). Globally almost 30% of countries did not report a dedicated training programme for the treatment and the management of PSUD patients (52% of low-income countries vs. 16% of high-income countries), being mainly included in a short cycle tertiary education programme (48%). Overall, 95% of countries documented that psychiatrists are commonly involved in the treatment of people with PSUD, followed by psychologists, who are involved in PSUD treatment and management in around 86% of the countries. Furthermore, more than 80% of European countries reported the availability of a post-graduate training programme for the treatment and management of PSUD for psychiatrists (14).

Contextually, psychiatrists and psychiatry trainees' attitudes toward PSUD patients largely differ across different countries and cultures, where people with PSUD are generally more exposed to psychiatrists' and health professionals' negative attitudes/perception as well stigmatizing behaviors, and language (15). Stigmatizing behaviors and attitudes displayed by both psychiatrists and other physicians may lead to an inadequate and inhomogeneous physical, mental health care and treatment, including prescribing non evidence-based pharmacological/not pharmacological treatments, prescribing an inadequate/insufficient posology and duration of therapy. Moreover, use of potentially stigmatizing language may lead mental health professionals to a poor/inadequate communication with their PSUD patients, displaying an overall judgmental and unempathetic attitude, and other problematic and potentially stigmatizing behaviors (16–19).

The present study aimed at evaluating the organization of the addiction psychiatry training, trainees' satisfaction, trainees' attitudes toward people who use psychoactive substances and addiction psychiatry, and how psychiatric trainees manage psychopharmacology and pharmacotherapy in the most common clinical presentations of people with PSUD and

their levels of confidence/perceived competence in the field of addiction psychiatry.

METHODS

Study Design

The EFPT-PSUD Study has been an international cross-sectional survey of European psychiatry trainees carried out in the context of the European Federation of Psychiatric Trainees (EFPT), the umbrella organization of the national trainees' associations in psychiatry in Europe (20, 21). Among the framework of the EFPT, a working group specifically dedicated to the PSUD developed a self-administered survey that was disseminated at European level, by involving both Child and Adolescent Psychiatry (CAP) and General Adult Psychiatric (GAP) trainees.

Pilot Phase

All active members of the EFPT-PSUD Working Group, constituted during the 2014 EFPT Forum in London (22) and initially comprising national representatives from 5 countries (Italy, Croatia, Lithuania, Denmark, and Estonia), firstly conducted a preliminary overview about the current state-of-the-art regarding the training in addiction psychiatry in the European CAP/GAP training programs, and subsequently developed the survey. The survey was initially piloted amongst the members of the EFPT-PSUD Working Group.

Full Study Phase

The previously developed survey was circulated at the European level both to CAP and GAP trainees. The survey was circulated to the national representatives of each 47 European countries of the Council of Europe plus Israel and Belarus.

The European countries not represented in the survey were those not able to identify a National Coordinator who would take over the responsibility of the study or those unable to collect at least 10 completed questionnaires from their own country.

Instrument

The questionnaire was a 76-item self-report survey (**Appendix 1** in the Supplementary Material). The questionnaire consisted of: (a) single answer and/or multiple answer questions (i.e., for evaluating trainees' knowledge in a specific field); (b) an increasing five-item Likert scale (i.e., for evaluating attitudes and interests toward the addiction medicine and psychiatry); and, (c) a series of open-ended questions (i.e., asking for further specification and/or clarification of the provided answers). In particular, the section on general knowledge on addiction consists of 36 items in which each question correctly answered gave 1 point (range score: 0–36). This section was developed by GDP, following the evidence-based practices of the Substance Abuse and Mental Health Services Administration (SAMHSA) (https://www.samhsa.gov/ebp-resource-center).

For the present article, we have focused on the following sections of the survey:

- General socio-demographic section;
- General information about training in GAP (General Adult Psychiatry) or Child and Adolescent Psychiatry (CAP), including experiences (if any) on addiction psychiatry;
- General attitudes and interest toward addictions, addiction psychiatry;
- Level of knowledge about addictions, addictive disorders, including treatment.

Data Collection

One national coordinator per each of 47 European countries of the Council of Europe plus Israel and Belarus facilitated the delivery of the survey through an online data collecting system (https://www.surveymonkey.com/r/EFPT-PSUDstudy) and/or, if necessary, delivering the questionnaire hand-by-hand, in a paper form (**Appendix 1**). The questionnaire was circulated in English across all European countries (in French language in France) and no translation in other languages was deemed necessary, as psychiatric trainees were deemed by their national coordinators to have sufficient command of English to reliably answer the questions (i.e., this was preliminarily evaluated by each national coordinator). Data were collected from 15th August 2015 to 15th October 2016. Annual EFPT forum as well as European and national congresses or educational events were chosen to reach out to all CAP/GAP trainees in each country or to involve national coordinators, needed for those countries still not represented in the sample of the survey. Moreover, European contact e-mail databases were periodically used to disseminate the link for the online survey (https://www.surveymonkey.com/r/EFPT-PSUDstudy). All hand-to-hand questionnaires completed were subsequently entered into the online study database by the National Coordinator via the online survey tool Survey Monkey. The online survey link was only accessible by invitation.

Inclusion Criteria

The inclusion criteria were: (i) being a CAP/GAP trainee, defined as a fully qualified medical doctor enrolled in a nationally recognized specialist training programme in CAP or GAP; (ii) belonging to one of the 47 European countries of the Council of Europe plus Israel and Belarus.

The participant countries included in the present analysis were those countries of whom each CAP/GAP National Coordinator was able to collect at least 10 completed questionnaires [not considering the last section regarding Novel Psychoactive Substances (NPS)]. Those countries with a National Coordinator who took responsibility to take part in the study but did not reach an enough minimum number of completed questionnaires were excluded in the present analysis (Greece, Belgium, Germany, Slovakia, Ukraine, Sweden, Denmark, and Israel). Amongst these, the following European countries participated in the present survey with a valid number of filled questionnaires: Albania, Austria, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Hungary, Ireland, Italy, Kosovo, Latvia, Lithuania, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Switzerland, Turkey, and UK.

Ethics Approval and Consent

The survey was conducted according to the principles of good scientific practice, which was supported by previous EFPT-sponsored psychiatry trainees' surveys (23). Ethical approval for the study has been sought and granted by the School of Pharmacy Ethics Committee at the University of Hertfordshire (December 15, 2010, reference code PHAEC/10-42), with a further extension of the approval granted in November 2013. The patients/participants provided their written online informed consent to participate in this study.

Before filling out the survey which was self-administered anonymously, all participants were asked to give written online informed consent before, as legally and ethically required.

Statistical Analysis

Data was analyzed using the Software Package for Social Sciences for Windows v. 24.0 (SPSS 24) (IBM Corp, Armonk NY). Categorical variables were summarized as *n* (%), and continuous variables as means [standard deviation (SD)]. Pearson's χ^2-tests were used to compare demographic and categorical variables, such as the trainees' attitudes toward addiction psychiatry. Student's *t*-tests and one-way analysis of variance (ANOVA)-tests were used to compare continuous variables, including comparisons of training experiences. Ordinal regression was used to model the predictors of trainee satisfaction. Variables added to the model included trainees' sub-specialty and percentage of training completed. The significance level was set *a priori* at $p \leq 0.05$, and all hypotheses were two-tailed.

RESULTS

Sampling and Sample Characteristics

The total number of questionnaires correctly filled during the collection process and afterwards included in the analysis was of 1,118, amongst all trainees in Europe who took part in the survey. However, after excluding missing data (i.e., including only complete questionnaires) only 1,049 responses were included (**Table 1**). There were differences in the gender distribution, being most of them women (68.7%) and this difference is statistically significant when we stratified the sample by subspecialty ($\chi^2 = 25$, $p < 0.001$), being 84.6% of the CAP sample represented by women, whilst in the GAP sample, a percentage of 64% was represented by women, by reaching a total amount of GAP and CAP trainees of 936 (after excluding those trainees in forensic psychiatry or others with an unspecified other psychiatry training). The mean age of respondents was 30.48 (±4.84) years, without any statistically significant differences between GAP and CAP samples. The majority (73.8%) were GAP trainees, whereas 15.4% were CAP trainees, whilst around 10.6% of the sample did not specify if they are GAP or CAP trainees. Amongst the respondents, the total number of years required to complete GAP and CAP training programs may largely differ across European countries. To adjust the analysis for this confounder, it was calculated the percentage of progression/completeness of individual training for each country, in order to measure the most reliable and objective variable. This variable reported that in an average of 67.4% of the total sample, CAP/GAP trainees were in the last quantile of their training programme, without any statistically significant difference between GAP and CAP (see **Figure 1**). The CAP/GAP trainees overall belong to 30 different countries, with the highest proportion of respondents amongst those training in France (16.3%), followed by Italy (5.7%), Spain (5.1%) and the UK (5.0%). See **Table 1** for further demographic features.

Trainees' Experience, Satisfaction, and Training in Addiction Psychiatry

Amongst those who answered the question "*Have you performed part of your psychiatric training in the treatment of patient with substance use disorder?*", only 59.9% of trainees reported to have spent part of their training in addiction psychiatry settings, with a statistically significant difference between GAP and CAP trainees ($p = 0.018$). Amongst those trainees who declared to have received training in addiction psychiatry during their psychiatry training, only 43% described that the PSUD training was not well-structured due to several reasons. First, the addiction training program is often too short to allow trainees to deepen knowledge on all theoretical and practical aspects of addiction psychiatry; second, during the addiction training program, CAP/GAP trainees are often alone in the management of PSUD patients (often without a dedicated supervisor/mentor); third, the addiction training program usually consists in a mere observership experience (without a practical frontline experience). Amongst those trainees who had training in addictions only 37% of them declared that they were not satisfied about the level of training offered, mainly stating lack of enough acquired skills and knowledge in the field, largely below their initial expectations. There was no significant difference in the percentage of training completed amongst those trainees who reported being satisfied with their addiction psychiatry training, compared to those trainees who did not document an enough level of satisfaction [$F_{(1,555)} = 2.244$, $p = 0.135$]. Trainees with larger caseloads had generally progressed further in their training, compared to those trainees with smaller caseloads [$F_{(5,551)} = 6.487$, $p < 0.001$]. Most of the sample (97%) agreed or strongly agreed that addiction represents a core curriculum for training. Subspecialty was a significant predictor of satisfaction with training ($\beta = 1.713$; $p = 0.042$), being GAP trainees overall more satisfied, compared to CAP trainees, even though this finding is not strictly correlated by the percentage of training completed ($\beta = 1.005$; $p = 0.176$).

Trainees' Attitudes Towards People Who Use Psychoactive Substances and Addiction Psychiatry

Approximately one third of the sample (33.27%) agreed or strongly agreed to be confident with their basic skills needed/requested necessary to work in addiction settings after their training ($\chi^2 = 82.864$; $p < 0.001$). Interestingly, on the other hand, around 66.9% of the trainees agreed or strongly agreed that "*Addiction psychiatrists are usually less skilled than their*

TABLE 1 | Demographic characteristics.

	Total Mean (SD)	GAP ($N = 774$) Mean (SD)	CAP ($N = 162$) Mean (SD)	Significance t
Age	30.48 (4.84)	30.43 (4.58)	30.79 (5.24)	$p = 0.899$
Training completed (%)	67.37 (28.01)	67.77 (28.44)	66.95 (28.64)	$p = 0.716$
	Frequency (%)	**Frequency (%)**	**Frequency (%)**	χ^2
Gender				$p < 0.001$
Male	328 (31.3%)	269 (34.8%)	25 (15.4%)	
Female	721 (68.7%)	505 (65.2%)	137 (84.6%)	
Country of training				$p = 0.221$
Croatia	38 (3.6%)	26 (3.4%)	5 (3.1%)	
Czech Republic	36 (3.4%)	28 (3.65%)	8 (4.9%)	
Finland	44 (4.2%)	32 (4.1%)	8 (4.9%)	
France	171 (16.3%)	101 (13.0%)	30 (18.5%)	
Ireland	40 (3.8%)	20 (2.6%)	5 (3.1%)	
Italy	57 (5.4%)	50 (6.5%)	7 (4.3%)	
Lithuania	45 (4.3%)	35 (4.5%)	10 (6.2%)	
Netherlands	35 (3.3%)	23 (3.0%)	3 (1.9%)	
Poland	47 (4.5%)	38 (4.9%)	6 (3.7%)	
Portugal	42 (4.0%)	37 (4.8%)	5 (3.1%)	
Romania	45 (4.3%)	39 (5.0%)	6 (3.7%)	
Slovenia	33 (3.1%)	22 (2.8%)	9 (5.6%)	
Spain	53 (5.1%)	47 (6.1%)	1 (0.6%)	
Switzerland	34 (3.2%)	27 (3.5%)	7 (4.3%)	
Turkey	40 (3.8%)	31 (4.0%)	9 (5.6%)	
UK	52 (5.0%)	30 (3.9%)	5 (3.1%)	
Other	237 (22.6%)	188 (24.3%)	38 (23.5%)	

GAP, General Adult Psychiatry; CAP, Child and Adolescent Psychiatry; SD, Standard Deviation; UK, United Kingdom.

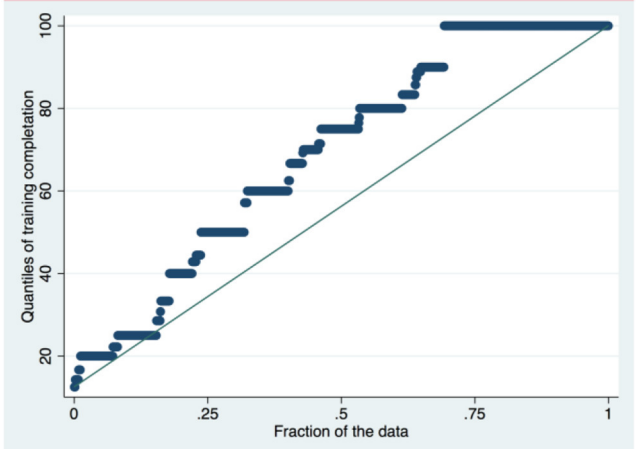

FIGURE 1 | Distribution of training completion.

colleagues working in GAP/CAP" (**Table 2**). Moreover, around 75.7% disagreed or strongly disagreed that addictions are mental disorders; similarly, 77.8% of the sample agreed or strongly agreed that people with drug addiction cannot be recovered (**Table 2**).

Over three-quarters of respondents (76.1%) knew/had previously known someone outside of their workplace with an addiction-related problem (**Table 3**). The findings showed that those who knew/had known someone with addiction related problems were significantly associated with a stronger desire to work in the addictions after their training [$\chi^2(4) = 16.311$, $p = 0.003$] (**Figure 2**).

Trainees' Basic Knowledge and Confidence/Perceived Competence in Addiction Psychiatry

Respondents who had treated someone with an addiction-related condition significantly declared to have almost completed their training, compared to those trainees who had not [$F_{(1,991)} = 99.155$, $p < 0.001$] (**Figure 3**). **Figure 4** represents the graphical distribution of the knowledge score, by indicating that most trainees responded correctly to most of the questions regarding their general and specific knowledge of addiction psychiatry (mean average 25.77 ± SD 3.59), with a minimum score of 7 and a maximum score of 34 (skewness = −0.956). There

TABLE 2 | Attitude of trainees who have/haven't performed part of their training in the treatment of a patient with addiction.

		Have you performed part of your psychiatric training in the treatment of patients with addiction?		
		Yes	No	
Illicit drugs (e.g., heroin) addicted are good people	Strongly agree	9	3	$\chi^2 = 8.773$ $p = 0.067$
	Agree	33	22	
	Neither agree or disagree	303	236	
	Disagree	101	52	
	Strongly disagree	62	60	
I don't feel confident with my skills to work in addiction	Strongly agree	36	22	$\chi^2 = 82.864$ $p < 0.001$
	Agree	178	44	
	Neither agree or disagree	125	84	
	Disagree	146	181	
	Strongly disagree	23	42	
I think that people with drug addiction cannot recover	Strongly agree	138	88	$\chi^2 = 3.872$ $p = 0.424$
	Agree	257	188	
	Neither agree or disagree	87	75	
	Disagree	25	19	
	Strongly disagree	1	3	
Addiction is a mental disorder	Strongly agree	5	4	$\chi^2 = 6.263$ $p = 0.180$
	Agree	25	15	
	Neither agree or disagree	59	61	
	Disagree	262	198	
	Strongly disagree	15	95	
Addiction psychiatrists are usually less skilled than their colleagues working in general adult and child adolescent psychiatry	Strongly agree	159	130	$\chi^2 = 6.565$ $p = 0.161$
	Agree	181	140	
	Neither agree or disagree	104	73	
	Disagree	57	24	
	Strongly disagree	7	6	

was no significant difference in terms of the most prevalent addiction-related condition that was treated/observed during their addiction psychiatry training [$F_{(4,479)} = 1.523$, $p = 0.194$]. However, those trainees who had treated alcohol withdrawal syndrome, delirium tremens, opioid withdrawal syndrome, or substance induced-psychosis were significantly more senior in their level of training completeness, compared to those trainees who had not treated these addiction-related conditions who were more junior (all p-values < 0.001). Similarly, those trainees prescribing acamprosate, naltrexone, methadone, and buprenorphine were also significantly further in their training than those who did not prescribe a medication for an addiction (all p-values < 0.001). In addition, GAP trainees more likely reported to have treated a person affected with an addiction during their training, compared to CAP trainees [$\chi^2_{(1)} = 8.328$, $p = 0.004$]. Likewise, GAP trainees more likely reported to have prescribed medication for an addiction-related condition, compared to CAP trainees [$\chi^2_{(1)} = 9.482$, $p = 0.002$]. Furthermore, GAP trainees reached higher scores, compared to those undergoing CAP training, when questioned about their general and specific knowledge of addictions [$F_{(1,802)} = 14.181$, $p < 0.001$]. Moreover, GAP trainees were more likely aware of the existance of legal highs/smart drugs/novel substances, compared to CAP trainees [$\chi^2_{(2)} = 25.663$, $p < 0.001$]. However, when the knowledge score includes in the analysis also those questions about legal highs/smart drugs/novel substances, there was no significant difference in the total score between GAP and CAP trainees [$F_{(1,531)} = 0.524$, $p = 0.470$].

DISCUSSION

Key Findings and Comparison With the Literature

PSUD have been historically perceived as personal, family, social, moral, or criminal issues rather than a health condition (24). Therefore, subjects with PSUD have been supposed to be better managed at the individual, family or justice level (i.e., through existing social infrastructure or civil and criminal justice interventions) (24). Indeed, criminalization of people with PSUD exacerbated their perceived and experienced stigma, avoidant attitudes and behaviors of contempt, by worsening their marginalization and poor access to adequate treatment and care (24). People with PSUD tend to be stigmatized due to their use of drugs and drug-seeking behaviors (24). Moreover, other PSUD-related risky behaviors, such as speeding/dangerous driving, violence, aggressiveness,

TABLE 3 | Attitude of trainees who have/haven't known someone outside their workplace with addiction related problems.

		I know/had known someone outside my workplace (family, friends, relatives, neighborhood) who has/had addiction related problems		
		Yes	**No**	
I am afraid to work with persons with cocaine addiction	Strongly agree	204	39	$\chi^2 = 14.623$ $p = 0.006$
	Agree	309	101	
	Neither agree or disagree	92	42	
	Disagree	62	20	
	Strongly disagree	7	5	
I am afraid to work with persons with alcohol	Strongly agree	283	68	$\chi^2 = 8.305$ $p = 0.081$
	Agree	298	97	
	Neither agree or disagree	64	30	
	Disagree	25	11	
	Strongly disagree	4	1	
Addiction is a mental disorder	Strongly agree	8	1	$\chi^2 = 14.525$ $p = 0.006$
	Agree	34	6	
	Neither agree or disagree	83	37	
	Disagree	339	121	
	Strongly disagree	210	42	
Individual psychotherapy should be preferred in treating addiction	Strongly agree	14	1	$\chi^2 = 12.680$ $p = 0.013$
	Agree	125	45	
	Neither agree or disagree	236	93	
	Disagree	238	52	
	Strongly disagree	61	16	

and impulse dysregulation, are barely seen as part of a complex disorder, so that people with PSUD are usually rejected by the society due to the supposed moral valence of these behaviors (24, 25). These patients may also be seen as a burden for the healthcare system, by indeed increasing the disparities of cares, the risk to not adequately provide evidence-based and effective treatments (19, 25). Due to this disadvantageous framework, patients with PSUD may develop a self-stigmatizing attitude as well (e.g., a subjective process characterized by negative feelings about own self, maladaptive behaviors, stereotype endorsement resulting from individual's experiences/perceptions/feelings and anticipation of negative social reactions) (26–29). In fact, potentially "stigmatized" attitudes and behaviors, overly provided by healthcare professionals, including psychiatrists and psychiatry trainees, may be potentially trigger and maintain these self-stigmatizing attitudes, as already reported in the literature and confirmed by our findings (16, 19, 26–29). Furthermore, subjects with PSUD are symbolically associated with a range of other stigmatized health conditions, including HIV/AIDS, HCV, risk and disinhibiting behaviors such as impaired driving, prodigality, criminality, risky sexual behaviors, and social issues (30, 31). Stigmatizing beliefs and behaviors about PSUD may be influenced by the level of knowledge (and education) about these mental health conditions and the personal experience with people affected with PSUD. Furthermore, it has been reported that media portrayal of people with PSUD and media coverage/level of news disseminated about significant and impactful related events, mainly occurring due to a drug intoxication and/or drug dependence/abuse/misuse, can significantly increase these stigmatizing beliefs and attitudes (29, 32).

Furthermore, addictions have not been historically recognized as conditions requiring a medical, psychological and psychopharmacological treatment (19). This is in line with our findings in which most GAP and CAP trainees declared that the addictions are not mental disorders. In fact, as previously documented in the literature, this overall consideration regrading PSUD appears to be widely spread not only at the general population level but also amongst mental health professionals who overall reported negative and pessimistic views about PSUD, people with PSUD and do not routinely screen patients in daily practice for addictions (15, 26, 33, 34).

However, the individual perceptions and attitudes towards people with PSUD may largely vary according to different factors. For instance, people are less likely to endorse the stereotype of violence together with a negative connotation of addiction disorders, if they have had direct contact with people (or also family members or close friends) who were affected with PSUD or did not experience violent acts by people affected with PSUD (35). This is comparable with our findings which demonstrated that those trainees who have/had experience with people with a PSUD significantly declared to have a stronger desire to work in the addiction field and with subjects with PSUD after their training.

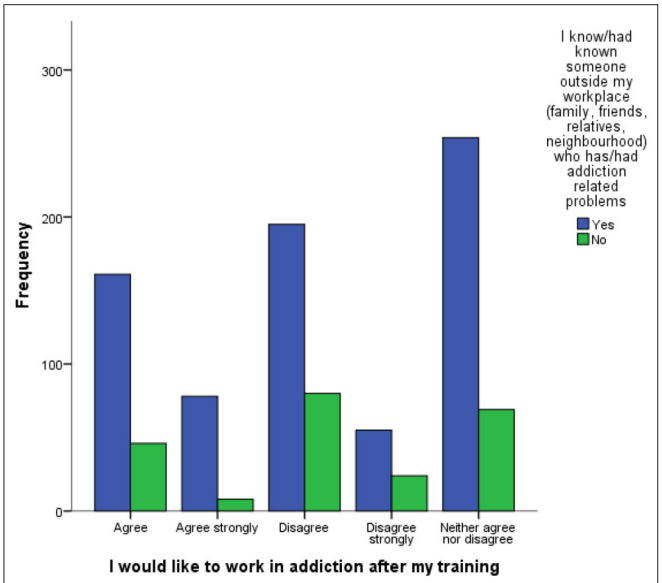

FIGURE 2 | Frequency of trainees who would like to work in addiction following completion (by those who have/haven't known someone outside the workplace who has had an addiction related problem).

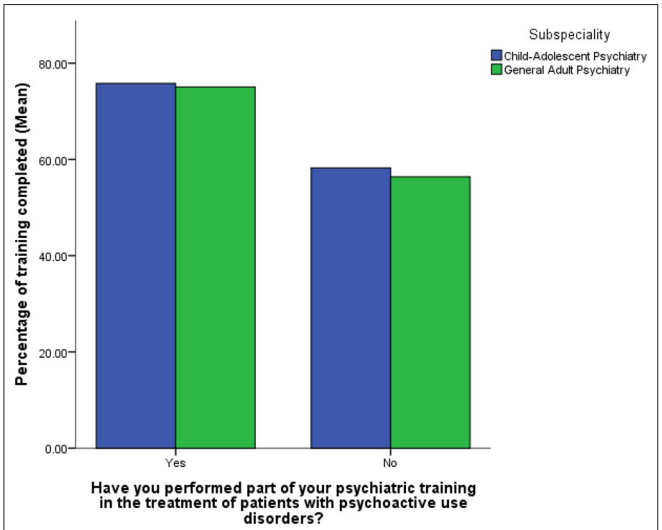

FIGURE 3 | Mean percentage of training completed in those who have/haven't worked with patients with psychoactive use disorders during their training (by sub-specialty).

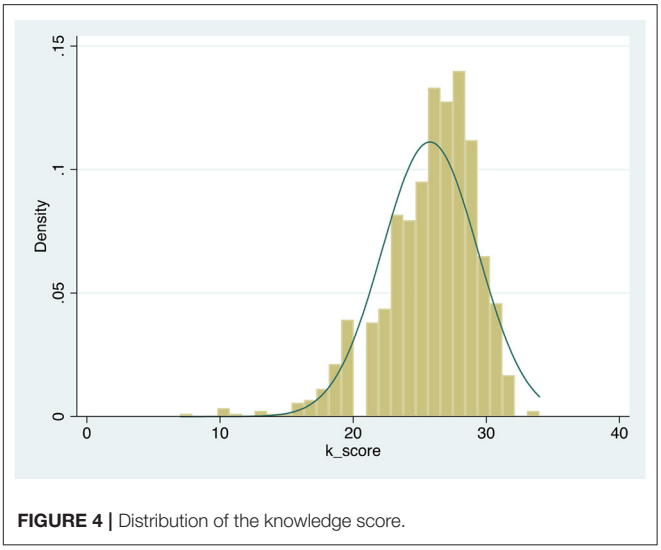

FIGURE 4 | Distribution of the knowledge score.

Furthermore, despite a compelling need for PSUD treatment in Europe, mental healthcare professionals (including psychiatry trainees) overall appear poorly or neither trained, nor especially eager to accept/tolerate patients with PSUD (15, 33, 34, 36). In general, psychiatrists do not feel competent/confident in treating addiction disorders, do not like working with patients affected with PSUD and do not find rewarding treating patients with PSUD (33, 37, 38). A lack of (practical) experience and/or an inadequate (theoretical and practical) training in addiction psychiatry may indeed result in an endless loop of incompetence and neglect regarding the addiction psychiatry, amongst mental health care professionals. However, despite the evidence demonstrating the need to improve addiction medicine's training not only amongst psychiatry trainees but also amongst all physician trainees, most medical students and CAP/GAP trainees generally receive an inadequate (practical and theoretical) training in the field of addiction medicine/psychiatry (33, 39, 40). Moreover, most CAP/GAP trainees generally display lacking core clinical and therapeutic competences, as required for working with patients with PSUD (33, 39, 40). Although formal addiction training within the medical field has been closely tied to psychiatry, psychiatric training generally provides a poor improvement and a limited level of knowledge over medical school, about addictions (39, 40). These considerations are particularly significant in the European countries, whereas there are several inequalities and heterogeneous training levels in addiction psychiatry, as documented by our findings. Furthermore, most CAP and GAP trainees reported to be less skilled in the addiction field, compared to other fields of psychiatry. Interestingly, there are not statistically significant differences between GAP and CAP trainees regarding this finding. This appears particularly relevant if we consider that CAP trainees should possess a comprehensive experience including behavioral, psychosocial and addiction problems particularly amongst youngsters/adolescents who have been well-demonstrated to be those patients more frequently exposed to drugs and/or other addictive behaviors, but also those patients more vulnerable toward the new onset of mental disorders associated with a PSUD (41).

Furthermore, an insufficient training experience with patients with PSUD, along with the lack of a highly-specialized faculty (i.e., short addiction training experience, lack of a supervisor/mentor during the addiction training, and poor quality of addiction training), may overall lead to a discouraging training experience amongst CAP/GAP trainees, as reported

in our study. Overall, one could argue that this general psychiatry trainees' attitudes and perceptions towards the addiction psychiatry might discourage trainees' interest and willingness to deepen the management and therapy of patients with PSUD, independently by their level of psychiatry training, as well as their interests in working in addiction psychiatry (38). Renner et al. (38) described the following main predictors of poor perception of careers in addiction medicine by GAP trainees: (a) the poor/not enough/lacking experience with patients with PSUD; (b) the perceived sensation and feeling to work with "difficult" patients; (c) the lack of a competent training in the addiction; (d) an overemphasis, during psychiatry training, about the detoxification process rather than a long-term rehabilitative and care program for the addiction-related conditions. Miller et al. (33) identified the following hypothesized barriers/determinants explaining the different attitudes and practices of medical students, trainees and physicians towards addiction psychiatry: (a) lack of acceptance of a medical model for addictive disorders; (b) lack of positive and/or optimistic attitudes about patients with PSUD, by accepting the prevalent stereotype of subjects with PSUD as those patients whose social and medical prognosis is poor; (c) curricula deficits throughout the Continuum Medical Education (CME) in the field of the addiction psychiatry/medicine, particularly the total time devoted to addictive disorders during the medical school and psychiatry training; (d) lack of parity and physician advocacy in medical education; (e) prejudices and misunderstandings about addictive disorders, along with ungrounded fears of huge costs connected with addiction treatment and the perception that addiction treatment owns a low ratio of benefits to costs; (f) personal and/or family history of drug and/or alcohol disorders. Conversely, Rush et al. (42) found that the factors associated with more positive attitudes towards the treatment of addictive disorders and subjects with PSUD may be represented by: (a) the number of subjects with PSUD treated/visited; (b) the physicians' perceived effectiveness in the management of the addictive disorders; and, (c) the numbers of hours of CME specifically addressed on the addictive disorders.

However, as widely reported in the literature, the level of knowledge and education about PSUD and addiction psychiatry can positively influence mental health professionals' attitudes and interests towards the field of addictions, limit the misdiagnosis and potentially reduce improper and inadequate treatment regimens for these disorders (43–45), even though other studies demonstrated a deterioration in attitudes throughout medical school years and suggested a continued decline throughout the years of training, mainly due to time and resources spent for those subjects with PSUD (19, 46–49). The enhancement of these beliefs appears to be more significant when we compared those subjects with PSUD with those with AUD (49). As proposed by Miller et al. (33), to achieve an adequate level of education and training in addiction psychiatry, it should be ensured that all trainees reach an enough and adequate knowledge and skills in the diagnosis and treatment of the addictive disorders, by favoring the development of curricula for the addictive disorders in all medical schools, residency training programs and CME; by supporting the research and revising all discriminatory policies that create barriers to the implementation of curricula in addictive disorders; by providing the detection and intervention for students, trainees and physicians who have addictive disorders; and, by supporting the parity between the addictive disorders and other medical and psychiatric diseases.

Main Strengths and Limitations

To the best of our knowledge, this has been the only study specifically investigating the levels of training, experiences, attitudes and perceptions as well as the level of perceived confidence and capacity in the management of people with a PSUD, carried out amongst European CAP/GAP trainees. The present survey also included a large sample size of CAP/GAP trainees in Europe ($n = 1{,}118$) which comprises many European countries ($n = 30$). Furthermore, collecting data from different European countries might lend strength to the generalization of these findings also to other WHO Regions, beyond European Region. Moreover, our study identifies gaps in knowledge by demonstrating that addiction psychiatry appears not to be adequately and homogeneously incorporated within the psychiatric training, across all European countries. Moreover, a key finding is represented by the significant number of recruited psychiatry's trainees who do not consider addiction as a psychiatric disorder.

Despite its original and poorly investigated topic, there are several limitations that should be here drawn up. Firstly, being a self-report questionnaire and partly online administered, potential recall, social desirability, and reporting biases may occur. Secondly, the sampling method may be hugely affected both by the fact that not in all European countries we reached an enough number of completed questionnaires or reached an available official national coordinator. In fact, some European countries initially included have been *a posteriori* excluded in our analysis as they did not reach an enough number of completed questionnaires (cut-off of 10 for each country), like Greece, Belgium, Germany, Slovakia, Ukraine, Sweden, Denmark, and Israel. Furthermore, sampling rates largely vary within different European countries, being some countries (i.e., Croatia, Finland, France, Ireland, Italy, Lithuania, Poland, Portugal, Romania, Slovenia, Spain, Turkey, and UK) most represented in our sample compared to Albania, Bosnia, Bulgaria, Czech Republic, Estonia, The Netherlands, Serbia, and Switzerland. The level of perceived confidence and knowledge in addiction psychiatry, being mainly based on a set of questionnaires, may also be susceptible to the updated information and new available and emerging pharmacological and not pharmacological treatments, may not completely reflect the current situation occurring at the time of writing of the present study. Moreover, the present study does not examine what happens once GAP/CAP residency is completed and the GAP/CAP enters career's practice. It should be relevant to document further data particularly regarding the level of attitude or perception of PSUD patients with added experiences and added continuing educational opportunities during their clinical career. Finally, the present study does not specifically define whether psychiatry trainees' attitudes differ towards caring for subjects with AUD and/or SUD.

Relevance of the Findings and Implications for Practice, Policies, and Research

The present study provides significant and valuable information on the current European CAP/GAP trainees' level of experiences, training, perceived knowledge/competence, and subjective attitudes/perceptions towards the addiction psychiatry. These findings not only serve to investigate the current European situation in terms of level of subspecialty offered in the addiction psychiatry as well as the potential differences across all analyzed European countries, but they might also investigate those situations which should be implemented/enhanced as lacking in providing opportunities both in terms of internship (practical training) and knowledge (theoretical training) in the field of the addictions. Moreover, addressing the identified reasons/factors determining a different level of training in addiction psychiatry as well as a different level of interest CAP/GAP trainees, in strenghtening knowledge in this field might be a way to modulate and act on these factors, to improve the CAP/GAP training conditions in the field of addiction psychiatry (50). Regarding the need to improve all CAP/GAP training programmes, the standardization of curricula would be important to produce both GAP and CAP trainees able and capable (self-confident) in the management and correct identification of both physical and mental/behavioral PSUD-related conditions. This should be part of the essential core knowledge that should be indispensable for all psychiatric practice. In terms of the enhancement of GAP/CAP trainees' education/knowledge in the addiction medicine and psychiatry, an implementation of a mandatory addiction rotation during the CAP and GAP training program, could greatly improve the level of trainees' confidence and competence in identifying and dealing with all different addictive disorders. Furthermore, in CAP and GAP training, the need to develop and satisfy objective measurable educational criteria must be balanced with the acquisition of subjective skills needed to treat subjects with PSUD effectively (e.g., increasing empathy and not judgmental approach as well as addressing stigma), as well as reaching an enough comfort in working with PSUD patients and obtaining a minimum sense of mastery in the field of the addictions. Finally, it might be suggested to all European GAP and CAP training programmes to administer to all psychiatry trainees at the end of their training program, validated tools for assessing addiction psychiatry training and early identify potential deficits, such as the Addiction Training Scale (ATS) (51).

These findings may assist the decision-makers to implement strategies to adapt their national diversities in CAP/GAP training programmes and make them homogenous especially at the European level. The need for psychiatry trainees' education and experience in treating patients with addiction problems has been outlined. Lastly, although these preliminary findings may help in mapping the reality of this field of psychiatry, further studies are needed to focus on the main motivations underpinning the existing differences across European countries in terms of level of training in addiction psychiatry (i.e., cultural and/or religious factors, epidemiological motivations, etc.) and consequences of different experiences/training in the level of knowledge of a CAP/GAP trainees as well as their attitude/perception towards addictions in general and people who use psychoactive substances. Moreover, it would also be of interest to repeat the present survey with identical methodology every 4 or 5 years (being the average duration of CAP/GAP European training) to assess potential trends in these findings and attitudes/opinions of psychiatry trainees over time and evaluate if any enhancing intervention has been provided at European and national level concerning addiction psychiatry training and evaluate if any positive/neutral/negative impact was reached amongst psychiatry trainees' attitudes and knowledge.

CONCLUSIONS

Despite the growing dissemination of addictive disorders across all European countries, addiction psychiatry seems to be an underdeveloped part of psychiatry within psychiatry training programmes. However, we found substantial consensus among all European psychiatry trainees that more education and experience in treating patients with addictive disorders should be guaranteed and be part of the core curricula in GAP and CAP training. Further research needs to be directed towards the causes of poor training as well as timings of these educational activities to optimize experiential education programs to be implemented within GAP and CAP training programs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical approval for the study has been sought and granted by the School of Pharmacy Ethics Committee at the University of Hertfordshire (December 15, 2010, Reference Code PHAEC/10-42), with a further extension of the approval Granted in November 2013. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LO, IR, GDP, MPo, DQ, and MM conceived and conceptualized the study. GDP, LO, and IR performed the survey, the methodology and the ways to disseminate the survey across all European countries. IR and GDP mainly dealt with data curation, collection and analysis. DQ performed formal analysis of data collected reported in this article. A preliminary draft was written by GDP, LO, IR, and MPi. LO wrote, revised and edited the final draft. MPi supervised the work and contributed to the final editing of this manuscript. All other co-authors equally collected data from their respective countries and provided further final feedback to the draft.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.585607/full#supplementary-material

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Gabapentinoid Abuse in France: Evidence on Health Consequences and New Points of Vigilance

Marine Tambon[1†], Camille Ponté[1†‡], Emilie Jouanjus[1,2‡], Nathalie Fouilhé[3‡], Joelle Micallef[4,5‡], Maryse Lapeyre-Mestre[1,2,6‡] and the French Addictovigilance Network (FAN)*

[1] Centre d'Evaluation et Information sur la Pharmacodépendance-Addictovigilance, Service de Pharmacologie Médicale et Clinique, CHU de Toulouse, Toulouse, France, [2] Unité Mixte de Recherche, 1027 Inserm-Université, Pharmacoépidémiologie, Université de Toulouse, Toulouse, France, [3] Centre d'Evaluation et Information sur la Pharmacodépendance-Addictovigilance, Service de Pharmacologie-Pharmacosurveillance, CHU Grenoble-Alpes, Grenoble, France, [4] Aix Marseille Univ, AP-HM, INSERM, Inst Neurosci Syst, Service de Pharmacologie Clinique et Pharmacovigilance, Marseille, France, [5] CEIP-Addictovigilance PACA Corse, Marseille, France, [6] Centre d'Investigation Clinique 1436, CHU de Toulouse, Toulouse, France

Introduction: Gabapentinoid drugs (gabapentin and pregabalin) are widely used worldwide for epileptic and pain disorders. First signals of gabapentinoid abuse occurred in the last decade. This study aims to describe clinical characteristics of gabapentinoid use related disorders and health consequences in France.

Materials and Methods: We designed a multisource investigation reviewing data reported to the French Addictovigilance Network (FAN) with pregabalin and gabapentin from 2010 to 2019. Information was obtained through the analysis of Spontaneous Reports (SRs) notified by health professionals and the pharmacoepidemiological surveys OSIAP (suspicious prescriptions forms indicators of potential abuse), OPPIDUM (observation of illicit drugs and misuse of psychotropic medications), DRAMES (death related to prescription drugs and other substances), and DTA (toxic deaths due to analgesics).

Results: Over 2010–2019 period, were collected: (i) 265 SRs (258 pregabalin; 7 gabapentin); (ii) 816 forged prescription forms (805 pregabalin, 10 gabapentin, 1 involving both drugs); (iii) 145 cases of gabapentinoid use in people who use drugs (121 pregabalin; 24 gabapentin) and (iv) 31 cases of gabapentinoid-related deaths (25 pregabalin; 6 gabapentin). Risk factors of gabapentinoid abuse were opioid use disorders or psychiatric history, but cases of primary abuse in subjects without any substance abuse history were observed. Adverse outcomes concern almost exclusively pregabalin, with coma, dyspnea, convulsion, and conduction disorders. Treatment demands increased from 10.6% in 2018 to 23.1% in 2019, with pregabalin cited as the first substance leading to addictological care in the 2019 OPPIDUM survey. Gabapentinoid-related deaths increased over time. Pregabalin has become the first drug mentioned in forged prescriptions in 2019 (23.8% of OSIAP), while it ranked at the 15th position in 2017 (2.6%).

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***Correspondence:**
Camille Ponté
ponte.c@chu-toulouse.fr

†These authors have contributed equally to this work and share first authorship

‡ORCID:
Camille Ponté
orcid.org/0000-0001-8616-5313
Emilie Jouanjus
orcid.org/0000-0002-3510-2475
Nathalie Fouilhé
orcid.org/0000-0002-5620-6804
Joelle Micallef
orcid.org/0000-0002-7172-7835
Maryse Lapeyre-Mestre
orcid.org/0000-0002-5494-5873

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Discussion: This study shows the importance of addictovigilance monitoring for gabapentinoids. Addictovigilance data helped to make visible the gabapentinoid-abuse related health harms (hospitalization for serious neurologic, psychiatric or cardiac effects, requests for addictological support and deaths) and to confirm the intrinsic abuse potential of pregabalin. These data highlight new points of vigilance considering observed primary abuse. At this point in France, the risk of abuse and related complications is very apparent with pregabalin. Still, it is identical to that observed elsewhere with gabapentin.

Keywords: addictovigilance, gabapentinoids, psychotropic adverse effects, addiction, prescription drug abuse

INTRODUCTION

Gabapentin and pregabalin are two pharmacologically closely related drugs, belonging to the class of gabapentinoids [mirogabalin, only available in Japan, represents the third member (1)]. This class present structural similarities with gamma-amino-butyric acid (GABA) without acting on its receptor. The mechanism of action of gabapentinoids is generally described as binding on the alpha2-voltage-dependent calcium channels in the central nervous system, reducing central neuronal excitability. This action is believed to contribute to the antinociceptive, anticonvulsant and anxiolytic properties of these drugs. Gabapentin (approved in the early 1990s) and pregabalin (approved in 2004) are widely used for epilepsy and neuropathic pain (gabapentin is indicated for post zoster pain). Pregabalin is also approved for generalized anxiety disorder and for fibromyalgia and gabapentin for restless leg syndrome only in the US. The European commercial success of pregabalin since its marketing authorization in 2004 has led to the expansion of its use in off-label indications [any type of pain or to manage benzodiazepines or alcohol withdrawal (2, 3)]. In 2010, toxicology and pharmacovigilance data as clinician reporting in Europe [Scandinavian countries, Germany and Southern Europe (4–7)] first reported involvement of pregabalin in deaths related to substance abuse. Since then, an increasing number of reviews have been published on the subject, arguing the evidence of gabapentinoid misuse and abuse. A minority of these reviews concluded that gabapentinoids has no appearing addictive potential themselves and may lead to abuse only by persons with opioid use disorders (8, 9). It should be noted that subjects with a history of psychiatric or substance use disorders are overall more at risk of such behaviors. Most of these reviews suggest that misuse and abuse occur more frequently in users of pregabalin compared with gabapentin (10–12). In France, only a few cases of gabapentin misuse and abuse have been reported until 2014 (13–15). In 2011, a first case of recreational use of pregabalin has been reported by a general practitioner in 2011 and received particular attention by the French Addictovigilance Network (FAN) as an early signal for pregabalin abuse potential. Data have been since collected leading to further evidence that pregabalin misuse and abuse is now widespread in France, with visible harmful consequences in terms of treatment demands, somatic complications, and even risk of death.

Based on data collected through the French addictovigilance system from 2010 to 2019, this study aims to describe clinical characteristics of pregabalin and gabapentin use related disorders and their health consequences, focusing on primary dependence potential, life-threatening complications and management of abuse and dependence.

MATERIALS AND METHODS

We designed a multisource investigation reviewing data reported to the French Addictovigilance Network (FAN). The FAN is made up of 13 Addictovigilance Centers, it was set up in 1990 under the supervision of the French Medicines Agency ("ANSM" for Agence Nationale de Sécurité des Médicaments et des Produits de Santé) to monitor the abuse potential of psychoactive substances (with the exclusion of tobacco and alcohol) (16–18).

Data Related to Spontaneous Reports (SRs) Notified by Health Professionals

All cases of pregabalin/gabapentin-related disorders reported between 2010 and 2019 were analyzed with data on individual features (age, gender, past medical history) and clinical features (clinical signs related to substance use, patterns of substance use). All psychoactive substances included, over the 2010–2019 period, the FAN has recorded more than 41,500 SRs.

Data Related to Forged/Falsified Prescriptions Forms Reported by Community Pharmacists (OSIAP Survey)

This survey aims to identify drugs liable to be diverted from their medical use or at risk of abuse or dependence. Prescription forms recorded from 2010 to 2019 including citations of pregabalin and gabapentin were analyzed. All prescription drugs included, over the 2010–2019 period, the FAN has recorded about 11,000 prescription forms (19, 20).

Data Related to Patterns of Psychoactive Drug Use Reported by People Who Use Drugs (PWUD) Visiting Specialized Addiction Care Centers (OPPIDUM Survey)

This annual, cross-sectional survey aims to collect information on self-reported drug use by PWUD. Data of individuals

reporting pregabalin and gabapentin use between 2010 and 2019 were analyzed. All psychoactive substances included, over the 2010–2019 period, the FAN has recorded data on around 52,000 individuals (21).

Data Related to Drug-Related Deaths From Toxicological and Medico-Legal Data (DRAMES and DTA Surveys)

These surveys aim to identify cases of death related to prescription drugs and other substances (DRAMES survey) or toxic deaths due to analgesics (DTA survey, since 2013). For a given case, each substance identified in the blood is subjected to a causality assessment, establishing the link between the substance and the cause of death. The strength of causal connection is determined by a score, from high (level 1) to low (level 4). The causal link is made on blood concentrations (or other matrices if no blood) quantification and relies on analysis of toxicology experts and different published references (22). For pregabalin, the retained therapeutic concentration is from 2 to 5 mg/L, toxic concentration is at 10 mg/L and lethal concentration at 25 mg/L and above (23), whether pregabalin is alone or in combination with other drugs. Cases of death for which pregabalin and gabapentin were confirmed and quantified, were analyzed, over the 2010–2018 period for DRAMES survey and over the 2013–2018 period for DTA survey. All psychoactive substances included, over the 2010–2018 period, the FAN has collected data on almost 4,000 deaths. The 2019 DRAMES/DTA data were not complete at the time of our study (because delay for forensic context); available information was analyzed.

Other data used into the multisource approach include the level of drug exposure in the French general population from the French Health Insurance System (Système National des Données de Santé, SNDS https://www.snds.gouv.fr/SNDS/Accueil) and the French Pharmacovigilance database for all reports of any adverse drug reaction (including misuse and abuse). **Figure 1** presents the partnership involved in the network providing field/post-marketing data and the sources of addictovigilance data used in this study (16). The level of exposure to pregabalin and gabapentin in the French general population for the 2010–2019 period was computed as the number of people living in France who received at least one prescription of these drugs each year.

To describe gabapentinoid use related disorders, the following terms and definitions were used in the manuscript:

- Misuse: use in a manner that is non consistent with the summary of the product characteristics (regarding therapeutic indications, route of administration or posology) or a nontherapeutic use of prescription drug (24)
- Abuse: misuse or illicit drug use leading to health harms (somatic or psychiatric, hospitalization, death, etc)
- Dependence: condition according to which, upon cessation, a withdrawal syndrome (somatic or psychiatric symptoms) emerges
- Substance use disorder: defined by the DSM-5 (25), when the level of available information is sufficient to conclude this or reported as such by a specialist in addiction.

As this study was performed retrospectively using routinely collected anonymous data, it did not require any ethics committee approval, in line with the French regulations for mandatory reporting of addiction cases by health professionals.

RESULTS

Over the 2010–2019 period, the following data were collected: (i) 265 SRs of gabapentinoid abuse (258 with pregabalin and 7 with gabapentin); (ii) 816 forged/falsified prescription forms (805 involving pregabalin, 10 gabapentin and 1 involving both drugs) from OSIAP survey; (iii) 145 cases of gabapentinoid use in people who use drugs (PWUD) (121 with pregabalin and 24 with gabapentin) from OPPIDUM survey; and (iv) 31 cases of gabapentinoid-related deaths (25 with pregabalin and 6 with gabapentin) from DRAMES and DTA surveys.

Evolution of Gabapentinoid Abuse Phenomenon in France From 2010 to 2019

During the study period, the consumption of both pregabalin and gabapentin increased significantly, with gabapentin level remaining about four times lower compared to pregabalin (**Figure 2**). In contrast, the proportion of falsified prescriptions with pregabalin increased sharply from 2018 onwards with a citation rate (number of pregabalin citations among all forged prescriptions collected) below 3.0% up to 2017 and increased to 11.9% in 2018 and 23.8% in 2019 (**Figure 2**). A similar pattern has been observed in other surveys (**Figure 3**). From 2010 to 2017, a gabapentinoid abuse has been reported in 24 cases (<0.5% of total of SRs per year). In 2018 and 2019, this figure increased significantly to 71 in 2018 (1.2% of total SRs) and 117 (2.0%) in 2019. In 2013, the first gabapentinoid-related deaths were reported with one case involving pregabalin. The number of reported deaths was at its maximum in 2018 ($n = 10$, data for 2019 being not completely collected at the time of the study). The number of gabapentinoid users among PWUD reached the highest level in 2019 with 40 (0.7% of the surveyed population) users, i.e., 2.6 times higher than in 2018. The gabapentinoid abuse phenomenon involved almost exclusively pregabalin and remained marginal for gabapentin.

Socio-Demographic Profiles of Problematic Users of Gabapentinoids

According to SRs, a total of 258 individuals with pregabalin abuse and 7 with gabapentin were reported. This population mainly consisted of men (72.5%). The median age was 30 years old over the period but dropped to 24 years old in 2019. The proportion of subjects under the age of eighteen was of 22.3%. Psychiatric history was reported in 70 (26.4%) patients, chronic pain in 69 (26.0%) and epilepsy in 6 (2.3%) patients. An existing substance use disorder was documented in 143 patients (54.0%, missing data 45.7%); but one reported case confirmed the absence of any substance use disorder for this patient. Substance use disorder data were available for 88 (61.5%) patients, with 61.3% of them ($N = 54$) having opioid use disorder.

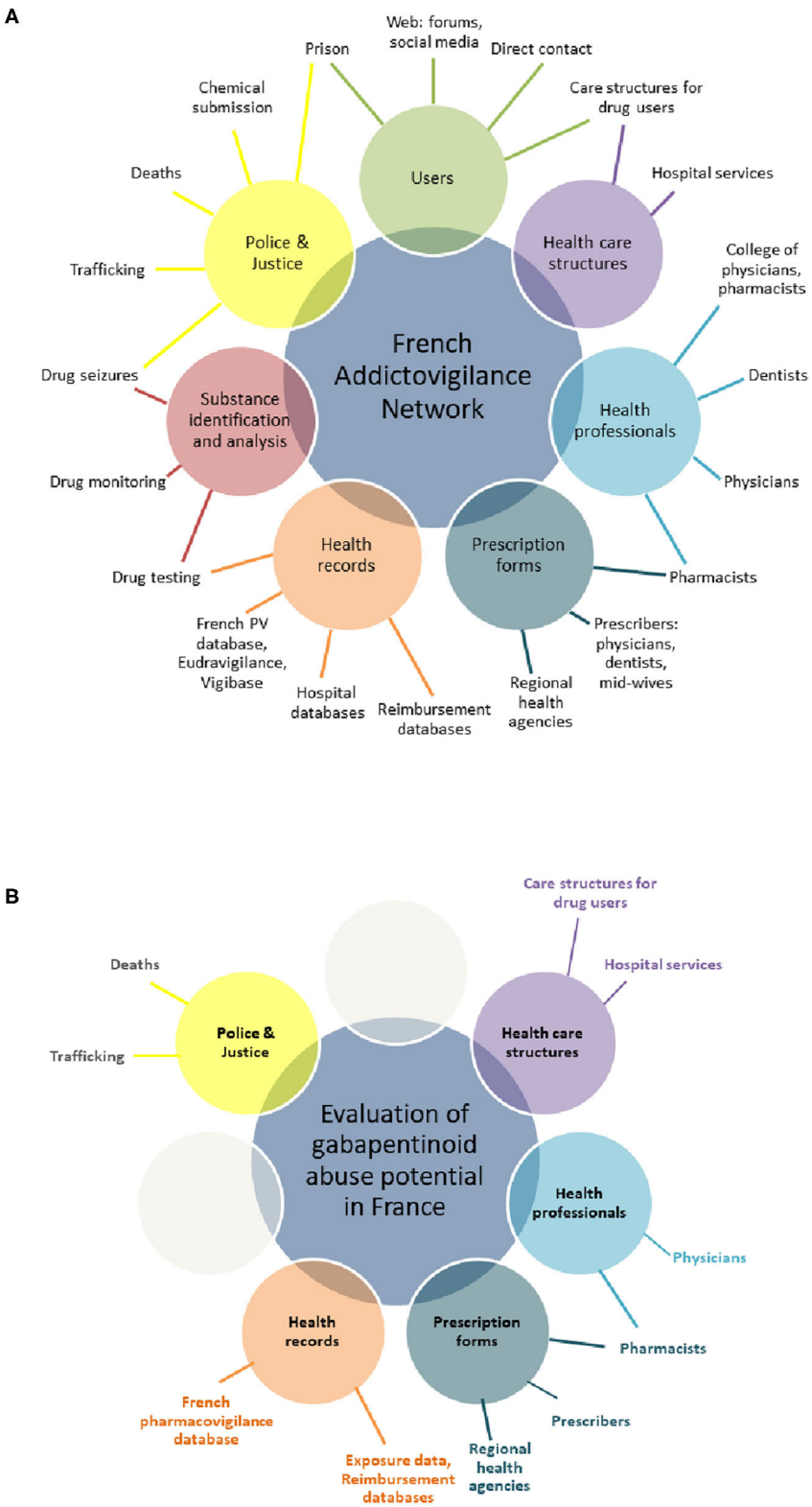

FIGURE 1 | The multidimensional French Addictovigilance Network: collaborative relationships and data sources involved in the national system **(A)** and the data sources used for the evaluation of gabapentinoid abuse potential **(B)**.

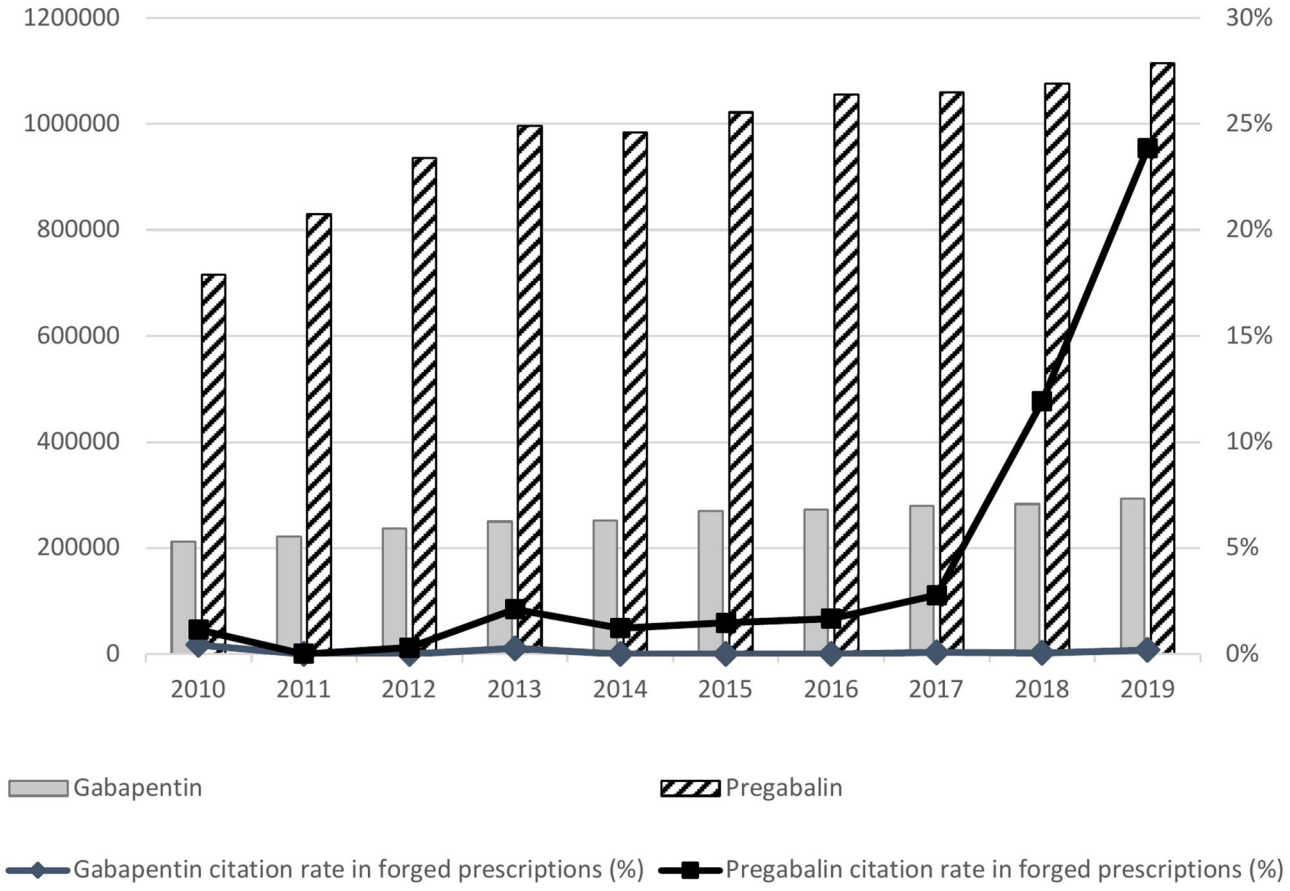

FIGURE 2 | Gabapentinoid abuse phenomenon in France from 2010 to 2019 through the monitoring of forged/falsified prescription forms (OSIAP survey) with regard to number of gabapentinoid users.

Given the limited data collected with gabapentin compared to pregabalin, the results presented in the following paragraphs 3.3 and 3.4 focus on pregabalin cases (gabapentin cases are excluded) (**Table 1**).

How Pregabalin Is Used in the Context of Abuse

According to the 258 SRs, pregabalin was use in combiation with other psychoactive substance (including alcohol) by 69 (26.7%) individuals (**Figure 4**). Among the desired non-therapeutic effects, euphoria ranked first reported by 28 (10.9%) individuals. It was followed by research of high in 23 (8.9%) individuals. Criteria related to substance use disorders were found: 20 (7.8%) individuals continued taking pregabalin to prevent the occurrence of withdrawal symptoms, and 3 (1.2%) took it by craving or routinely. Pregabalin was either used as a substitute or to prevent alternative drug use by 12 (4.7%) subjects [mainly benzodiazepines (5/12), opioids (5/12) and cocaine (2/12)] or to potentiate effects of other drugs [opioids (2/3) and cocaine (1/3)]. Pregabalin was used in the context of a drug experimentation for 2 (0.8%) subjects, including one by intranasal route. Oral administration was preferred but intranasal use was reported occasionally. Also, one subject inhaled ("smoked") pregabalin by a process similar to that used to prepare free-base cocaine. Regarding frequency intake, 138 (53.5%) individuals used pregabalin daily. From detailed cases (68.8%) the median dose was of 900 mg per day [Q1 = 450; Q3 = 1,200], with a maximum reported dose of 12.6 grams per day after 4 months of pregabalin exposure in a context of substance addiction transfer from buprenorphine to pregabalin. There were 71 (27.5%) cases relative to acute exposure of pregabalin; in these cases, the maximum reported dose (out of deliberate self-poisoning contexts) was 3.6 grams per intake to reach high and hypnotic effects. In 20 (7.8%) cases, the subjects consumed pregabalin occasionally or over a few days. The information on frequency or doses consumed was missing in 29 (11.2%) cases. Pregabalin was obtained illegally by 94 (57.7%, 95 missing data) subjects through illicit market, forged/falsified prescriptions or medical/pharmaceutical nomadism. In 70 (42.9%) cases, a valid prescription form was used. In one case, pregabalin was purchased in pharmacy without prescription (outside France). Data from 2019 OSIAP survey have shown that pregabalin has become the first drug mentioned in forged/falsified prescriptions forms presented in pharmacy (citation rate of 23.8%), while

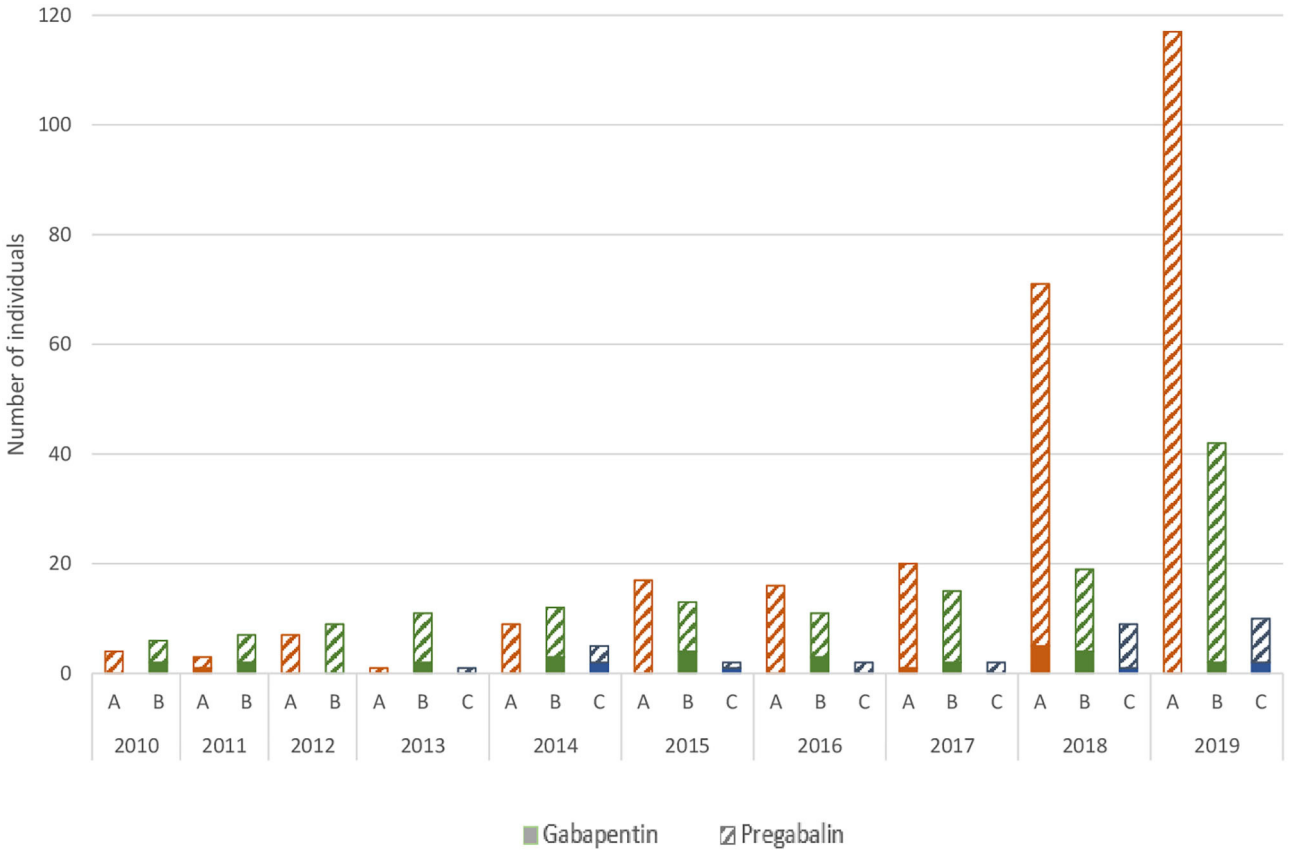

FIGURE 3 | Number of individuals affected by gabapentinoid related disorders through addictovigilance data sources (A) (orange): number of gabapentinoid related disorders from Spontaneous Reports (SRs). (B) (green): number of gabapentinoid users in people who use drugs (OPPIDUM survey). (C) (blue): number of gabapentinoid-related deaths (DRAMES and DTA surveys) - data collection uncompleted for 2019.

TABLE 1 | Main characteristics based on the 258 NotS (spontaneous reports) of pregabalin use disorders collected by the French Addictovigilance Network from 2010 to 2019.

1	The dynamics of pregabalin problematic use phenomenon intensified in France from 2018 and still growing in 2019. Among the 258 collected NotS, 183 (70.9%) occurred in 2018 and 2019.
2	Subjects were mainly men (72.5%), young (median age of 24 years in 2019). An existing substance use disorder was documented in 54% patients, including subjects with no opioid use disorder, and one reported case confirmed the lack of any substance use disorder for this patient.
3	Pregabalin was preferentially misused by the oral route, at high dose [median daily dose at 900 mg (Q1: 450; Q3: 1,200)]; occasional intakes until (3.6 grams) and illegally obtained (false prescription forms and street market). Among desired non-therapeutic effects, euphoria ranked first cited by 28 (10.9%) individuals followed by research of high in 23 (8.9%) of them.
4	Pregabalin abuse frequently led to neurological (81.6%) and psychiatric (34.4%) complications alone or in combination. A convulsive episode and a cardiac serious complication (atrioventricular block) occurred with pregabalin alone.
5	Ninety patients (34.9%) presented criteria of pregabalin use disorder, whether the subjects used it to obtain therapeutic effects or not. Between 2018 and 2019, the proportion of individuals demanding for specialized addiction care have increased from 10.6 to 23.1%. Withdrawal strategies were instituted by health professionals (hospitalization, gradual tapering off, medication support).

it ranked at the 15th position in the 2017 survey (citation rate of 2.6%) (**Figure 2**). The 300 mg dosage was the most concerned (67.3% of citations of pregabalin, missing data in 20.1%). Pregabalin street names have been reported: "l'extase" (bliss), "saroukh," "fusée" (rocket) or "taxi," and street prices: for the 150 mg dosage, 10 euros per 14 capsules, for the 300 mg dosage, 1–2 euros each capsule or 30 euros the box of 56 capsules.

Pregabalin-Related Complications in the Context of Abuse

Clinical Symptoms

Among the 258 patients presenting a problematic use of pregabalin, a hospital based care was needed in 100 (38.8%) cases and 125 (48.4%) have presented clinical complications: 106 in a context of polydrug use and 19 with pregabalin alone (**Table 2**).

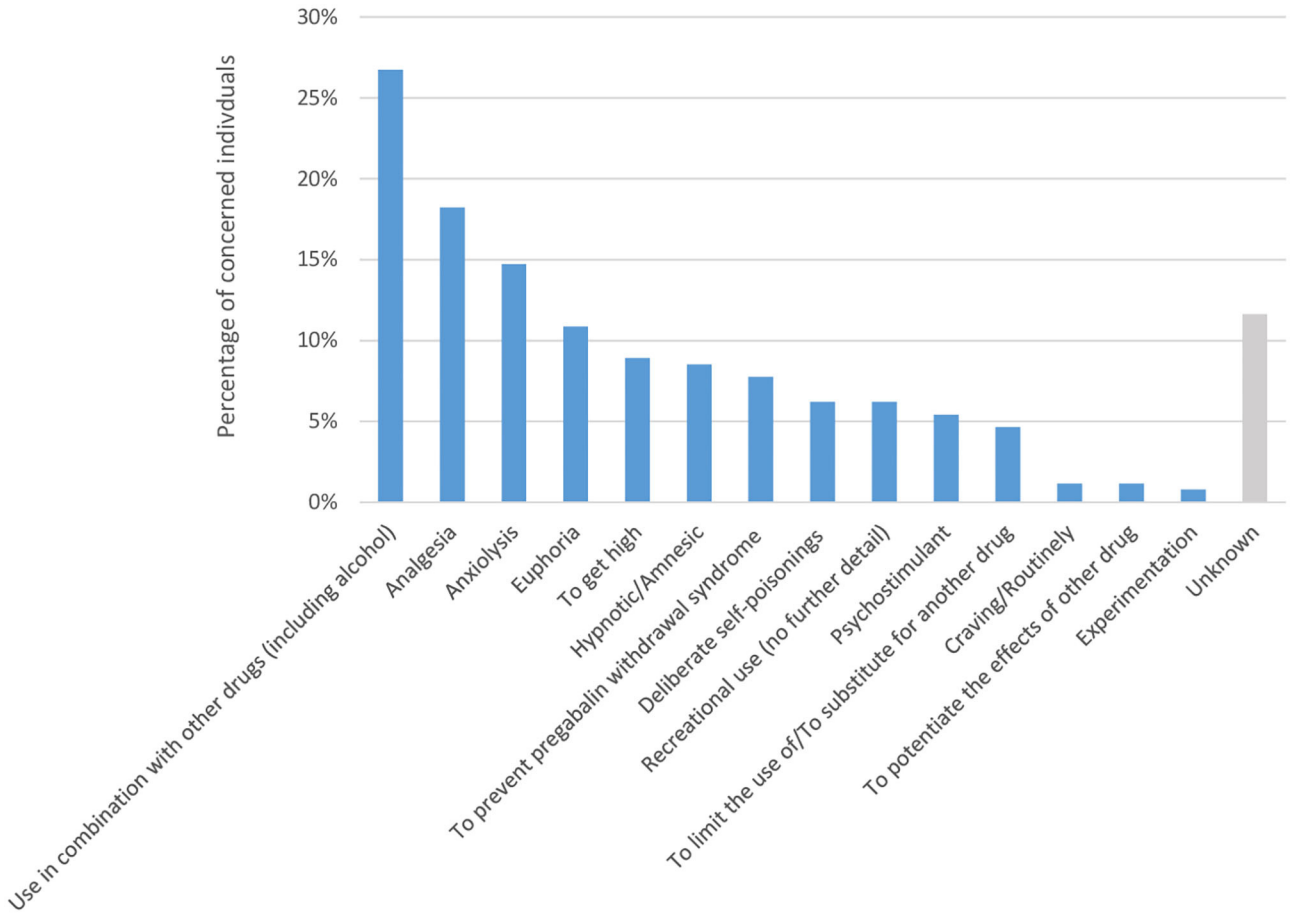

FIGURE 4 | Context of use or users' motivations to misuse pregabalin, in number of citations out of the 258 subjects with a pregabalin use disorder.

Among complications with pregabalin alone as in combination, neurological complications ranked first, concerned 81.6% of patients, mainly represented by consciousness impairment. Coma occurred in 12 patients in polydrug use context only, with benzodiazepine being co-ingested in 10/12 cases. The convulsive episode with pregabalin alone occurred in a 15-year-old girl without any history of epilepsy after an intake of 1,200 mg. Psychiatric complications came second with pregabalin alone as in-combination, concerned 34.4% of patients, and particularly behavioral issues such as agitation, aggressiveness, impulsiveness or disinhibition. Among psychotic symptoms, hallucinations were reported three times, all occurred with pregabalin combinations (1 case with alcohol after occasional pregabalin intake of 400 mg, 1 case with buprenorphine and oxazepam and 1 case with cannabis), in subjects without any psychotic history. Euphoria was reported with pregabalin alone (after an intake of 600 mg by oral route). Clinical presentations of opioid overdose (not included in impaired consciousness/miosis/dyspnea categories) concerned 11 (8.8%) patients, exclusively in the context of polyconsumption but not exclusively with opioid substances. Dyspnea (out of opioid overdose presentation) concerned 4 (3.2%) patients who have used pregabalin with other drugs, mainly opioids (3/4 cases). Two serious cardiac complications have been reported: an atrioventricular block in a male aged 35 using pregabalin by intranasal route for several months and hypertrophic cardiomyopathy in a male aged 17 who regularly used clonazepam and cannabis.

Addictological Complications and Demands for Specialized Care

Among the 258 pregabalin abuse SRs, 90 (34.9%) presented criteria of a pregabalin use disorder, whether the subjects used it to obtain therapeutic effects or not. Time to onset was specified in 48 (53.3%) cases, and the shortest was about 2 months. Over the 2010–2019 period, 49 (19.0%) subjects have requested addictological support due to pregabalin problematic use or were referred to specialized addiction care. Between 2018 and 2019, the proportion of subjects demanding for specialized addiction care have increased from 10.6 to 23.1%. Withdrawal strategies consisted in hospitalization to stop using pregabalin [12 (24.5%) subjects] or ambulatory, in gradual tapering off (9, 18.4%) or by introducing medication such as benzodiazepine, sedative antipsychotic or antidepressant (5, 10.2%). A prior

TABLE 2 | Clinical complications due to pregabalin reported in spontaneous reports (SRs) from 2010 to 2019.

	All pregabalin exposures	(%)	Pregabalin-only	(%)	Pregabalin in co-consumption	(%)	Co-consumed reported substances (*n*)
Number of patients	**258**		**73**		**185**		
Number of patients with reported clinical complications	**125**	**48.4%**	**19**	**26.0%**	**106**	**57.3%**	
Neurological complications	**102**	**81.6%**	**16**	**84.2%**	**86**	**81.1%**	
Impaired consciousness (out of clinical "triad" of opioid overdose*)	68	66.7%	11	68.8%	57	66.3%	Benzodiazepine (33); Opioids (17); Psychostimulants (19); Alcohol (18); Other psychotropic drugs (15); Cannabis (14)
Incl. Coma (GSC < 9)	*12*	*11.8%*	*0*		*12*	*14.0%*	*Benzodiazepine (10); Other psychotropic drugs (6); Opioids (5); Psychostimulants (5); Alcohol (5); Cannabis (3)*
Psychomotor retardation - Dizziness - Ataxia	19	18.6%	5	31.3%	14	16.3%	Opioids (5); Cannabis (5); Benzodiazepine (4); Psychostimulants (3); Alcohol (3); Other psychotropic drugs (2)
Involuntary/abnormal movements (dyskinesia, tremor, nystagmus, chorea)	8	7.8%	0		8	9.3%	Cannabis (3); Alcohol (3); Benzodiazepine (2); Opioids (2); Psychostimulants (2); Other psychotropic drugs (2)
Convulsion	7	6.9%	1	6.3%	6	7.0%	Opioids (3); Psychostimulants (3); Other psychotropic drugs (3); Alcohol (3); Benzodiazepine (2); Cannabis (2)
Miosis (out of clinical 'triad' of opioid overdose)	10	9.8%	0		10	11.6%	Cannabis (6); Benzodiazepine (5); Psychostimulants (4); Other psychotropic drugs (4); Alcohol (4); Opioids (3)
Mydriasis	7	6.9%	1	6.3%	6	7.0%	Alcohol (4); Psychostimulants (3); Cannabis (3); Benzodiazepine (2); Opioids (2)
Psychiatric complications	**43**	**34.4%**	**5**	**26.3%**	**38**	**35.8%**	
Behavioral issues (agitation, aggressiveness, impulsiveness, disinhibition)	27	62.8%	3	60.0%	24	63.2%	Benzodiazepine (11); Psychostimulants (8); Cannabis (8); Opioids (7); Alcohol (5); Other psychotropic drugs (4)
Depressed mood, dysthymia	7	16.3%	1	20.0%	6	15.8%	Benzodiazepine (4); Psychostimulants (3); Alcohol (2); Opioids (2); Other psychotropic drugs (1)
Psychotic symptoms (delirium, hallucinations)	6	14.0%	0		6	15.8%	Opioids (2); Alcohol (2); Cannabis (2); Psychostimulants (1); Other psychotropic drugs (1); Benzodiazepine (1)
Anxiety	4	9.3%	1	20.0%	3	7.9%	Psychostimulants (2); Benzodiazepine (1); Cannabis (1); Other psychotropic drugs (1)
Euphoria	2	4.7%	1	20.0%	1	2.6%	Opioids (1)
Clinical presentation of opioid overdose* (uncounted elsewhere)	**11**	**8.8%**	**0**		**11**	**10.4%**	Benzodiazepine (8); Opioids (8); Psychostimulants (7); Cannabis (6); Other psychotropic drugs (2); Alcohol (1)
Respiratory complications	**4**	**3.2%**	**0**		**4**	**3.8%**	
Dyspnea (out of clinical 'triad' of opioid overdose)	4	100.0%	0		4	100.0%	Opioids (3); Psychostimulants (2); Benzodiazepine (1); Cannabis (1); Other psychotropic drugs (1)
Cardiac complications	**2**	**1.6%**	**1**	**5.3%**	**1**	**0.9%**	
Atrioventricular block	1	50.0%	1	100.0%	0		
Hypertrophic cardiomyopathy	1	50.0%	0		1	100.0%	Benzodiazepine (1); Cannabis (1)
Others	**3**	**2.4%**	**1**	**5.3%**	**2**	**1.9%**	
Hyperglycemia	1	33.3%	0		1	50.0%	Opioids (1); Psychostimulants (1); Cannabis (1); Alcohol (1)
Hypoglycemia	2	66.7%	1		1	50.0%	Benzodiazepine (1); Psychostimulants (1); Cannabis (1)

**impaired consciousness and myosis and bradypnea. Bold values are indicates in main titles. Italic values are i[illegible] sub-category (among impaired consciousness there was cases of coma).*

withdrawal attempt was reported in 13 (26.5%) subjects. Data from 2019 OPPIDUM survey have shown the highest level of pregabalin consumption in individuals seeking addiction care (**Figure 3**). In 2019, for the first time since the beginning of the OPPIDUM investigation, two subjects reported pregabalin as the first psychoactive substance that leads to dependence.

Pregabalin Related Deaths

From 2010 to 2018, pregabalin was detected and quantified in 51 cases of death. Pregabalin was responsible for death (level 1 of causal connection) in 17 cases (**Table 3**); alone (case 12) or in combination with other drugs (all other cases). The most frequently detected drugs assessed as co-responsible for death were opioids involved in 12/16 cases (with tramadol and methadone, respectively, involved in 5 and 4 cases). The blood concentrations were lethal in 8 cases, ranged from 26 to 154 mg/L (cases 1–8) and toxic in 9 cases (cases 9–17), ranged from 9 to 21 mg/L. The first pregabalin-related death was recorded in 2013. From 2013 to 2017, one to three pregabalin related deaths were reported each year, whereas the year 2018 counted 8 deaths (which represents 1.4% of all deaths due to drugs in 2018). Among the 17 cases, 9 have been reported in a context of substance use disorders and exclusively concerned men with a median age of 34 years old while the remaining 8 cases without substance use disorder context concerned mainly women (6/8 cases) with a median age of 50 years old. In the same period, only 4 cases of gabapentin-related deaths were reported over the 2010–2018 period. The data of the year 2019 were not completely available at the time of this study (because delay for forensic context), but 8 cases involving pregabalin and 2 cases involving gabapentin had already been reported in that year (**Figure 3**).

DISCUSSION

This paper aims to describe gabapentinoid use related disorders and their health consequences in France using multi-sourced information and pharmacological expertise. From 2010 to 2019, the general French population has been increasingly exposed to gabapentinoids and particularly pregabalin, which has led to an expanding risk level of adverse events including substance use disorders. The dynamics of gabapentinoid, particularly pregabalin, abuse phenomenon is recent, intensified from 2018 and still grown in 2019. Indeed, over the 2010–2019 period, 70.9% of abuse cases reported to the FAN occurred in 2018 and 2019. Health indicators were reflecting this growth: hospital based care for serious neurologic, psychiatric or cardiac complications, demands for addiction care and deaths. Over a year (between 2018 and 2019), the proportion of subjects demanding for addiction care increased from 10.6 to 23.1%. French practitioners are currently facing the management of gabapentinoid withdrawals and have initiated strategies (hospitalization, tapering off, introducing medication), despite having proper guidelines (26). Based on the rise of pregabalin involved in overdose deaths worldwide (27–33), the FAN worked jointly with the French Society of Analytical Toxicology (Société Française de Toxicologie Analytique) to include gabapentinoids in toxicological investigations in clinical situations involving new psychoactive substances and deaths encountered in the practice of forensic toxicology (34). Such awareness could have explained the increase of reported gabapentinoid-related deaths. It certainly helped to better assess gabapentinoid use disorders related harms (35). Experimental studies have shown that the combination of pregabalin with opioids has an additive effect or reverse tolerance to depress respiration and therefore increases the risk of acute overdose death (36); this was also observed in observational studies with gabapentin and pregabalin in patients exposed to opioids (for maintenance therapy) or for pain (37–40).

Gabapentinoids (gabapentin and pregabalin) exhibit calcium channel antagonism and attenuate calcium influx, which can explain unwanted electrophysiological effects. By this way, they present a similar spectrum of adverse drug reactions, which are dose-dependent. Some studies highlighted the implication of gabapentin and pregabalin in cardiac conduction disorders (15, 41). These deleterious cardiac outcomes were observed in case of misuse and abuse of high doses of pregabalin in our study even if rarely reported in the literature (42). We also cannot exclude the implication of gabapentinoids in overdose death not only through exacerbating respiratory depression but also through dysrhythmic disorders.

Along with the population approach, published data and those collected in this study have demonstrated that pregabalin presents a true abuse potential by its own. Clinical and experimental studies have shown the "drug-liking" and reinforcing effects of pregabalin (37, 43), not correlated with the mesolimbic dopaminergic system but potentially mediated through a possible glutamatergic mechanism (44–46). This rewarding effect is supported by data collected by the FAN through spontaneous reports with 10.9% of problematic users searching for euphoria, 8.9% to get high, 5.4% searching for psychostimulation and 1.2% feeling a craving for pregabalin or routinely use it. Of note, two subjects used pregabalin in the context of drug experimentation. These elements are in favor of an intrinsic attractiveness of pregabalin. Concerning gabapentin, experimental studies have shown that gabapentin induced drug-seeking behavior but only with the highest dose (47). This has also been demonstrated with mirogabalin (48). Published literature has shown that the risk of gabapentinoid abuse increased in subjects with a history of substance use disorder, particularly in those with opioid use disorder (8, 9, 49–54). The present data suggest that abuse could be observed in subjects without any opioid abuse history; within the 265 spontaneous reports of gabapentinoid abuse collected, 38.7% of subjects with a substance abuse disorder had no opioid use disorder. In addition, a case of pregabalin abuse concerned a patient without any substance use disorder, which constitutes an early signal given the well-known under-reporting phenomenon (14, 55). Other elements are in favor of the possible occurrence of pregabalin *de novo* dependence; in the 2019 OPPIDUM survey, for the first time, two subjects cited pregabalin as the first psychoactive substance that led to dependence (implying that the pregabalin use disorder was at the cause of the demand for addiction care), which is also an emerging signal. Some international studies in the general population have shown that from 8 to 12% of subjects initiating prescribed pregabalin

TABLE 3 | Pregabalin-attributed deaths: data from DRAMES and DTA surveys.

Case	Gender, Age (y)	Drug responsible for death and blood concentrations				Other drugs detected	Autopsy data	Context of death, individual health history
1	M, 43	Pregabalin 154 mg/L	Cocaine 1,750 μg/L			Cyamemazine, venlafaxine, cannabis	Toxic death. Drug use by intravenous administration.	Context of abuse/dependence. Found at his home, injection drug use equipment next to him. Prescribed pregabalin.
2	M, 35	Pregabalin 76 mg/L	Cocaine 128 μg/L			Diazepam, nordiazepam	Acute heart rhythm disorder or ischemia. Possible complication of body packing.	Context of abuse/dependence. Psychiatric history, found at his home in a state of putrefaction. Notion of alcohol abuse. Prescribed pregabalin.
3	M, 40	Pregabalin 59.5 mg/L	Tramadol 12,800 μg/L				Toxic death secondary to pulmonary edema.	History of chronic back pain. Died at his home. Prescribed pregabalin.
4	M, 32	Pregabalin 46 mg/L	Methadone 723 μg/L	Olanzapine 650 μg/L		Diazepam, nordiazepam, mianserine, zopiclone, ethanol	Asphyxia probably toxic.	Context of abuse/dependence. History of methadone abuse (intranasal use and doctor shopping behavior), ongoing drug withdrawal, found in his vehicle, alcohol, methadone packages and intranasal equipment next to him.
5	M, 44	Pregabalin 45.3 mg/L	Buprenorphine 0.37 μg/L	Oxazepam 2,860 μg/L		Diazepam, nordiazepam, levetiracetam, zopiclone	Toxic death secondary to pulmonary edema.	Context of abuse/dependence. On buprenorphine maintenance therapy. Increased drug use in the context of traumatic pain 6 months ago with doctor shopping behavior.
6	F, 40	Pregabalin 40.6 mg/L	Tramadol 6,880 μg/L	Amitriptyline 3,400 μg/L		Oxazepam, venlafaxine, lamotrigine	Pink foam on lips and nose.	History of bipolar disorder and alcohol addiction. Context of suicide with drug medications next to her and a suicide note.
7	M, 45	Pregabalin 29.8 mg/L	Buprenorphine 4.39 μg/L	Olanzapine 460 μg/L		Clonazepam, cannabis	Toxic death secondary to nervous system and respiratory depression. Cirrhotic subject.	Context of abuse/dependence. Psychiatric, epileptic and drug addiction history, died at his home. Medication drugs next to him.
8	M, 29	Pregabalin 26 mg/L	Methadone 43 μg/L			Phenobarbital, fluoxetine, ethanol	Not known	Context of abuse/dependence. Found in a state of putrefaction with drug medications next to him.
9	F, 38	Pregabalin 21 mg/L	Lorazepam 440 μg/L	Quetiapine 4,420 μg/L	Tramadol 4,650 μg/L	Venlafaxine 3,360 μg/L	Dosulepine, duloxetine	Toxic death secondary to cardio-respiratory decompensation.	Context of suicide. Pregabalin used by oral route.

(Continued)

TABLE 3 | Continued

Case	Gender, Age (y)	Drug responsible for death and blood concentrations				Other drugs detected	Autopsy data	Context of death, individual health history
10	F, 76	Pregabalin 19.4 mg/L	Tramadol 1,300 μg/L	Flecainide 2,100 μg/L		Ethanol	Possible toxic death.	History of cardiac issues.
11	F, 47	Pregabalin 17 mg/L	Hydroxyzine 660 μg/L	Codeine 1,538 μg/L	Tramadol 1,300 μg/L	Paracetamol, cyamemazine, zopiclone, oxazepam	Acute pulmonary edema.	Died at her home. Prescribed pregabalin. Pregabalin used by oral route.
12	F, 63	Pregabalin 17 mg/L				Tramadol, cyamemazine	Possible toxic death secondary to bronchial inhalation due to coma.	History of depressive syndrome. Prescribed pregabalin.
13	M, 33	Pregabalin 17 mg/L	Methadone 333 μg/L			Buprenorphine, cyamemazine, diazepam, mianserine, paroxetine, cannabis	No	Context of abuse/dependence. On buprenorphine, died in detention.
14	M, 25	Pregabalin 12.6 mg/L	Methadone 46.7 μg/L			Diazepam, nordiazepam, temazepam, THC	Not known	Context of abuse/dependence. History of cannabis and alcohol abuse. No information available on methadone use.
15	F, 53	Pregabalin 11.7 mg/L	Amitriptyline 16.6 μg/L	Bromazepam 1,140 μg/L	Venlafaxine 840 μg/L	Nordiazepam	Possible toxic death or natural cardiac death	History of depression, found at his home, alcohol and medication drugs next to her. No notion of pregabalin treatment.
16	M, 29	Pregabalin 11 mg/L	Benzoylecgonine 930 μg/L				Mechanical asphyxiation by false food route due to toxic overdose.	Context of abuse/dependence. History of depressive syndrome and cocaine use, died at his home. Notion of alcohol use the day before.
17	F, 53	Pregabalin 9 mg/L	Amitriptyline 290 μg/L	Morphine 125 μg/L	Oxazepam 6,170 μg/L	Zolpidem	Organ damages due to multiple pathologies.	Prescribed pregabalin.

M, Male; F, Female; Y, years.

TABLE 4 | International regulatory status, amendments or monitoring of dispensing for pregabalin and gabapentin.

Year	Month	Country	Measure
2005	July	United States of America (USA)	Pregabalin: Drug Schedule V Controlled Substances (Federal law).
2015	May	Saoudi Arabia	Pregabalin: Limited prescription, dispensing only in state health-care structures and use of a prescribing register.
	October	Russia	Pregabalin: Listed as controlled medicine
	December	United Arab Emirates	Pregabalin and Gabapentin: List of Controlled Medicines and Medications, Narcotic and Controlled Prescriptions. Limited prescription to 3 days for general practioners, 2 weeks for specialists, 4 weeks in hospital. Prescription validity: once (no possible renewal). Register for prescribers and pharmacies and specific prescription support provided by the Ministry of Health.
2016	August	Minnesota (USA)	Gabapentin: Mandated reporting to a PDMP
	December	Argentina	Pregabalin: Listed as Other Substance for Special Control
		Ohio (USA)	Gabapentin: Mandated reporting to a PDMP
2017	February	Virginia (USA)	Gabapentin: Mandated reporting to a PDMP
	May	Wyoming (USA)	Gabapentin: Mandated reporting to a PDMP
	July	Armenia	Pregabalin: Listed as controlled substance
		Kentucky (USA)	Gabapentin: Drug Schedule V Controlled Substances with mandated reporting to a PDMP (State law)
		West Virginia (USA)	Gabapentin: Mandated reporting to a PDMP
	August	Massachusetts (USA)	Gabapentin: Mandated reporting to a PDMP
		North Dakota (USA)	Gabapentin: Mandated reporting to a PDMP
	November	Turkey	Pregabalin: Prescription validity for 1 year. Specialized opinion (neurologist or psychiatrist) for chronic prescription. Electronic prescription since January 2018.
	November	Jordan	Pregabalin: Listed as controlled substance, second table (Drugs, Psychotropic substances and Precursor chemicals appended to the Narcotic Drugs and Psychotropic Substances Law no. 23 of 2016). Limited packaging to 64 tablets. Precribing and dispensing register.
2018	January	Nebraska	Gabapentin: Mandated reporting to a PDMP
	April	Norway	Pregabalin: Schedule B (alongside benzodiazepine)
	May	New Jersey (USA)	Gabapentin: Mandated reporting to a PDMP
	June	West Virginia (USA)	Gabapentin: Drug Schedule V Controlled Substances (State law)
	July	Sweden	Pregabalin: List of substances to be considered narcotics under the Penal Law on Narcotics.
		Tennessee (USA)	Gabapentin: Drug Schedule V Controlled Substances
		Kansas (USA)	Gabapentin: "Drug of concern," mandated reporting to a PDMP
2019	January	Michigan (USA)	Gabapentin: Drug Schedule V Controlled Substances (State law)
	April	United-Kingdom	Pregabalin and Gabapentin: Category C (prescribing and dispensing restrictions comparable to benzodiazepine)
	June	Washington (USA)	Gabapentin: Mandated reporting to a PDMP
	July	Virginia (USA)	Gabapentin: Drug Schedule V Controlled Substances (State law)

PDMP, Prescription Drug Monitoring Program.

presented a misuse (56–58). In the French cohort study, a possible evolution toward a primary addiction was found for 11% of the gabapentinoid misusers without previous any history of drug use disorder before drug initiation, whereas it was 1.6 times lower for duloxetine misusers (56).

At this stage in France, the risk of abuse of pregabalin is indisputable, and its harmful consequences are becoming problematic on a population scale. The potential of gabapentin abuse exists and has been observed elsewhere, in the USA and the UK (8, 11, 12, 38, 39, 59). It is still not very apparent in France (13); this discrepancy could be due to the level of use, which is about four times lower for gabapentin than pregabalin. Moreover, geographical variations must be interpreted with caution and could be partly explained by the health professionals' awareness regarding the abuse potential of these drugs (37–39, 59–61).

This paper shows the importance of specific post-marketing monitoring on substance use related disorders (that is addictovigilance). The isolated analysis of pregabalin exposure data could not have revealed the suspected misuse behaviors to obtain this drug highlighted by OSIAP survey. Along with spontaneous reports, these data support the growing ease of access to pregabalin through street market with falsified or valid prescription forms. Moreover, at the time of pregabalin marketing approval, pre-clinical and clinical studies on abuse potential were limited, and states decisions were different in the USA and Europe. Based on a clinical abuse liability study showing that pregabalin (450 mg) could be as attractive as diazepam (30 mg) leading subjective effects of "drug-liking" and higher reported euphoria as an adverse reaction in clinical trials compared to placebo (4 vs. 1% of patients), the FDA scheduled pregabalin as a controlled substance (Schedule V) indicating that

it had abuse potential, while the EMA did not at once, even in 2006 when extending market approval to generalized anxiety disorder was submitted and concluded to a low abuse potential in analogy with gabapentin (62, 63). Since, the phenomenon of abuse of gabapentinoids has spread to an international level (Europe, Australia, USA). Since 2015, a dozen countries around the world have regulated the prescription and dispensing procedures for pregabalin, and several have extended these restrictions to gabapentin (**Table 4**) (64). In France, proposals for regulatory measures have been made and are currently being considered by the French Medicines Agency. Health damages due to gabapentinoid abuse are to balance with their clinical efficacy. Precisely, after a growing enthusiasm for the multiform therapeutic virtues claimed by various promoters of this drug, a growing number of publications highlight the insufficient or unproven effectiveness of pregabalin in neuropathic pain and fibromyalgia (65), as well as in the management of substance use disorders (66, 67) or long-term beneficial impact in post-traumatic stress disorder (68). Finally, recent observations from population-based studies, and animal models, have demonstrated that association of gabapentinoids and opioids (analgesics, maintenance drugs, or illicit opioids) significantly increase the risk of opioid death, with the reversibility of tolerance for opioid respiratory depression (36–38, 40).

In clinical practice, based on available guides (69, 70), results of this study and published data, some recommendations may be proposed at different steps. Before prescribing gabapentinoids, the medical questioning should search for possible psychiatric or substance abuse (including alcohol and tobacco) history. To consider other drugs taken, whenever prescribed or not, should avoid potentially dangerous drug-drug interactions such as gabapentinoid-opioid interaction on respiratory distress. Or, at least get to know the patients/users of respiratory distress symptoms and the first emergency actions. During a gabapentinoid medication, the minimal effective dose should be taken and the benefits/risks balance evaluated at each prescription and refill. Considering substance disorders-related risks, the following signs should be monitored and raised prescriber's attention: tolerance (that is, the reduction of effects as exposure continues at constant dose, or the corollary of this, the need to increase doses to achieve the desired effects), searching for psychoactive effects other than those of the initial indication, drug-seeking behavior (71) or the occurrence of withdrawal symptoms during discontinuation/between gabapentinoid intakes. If possible, due to withdrawal syndrome, gabapentinoid discontinuation may be planned and used schedules. A hospitalization could be proposed if experiencing withdrawal difficulties or existing substance use disorder or psychiatric co-morbidities. The absence of a substance use transfer at the time of discontinuation should be monitored (68). To improve the knowledge on the evaluation of drugs in real life, at any time of management, to report any adverse event, including those related to substance use disorders, to the territorial vigilance systems.

The strength of this study is to cross results of different data sources collected over a recent 10 years' period, for both pregabalin and gabapentin drugs. However, there are limitations related to the four addictovigilance data sources used. The level of reported information in SRs could be different from one case to another, on individuals or clinical features, depending on the person filling the reporting form and available/patient-provided information at time of reporting. Moreover, it could exist an awareness bias with pregabalin compared to gabapentin, with first specific sensitizations of French health professionals on pregabalin misuse since 2016 (72). The pharmacoepidemiological studies OSIAP, OPPIDUM, and DRAMES/DTA could presented bias related to participation and reported information. It has to be note that the results of DRAMES/DTA surveys should not be considered as an exhaustive description of drug-related deaths in France. They are based on voluntary participation of expert toxicologists, requested toxicological analysis carried out by judicial authorities and the spectrum of substances analyzed (73). Besides these limits, DRAMES/DTA surveys are currently references for the assessment of drug-related deaths in France.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: According to the French laws (Articles R.5132-113 and R.5132-114), each case was recorded in the French Addictovigilance database, in an anonymous way. All authors had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Requests to access these datasets should be directed to Camille Ponté, ponte.c@chu-toulouse.fr.

AUTHOR CONTRIBUTIONS

MT and CP analyzed and interpreted data. EJ, NF, and JM, respectively, managed the national OSIAP, DRAMES/DTA, and OPPIDUM database and extracted the data. MLM was responsible for the study conception and design. MT, CP, EJ, NF, JM, and MLM took part in drafting the manuscript and critical revision, and all authors approved the final version.

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LIST OF THE FAN INVESTIGATORS

Amélie Daveluy (Addictovigilance Center, Bordeaux), Reynald Le Boisselier (Addictovigilance Center, Caen), Christine Fournier-Choma (Addictovigilance Center, Clermont-Ferrand), Bruno Revol (Addictovigilance Center, Grenoble), Sylvie Deheul (Addictovigilance Center, Lille), Cécile Chevallier (Addictovigilance Center, Lyon), Liselotte Pochard (Addictovigilance Center, Marseille), Hélène Peyrière (Addictovigilance Center, Montpellier), Valérie Gibaja (Addictovigilance Center, Nancy), Marylène Guerlais (Addictovigilance Center, Nantes), Julie Heredia (Addictovigilance Center, Paris), Marie-Christine Perault Pochat (Addictovigilance Center, Poitiers), Florence Fabre (Addictovigilance Center, Toulouse)

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Continuous Infusion of Flumazenil in the Management of Benzodiazepines Detoxification

Anna Benini[1], *Rossella Gottardo*[2], *Cristiano Chiamulera*[1], *Anna Bertoldi*[3], *Lorenzo Zamboni*[3]* *and Fabio Lugoboni*[3]

[1] Department of Diagnostics and Public Health, University of Verona, Verona, Italy, [2] Forensic Toxicology Laboratory, Department of Diagnostics and Public Health, University of Verona, Verona, Italy, [3] Department of Internal Medicine, Addiction Unit, Verona University Hospital, Verona, Italy

An effective approach in the treatment of benzodiazepine (BZD) overdosing and detoxification is flumazenil (FLU). Studies in chronic users who discontinued BZD in a clinical setting suggested that multiple slow bolus infusions of FLU reduce BZD withdrawal symptoms. The aim of this study was to confirm FLU efficacy for reducing BZD withdrawal syndrome by means of continuous elastomeric infusion, correlated to drugs plasma level and patients' compliance.

Methods: Seven-day FLU 1 mg/day subcutaneously injected through an elastomeric pump and BZDs lormetazepam, clonazepam, and lorazepam were assessed by HPLC-MS/MS in serum of patients before and after 4 and 7 days of FLU continuous infusion treatment. Changes in withdrawal severity were assessed by using the BZD Withdrawal Scale (BWS).

Results: Fourteen patients (mean age ± SD 42.5 ± 8.0 years, 5 male and 9 female), admitted to the hospital for high-dose BZD detoxification, were enrolled in the study. Serum FLU concentrations significantly decreased from 0.54 ± 0.33 ng/ml (mean ± SD) after 4 days of treatment to 0.1 ± 0.2 ng/ml at the end of infusion. Lormetazepam concentrations were 502.5 ± 610.0 ng/ml at hospital admission, 26.2 ± 26.8 ng/ml after 4 days, and 0 at the end of treatment. BWS values decreased during FLU treatment temporal period. FLU was well-tolerated by patients.

Conclusions: Elastomeric FLU infusion for BZD detoxification is a feasible administration device to maintain adequate, constant, and tolerated FLU concentrations for reducing BZD withdrawal symptoms.

Keywords: benzodiazepine, flumazenil, withdrawal, high dose, detoxifcation

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***Correspondence:**
Lorenzo Zamboni
lorenzo.zamboni88@gmail.com

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INTRODUCTION

Although benzodiazepines (BZDs) constitute one of the most broadly prescribed drug classes worldwide, the frequent and often inappropriate use is a problem that remains considerably underestimated by practitioners and most regulatory agencies (1). BZD can produce tolerance and dependence; thus, their use is recommended for a limited time (2). Surveys carried out in the 1990s in France, Germany, Italy, and the United Kingdom showed that 3.9% of hypnotic drug users and 3.2% of anxiolytic drug users had been taking a dose exceeding the recommended

one (2–4). In Italy, about 7.5–10% of adult population are BDZ users, half of these being long-term users (LTU) with a diagnosis of BZD use disorder (5). Another study conducted in Italy showed that 14.0% of patients visiting general practitioners were taking BZDs, with 4.7% of the total sample being LTU, using BZDs daily for at least 12 months (6).

BZD tolerance was first reported in 1961 (7), but this phenomenon has been often obscured by the enthusiastic use of these drugs, which were able to replace barbiturates. The low toxicity coupled to a high potential of tolerance can lead to very high-dose misuse (8). From a clinical point of view, the only proposed solution of a gradual reduction of BZD is too simplistic. For long-term users, in general, if properly applied, gradually reducing the dosage works, but it is much less effective for high-dose users (2, 8, 9). This is worth mentioning because withdrawing from high doses of BZD carries significant risk for the health of the patient (2, 10).

It is in this area of HDUs that the use of flumazenil (FLU), used worldwide to treat the overdose of BZD, has been demonstrated as effective (9, 11–13). Experimental findings have shown that FLU acts as a BZD partial agonist with a weak intrinsic activity, when administered by slow intravenous infusion. While withdrawal symptoms may be brought on by the use of FLU, BZD-tolerant patients only reported mild symptoms (14, 15).

BZDs positively modulate γ-aminobutyric acid (GABA) through distinct binding sites on $GABA_A$ receptors, and there is little variation among BZDs in pharmacodynamical factors such as selectivity and efficacy. Consequently, the choice of a particular BZD for clinical use is primarily based on pharmacokinetic features. Only one drug, flumazenil (FLU), is currently approved to reverse the effects of BZDs. FLU is a BZD partial agonist commonly used in the treatment of BZD overdose. Studies in chronic users who have discontinued BZDs suggested that multiple slow bolus infusions of FLU reduce the symptoms of BZD withdrawal when compared to placebo (9). The mechanism of FLU action remains, however, unclear: its action may facilitate the coupling of $GABA_A$ and BZD receptor complexes, presumably by reversing the down-regulation/uncoupling that occurs with long-term BZD use (16). This mechanism is supposed to underlie FLU's weak agonist action and may explain its ability to attenuate BZD withdrawal symptoms (9). FLU does not antagonize the effects of other CNS sedative-hypnotics, such as ethanol, opioids, or general anesthetics (17).

FLU owns a rapid and extensive distribution phase with high volume of distribution and a second phase with fast metabolic elimination and short half-life (18). Its brief BZD-antagonism duration is due to a rapid hepatic elimination, determining its short half-life (60–90 min) and high plasma clearance (31–78 l/h). The low plasma protein binding of FLU (about 50%) does not limit its wide distribution (apparent distribution volume 0.6–1.6 l/kg) or its partly flow-dependent hepatic elimination (19, 20). Pharmacokinetic parameters of FLU do not change whether the drug is administered alone or in combination with other BZDs (18). For BZD detoxification, a viable method is the intravenous administration of FLU by using multiple bolus infusions either alone (14, 21) or in combination with tapering doses of BZDs (11).

The pharmacodynamical mechanisms of FLU are therefore crucial to determine its clinical effect, which could be achieved thanks to specific FLU infusion parameters in order to guarantee timing and extent of receptor occupancy (14). Thus, the choice of the most appropriate mode of delivery must be based on the correlation between FLU infusion parameters, plasma levels, and clinical endpoint. Our addiction unit has been employing FLU for high-dose BZD detoxifications since 2003, initially by means of endovenous continuous infusion administered by day. Such mode of delivery was both inconstant at maintaining adequate serum levels, being unfeasible for the night, and uncomfortable for the patient. In order to maintain constant serum concentration of FLU and to reduce modality of administration from multiple to single, we aimed to deliver FLU by slow subcutaneous infusion by using an elastomeric infusion pump at constant flow. In this study, we correlated the efficacy of continuous elastomeric FLU infusion on BZD withdrawal clinical endpoint to both drugs' (FLU and BZDs) plasma levels and, of equal importance, to patients' compliance and tolerance to treatment.

MATERIALS AND METHODS

This study was approved by the Ethical Review Board of the University Hospital (protocol number: 50771; prog. n. 683CESC). Informed consent was obtained from each subject.

Subjects

Five male and nine female patients (mean age ± SD 42.5 ± 8.0 years), admitted to the hospital for BZD detoxification, were enrolled in the study (see **Table 1** for patients' characteristics). The BZD use was stopped on day 1 of admission. The therapy with antidepressants, if any (**Table 1**), was maintained and continued after discharge.

All patients reported a history of BZD dependence according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (22). Before hospitalization, all patients were interviewed by a physician to assess degree of BZD dependence and general health conditions. All patients had voluntarily contacted the Addiction Unit of Verona University Hospital and were aware of their BZD dependence.

Inclusion criteria were as follows: (i) age older than 18 years; (ii) diagnosis of BZD use disorder according to the DSM-5 criteria; (iii) BZD abuse lasting more than 6 months; and (iv) high dose of BZD abuse, meaning BZD intake exceeding at least five times the recommended daily amount (e.g., >50 mg in diazepam equivalents). Individuals were excluded if presenting the following: (i) current substance use disorder, defined as a history of illicit drug dependence or abuse within the previous 6 months; (ii) active medical illnesses or psychosis; and (iii) previous history of seizures, but not due to BZD withdrawal.

Elastomeric Pump

Patients were treated with a solution containing 7 mg of flumazenil (Anexate®, Roche), available commercially in 0.5 mg/5 ml vials at pH = 4. The elastomeric pump (Infusor LV 1.5, code 2C1087K, Baxter S.p.A., Rome, Italy) was arranged with a

TABLE 1 | Patients' characteristics.

Patient number	Gender (M/F)	Age (years)	Reported BDZ dosage at admission	Antide pressant
1	M	38	LRZ 25 mg/day CLO 2 mg/day	Agomelatine
2	M	44	LRM 75 mg/day	None
3	F	42	LRM 75 mg/day	Duloxetine
4	F	55	ALP 35 mg/day	Escitalopram
5	F	47	CLO 12 mg/day	Mirtazapine
6	F	52	LRM 25 mg/day LRM 12 mg/day DZP 100 mg/day DZP 30 mg/day FLZ 180 mg/day TRZ 1.5 mg/day LRZ 15 mg/day ALP 4 mg/day CLO 12 mg/day	Venlafaxine plus agomelatine
7	F	47	LRM 400 mg/day DLZ 12 mg/day	Agomelatine
8	F	37	LRM 40 mg/day	Agomelatine
9	M	36	LRM 150 mg/day	None
10	F	43	LRZ 50 mg/day	Citalopram
11	F	31	LRM 100 mg/day	Paroxetine
12	F	30	LRM 75 mg/day	Sertraline
13	M	38	ALP 15 mg/day	Escitalopram
14	M	32	LRM 150 mg/day	Citalopram

ALP, aprazolam; CLO, clonazepam; DLZ, delorazepam; DZP, diazepam; F, female; FLZ, flurazepam; LRM, lormetazepam; LRZ, lorazepam; M, male; TRZ, triazolam.

maximum capacity of 250 ml and constant release of 1.5 ml/h for 7 days. The pump was connected to the patient's anterior abdominal wall via a butterfly needle inserted subcutaneously. The pump, releasing 1 mg of flumazenil every 24 h, was then placed in a small bag that could be carried attached to the belt or on the shoulder. Patients' tolerance for the infusion device was investigated on a daily basis, through clinical examination and interview.

Throughout the detoxification, FLU subcutaneous infusion (FLU-SI) was associated with therapeutic doses of clonazepam, orally administered every day in the evening and gradually tapered from 6 mg on the 1st day to 0.5–2.0 mg on the last day of treatment. The different speed in the tapering of clonazepam was due to clinical criteria, in particular we considered the quality of sleep and the intensity of withdrawal symptoms. In this way, at the end of hospitalization, 3/14 patients were discharged with no clonazepam, and 11/14 (78.6%) patients were discharged with a low dose of clonazepam ranging from 0.5 to 2.0 mg/day; these patients were recommended to gradually taper it in a few weeks (8). Unfortunately, patients were not followed-up as outpatients, and we cannot be sure whether they succeeded in tapering and eventually stopping clonazepam.

Ten days prior to the admission, anti-epileptic prophylaxis (1 g/day valproic acid or levetiracetam) was given to all patients in order to prevent seizures during treatment. Anti-epileptic treatment was maintained during the hospital stay and for further 20–40 days after discharge.

Patients under concurrent treatment with antidepressant (12/14 patients, see **Table 1**) were maintained under this pharmacotherapy.

Sampling Protocol

Blood samples were collected without anticoagulant at the moment of admission, after 4 days of FLU treatment, and at the end of the 7 days of treatment, before discharge from the addiction unit.

Samples were centrifuged (3,000 rpm, 10 min) and sera were frozen at −80°C until HPLC-MS analysis.

Flumazenil and Main BZD Concentration Analysis

Blank serum samples, used for the development and validation of the procedure, were obtained from healthy volunteers abstinent from any drug during the week before sampling. A 250-μl aliquot of serum was added to an equal volume of 0.1 M phosphate solution (pH 8.8), and the mixture was spiked with the IS (diazepam-D5) to have a final concentration of 40 ng/ml. The mixtures were added with 1.5 ml of ethyl acetate, then extracted by vortex-mixing for 1 min, and centrifuged at 4,000 rpm for 15 min. The organic phase was then evaporated to dryness under nitrogen stream and the residue dissolved in 50 μl of ultrapure water.

The determination of FLU and lormetazepam was obtained by using a model 1290 UHPLC coupled to a model 6450 triple quadruple mass spectrometer (Agilent Technologies, Waldbronn, Germany) operating in positive ionization mode. Gradient elution was performed on a UHPLC ZORBAX Eclipse reversed-phase column (RRHD 2.1 mm × 100 mm, 1.8 μm) (Agilent) by mixing 5 mM aqueous ammonium formate containing 0.01% formic acid (eluent A) and acetonitrile added with 0.01% formic acid at a flow rate of 0.5 ml/min (eluent B) from 10 to 95% B in 7 min. The analyses were performed in multiple reaction ion monitoring (MRM) mode using the following ion transitions: FLU 304 217, 232, and 258 (collision energy: 20 eV); lormetazepam 335 317, 289, and 177.0 (collision energy: 20 eV); and diazepam-D5 290 262 (collision energy: 27 eV).

Method was linear in the concentration range of 78–5,000 pg/ml for FLU and of 3–200 ng/ml for lormetazepam. Lower limit of quantification (LLOQ) corresponded to 78 pg/ml for FLU and 3 ng/ml for lormetazepam.

Precision (% CV) of the assay was ≤9.8% for both the analytes, whereas the inter-assay accuracy was ≤3.8 and ≤4.7%, respectively. The accuracy and CVs for day-to-day tests resulted always below 7.93%.

Withdrawal Assessment

A Benzodiazepine Withdrawal Scale (BWS) form exploring withdrawal symptoms (33 items each with a score of 0–4 from best to worst) was given to each patient for daily report (23).

Statistical Analysis

Statistical analysis was performed using the software Graph Pad PRISM version 6.0. The results were expressed as mean ± standard error of the mean (SEM). Student's *t*-test was utilized for statistical analysis by comparing different treatment times of the same group of patients.

RESULTS

Drug plasma levels are shown in **Figure 1**. Plasma FLU concentrations were 0.54 ± 0.089 ng/ml (mean ± SEM) at T1 after 4 days of continuous subcutaneous infusion, ranging from 0.14 to 1.4 ng/ml. Values recorded at T2 (end of therapy) were 0.09 ± 0.05 ng/ml, with FLU concentrations below limits of detection in 10 patients out of 14.

Lormetazepam (LRM) levels were 502.5 ± 163.0 ng/ml at T0 baseline. A significant decrease (11.2 ± 5.7 ng/ml; $p = 0.008$) in LRM levels was recorded at T1 and 0.43 ± 0.43 ng/ml at T2. High LRM plasma levels recorded at T0 are in agreement with patients' self-report of BZD use at admission, whereas low T1 and T2 levels confirmed compliance to detoxification treatment.

Lorazepam (LRZ) levels showed a similar pattern, with high initial plasma concentrations (83.1 ± 27.4 ng/ml), then a significant decrease to 20.4 ± 11.4 ng/ml ($p = 0.01$) at T1 and 9.4 ± 5.6 ng/ml at T2 after 7 days of FLU administration.

Clonazepam (CLN) plasma levels were low at T0 (14.0 ± 8.6 ng/ml), 35.5 ± 5.0 ng/ml at T1, and 25.4 ± 3.9 ng/ml at T2. Note that three patients were treated with CLN before hospital admission (see **Table 1**).

According to different BZD behaviors, BWS showed a decrease from 26.4 to 17.7 points, as portrayed in **Figure 2**. During the treatment, 10/14 subjects (71.4%) completed the Benzodiazepine Withdrawal Scale (BWS) with scores ranging from 0 to 132 on a daily basis, in order to subjectively assess their withdrawal symptoms. Four out of 14 patients could not complete the BWS. As shown in **Figure 2**, BWS improved significantly during FLU treatment in all subjects. No major event (i.e., convulsive crisis) occurred.

The elastomeric pump was well tolerated by patients. Since FLU is further diluted in a saline solution inside the device, no skin irritation around the insertion of the needle was noticed. Since elastomeric pumps are light and compact, patients appreciated the freedom of movement and rated them as painless, safe, and comfortable, with no bound to the pump and respecting the privacy about the therapy, whereas nurses acknowledged they required less time to manage them.

DISCUSSION

BZD represents a class of drugs characterized by low acute toxicity even at high doses in the absence of any concurrent drug abuse such as alcohol and opioids (2). Literature data on the toxicity of high-dose BZD are old and mostly based on anecdotal case reports. The lack of clinical studies and the high tolerability of these drugs have produced the erroneous perception that the administration of high doses of BZD for a prolonged time, although not recommended, could be not harmful. However, several complications have been associated to chronic BZD consumption, such as memory and attention deficit, inability to learn, increased risk of falls, road accidents, depression, and reduced quality of life (Lugoboni DAD 2014). Thus, although the prolonged use of high dose of BZD seems not to induce liver toxicity, it remains a serious health concern (24). The severe discomfort experienced by patients stopping long-term BZD use led to the development of treatment strategies for discontinuing these medications (1, 10). The common management of BZD withdrawal syndrome includes, either individually or in combination: (i) a gradual tapering of the drug; (ii) switching to an equivalent dose of a long half-life BZD before tapering withdrawal (10, 25); and (iii) adding medications prior to detoxification and continuing those medications after BZD discontinuation (1, 10). A potential approach is the abrupt discontinuation of the medication and a rapid BZD detoxification using FLU. FLU is commonly used in the treatment of BZD overdose; it is usually considered a BZD antagonist (9). When compared to placebo, bolus infusion of flumazenil (1 mg in 5 min) produced effects similar to BZD withdrawal in BZD users (23, 26). Nonetheless, results of studies in chronic BZD users who have discontinued BZD use suggest that multiple slow bolus infusions of flumazenil reduce the symptoms of withdrawal (9, 11, 21, 27).

Subcutaneous route of FLU administration was previously described only in three patients (14), suggesting the usefulness of this route for its excellent tolerability, efficacy, and improvement on measure of psychological distress. According to these data, we decided to administer FLU by subcutaneous route utilizing elastomeric pumps normally used for pain control in cancer patients or, more recently, for continuous infusion of antibiotics (28) or for treatment of idiopathic hypersomnia (29).

To our knowledge, the results present in this paper are the first data of FLU serum concentrations following subcutaneous infusion by elastomeric pump described in literature. FLU serum concentrations were low, but consistent with data of FLU administered by i.v. route (14).

FLU is characterized by short half-life (0.8–1.2 h) (30) and requires repeated doses or continuous infusion to reverse BZD overdose. In spite of its low lipophilicity, FLU has a large volume of distribution, and its weak binding to plasma proteins explains its rapid distribution. Moreover, FLU is extensively metabolized by hepatic cytochromes P450 3A4, 3A5, and 2C9 and readily eliminated. Maximum brain concentrations are reached 5 to 8 min after i.v. administration (31).

Subcutaneous administration of flumazenil eliminates some problems with first-pass hepatic metabolism observed orally and is likely to facilitate better absorption. Subcutaneous administration also provides continuous dosing, which would be hard to achieve with oral or sublingual administration, and the slow absorption may abrogate side effects related to high serum concentrations. The subcutaneous route is easier to establish than the intravenous administration, and there is no risk for patient's veins. Study data suggested that flumazenil administered by the s.c. route might have equitable clinical benefits to i.v. administration, but it might be superior in that it requires less

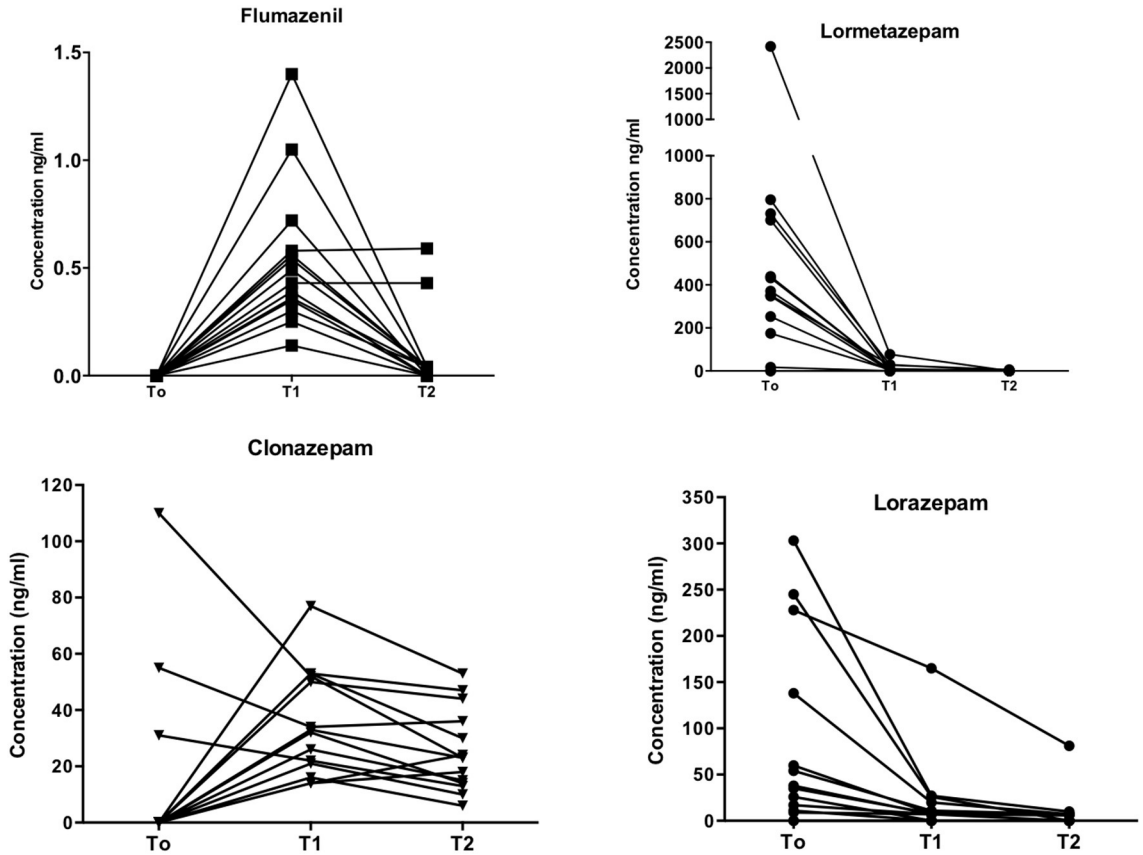

FIGURE 1 | Drugs plasma levels. Individual plasma levels (ng/ml; ordinates) for flumazenil, lormetazepam, clonazepam, and lorazepam at different time-points (abscissa), i.e., at admission (T0), four (T1) and seven days after flumazenil start of elastomeric infusion.

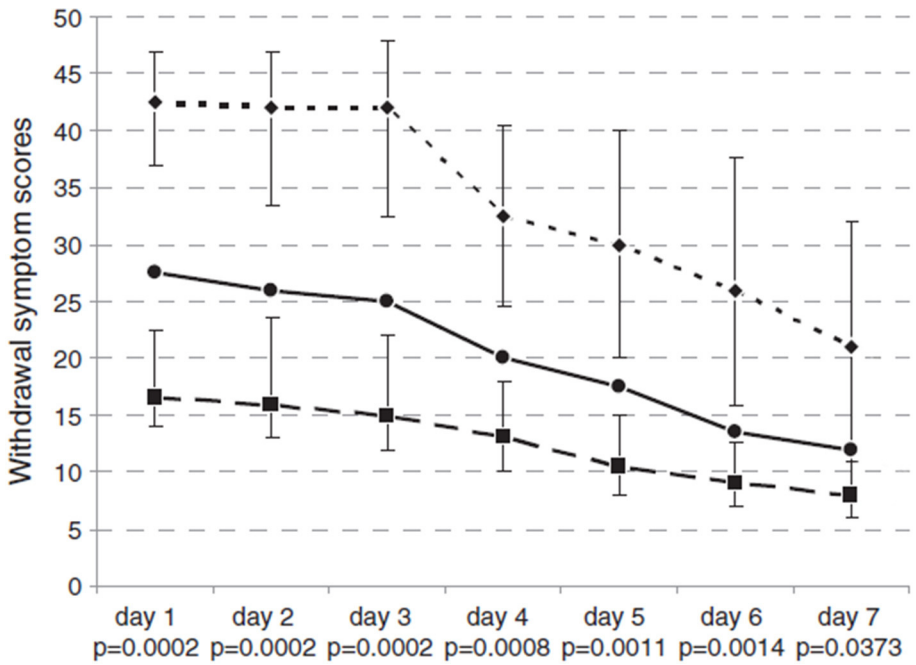

FIGURE 2 | Withdrawal Symptom Scores from day 1 to day 7 of FLU-SI treatment.

clinical monitoring and is likely associated with less equipment problems (i.e., dislodged or blocked i.v. needle/line) and adverse events (i.e., venous tissue irritation). These advantages, as well as an improved patient mobility over the treatment period, will also likely result in increased patient satisfaction (9, 14).

The subcutaneous route of administration may be associated to the absence of adverse events associated with i.v. FLU administration. In fact, our patients did not report any kind of adverse events such as those frequently reported during or after FLU administration (8, 14, 32).

Our results demonstrated low and constant serum concentrations during all treatment and a prompt decrease nearly to 0 at the end of treatment, protecting patients from peak serum levels. We utilized an elastomeric infusion pump mostly utilized in our hospital for analgesic purposes.

Several elastomeric pumps are commercially available, and they are calibrated in different conditions, including operating temperature and pressure, viscosity of fluid, backpressure, and time recommended between filling of the device and beginning of the infusion. All of these factors affect the infusion rate of pumps. Elastomeric infusion pumps are feasible to use and less bed bounding for patients, although a little less precise than other pumps.

Moreover, Höjer et al. (33) studied the stability of infusion solutions of flumazenil in concentrations of 1.0 and 5.0 μg/ml stored for periods of up to 9 months and concluded that the stability of flumazenil in infusion solution was satisfactory.

Importantly, serum levels of other BZDs (such as LRM and LRZ) are 0 after 4 days of FLU administration, proving both the efficacy of FLU and patients' compliance despite the elevated BZD plasma levels measured at the beginning of the treatment. The good patients' compliance was confirmed by CLN concentrations in serum that showed a trend to decrease after 7 days. Most interestingly, during the detoxification process, all patients reported low levels of craving for BZD, which might represent a rarely seen feature in the spectrum of drug detoxification. According to previous studies, high-dose BZD chronic use determines a severe impairment of psychological, physical, and social functioning, along with a significant reduction of quality of life (34, 35).

The main limitation to this study is the lack of a follow-up phase to determine whether all patients were successfully able to taper and suspend clonazepam and to assess the relapse rate. Another limitation of the study is its monocentric design. The problem is not new. Although more than 30 years have passed since the first studies of the efficacy of FLU in the treatment of addiction to high doses of BZD, to our knowledge, there are no more than five centers worldwide offering this treatment. This continues to represent a major obstacle to the definition of more shared and standardized protocols. Currently, FLU protocol is the same for all patients, regardless of sex, age, BMI, and BZD daily intake. Future prospects should include further investigations of the individual variables and clinical outcomes in order to individualize the detoxification therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CE 292CESC. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ABen and RG equally contributed for the analytes'plasma measurements. ABen, CC, and ABer contributed to the manuscript's draft and proofreading. LZ processed the statistical analysis and FL followed the clinical part and designed the study. All authors contributed to the article and approved the submitted version.

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The authors would like to remember the figure of Malcolm Lader (1936–2020), our mentor in pharmacological research on benzodiazepines and their misuse.

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CASE REPORT
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Case Report: Treatment of Kratom Use Disorder With a Classical Tricyclic Antidepressant

Alessandro E. Vento[1,2], *Simone de Persis*[3], *Sergio De Filippis*[4], *Fabrizio Schifano*[5], *Flavia Napoletano*[5], *John M. Corkery*[5] *and Georgios D. Kotzalidis*[4,6]*

[1] ASL (Azienda Sanitaria Locale) Roma 2, Rome, Italy, [2] Addictions' Observatory (ODDPSS), Rome, Italy, [3] ASL, Rieti, Italy, [4] Villa von Siebenthal Neuropsychiatric Clinic and Hospital, Genzano di Roma, Italy, [5] Psychopharmacology, Drug Misuse & Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom, [6] NESMOS Department (Neurosciences, Mental Health, and Sensory Organs), School of Medicine and Psychology, Sant'Andrea Hospital, Sapienza University, Rome, Italy

Kratom or *Mitragyna speciosa* (Korth.) is an evergreen tree of the coffee family native to South-East Asia and Australasia. It is used by locals recreationally to induce stimulant and sedative effects and medically to soothe pain and opiate withdrawal. Its leaves are smoked, chewed, or infused, or ground to yield powders or extracts for use as liquids. It contains more than 40 alkaloids; among these, mitragynine and 7-hydroxymitragynine are endowed with variable mu, delta, and kappa opioid stimulating properties (with 7-hydroxymitragynine having a more balanced affinity), rhynchophylline, which is a non-competitive NMDA glutamate receptor antagonist, but is present in negligible quantities, and raubasine, which inhibits α_1-adrenceptors preferentially over α_2-adrenceptors, while the latter are bound by 7-hydroxymitragynine, while mitragynine counters 5-HT_{2A} receptors. This complexity of neurochemical mechanisms may account for kratom's sedative-analgesic and stimulant effects. It is commonly held that kratom at low doses is stimulant and at higher doses sedative, but no cut-off has been possible to define. Long-term use of kratom may produce physical and psychological effects that are very similar to its withdrawal syndrome, that is, anxiety, irritability, mood, eating, and sleep disorders, other than physical symptoms resembling opiate withdrawal. Kratom's regulatory status varies across countries; in Italy, both mitragynine and the entire tree and its parts are included among regulated substances. We describe the case of a patient who developed anxiety and dysphoric mood and insomnia while using kratom, with these symptoms persisting after withdrawal. He did not respond to a variety of antidepressant combinations and tramadol for various months, and responded after 1 month of clomipramine. Well-being persisted after discontinuing tramadol.

Keywords: kratom, mitragynine, substance use disorder, clomipramine, withdrawal syndrome

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Susruta Majumdar,
St. Louis College of Pharmacy, United States

***Correspondence:**
Georgios D. Kotzalidis
giorgio.kotzalidis@uniroma1.it

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INTRODUCTION

The interest of the medical world in *Mitragyna speciosa* Korthals (MsK) dates back to the 1950s (1–6). MsK (kratom) was first described by the Dutch colonial botanist Pieter Korthals in 1839 and is indigenous to Thailand, Indonesia, Malaysia, Myanmar, and Papua New Guinea, where it has been used in traditional medicine and religious (7) contexts since at least the 19th Century, as well as a voluptuary substance

use (a surrogate to opium) well before Korthals' description (8, 9). In these countries, leaves of MsK are first dried and then chewed or consumed as smoke in long pipes, extract, or powder, or brewed into a tea (10). Mixtures with other substances are also made, thus increasing dangerousness of consumption. Some of them are confectioned into pills (11). Concern over its use was not raised until recently, when it became largely available in Western countries and its toxic potential realized. A first Malaysian report found kratom consumers to develop addiction and psychiatric symptoms (12), while its psychoactive properties were detailed in the late 1980s (13).

MsK alkaloids were quantitatively determined in its leaves after separation by thin-layer chromatography, with ultraviolet spectrophotometry (14), with colorimetry (15), densitometry (16); indoles and oxindoles were identified in the first place (17). Since then, more than 25 significant alkaloids were identified (11). The corynanthe-type indole mitragynine contributes 66% to MsK alkaloids, paynantheine 9%, 7-hydroxymitragynine 2%, and speciociliatine 1%; other alkaloids contribute <1% each (11). However, their contribution varies across locations (18) and products sold across the world might not always contain MsK at all (19). The first whose structure was determined in 1958 was mitraphylline (20), with many other alkaloids following suit (18). The MsK alkaloids may differ in their brain accessibility and crossing of the blood-brain barrier; for example, mitragynine penetrates in the brain significantly more than 7-hydroxymitragynine, at least in the rat (21). However, the latter is held to be responsible for almost all kratom effects on opioid receptors, and despite low content, it is produced by cytochrome P450 (CYP3A4 isoenzyme) conversion from mitragynine (22).

Other biochemically and neurochemically interesting compounds include rhynchophylline derivatives (23, 24), which down-regulate NMDA-mediated responses in animals (25–27), and a yohimbine and mitragynine analog, ajmalicine or raubasine (28), which differently from mitragynine (29), inhibits α_2-adrenoceptors, although less than α_1-adrenoceptors (30–32). Of note, kratom alkaloids closely interact with α_2 adrenoceptors, and mitragynine and 7-hydroxymitragynine bind them (33). Furthermore, mitragynine inhibits the activity of 5-HT_{2A} receptors, although indirectly so (29, 34, 35), as it shows a $K_i > 10\,\mu M$ for the 5-HT_{2A} receptor (36). It is possible that the interplay between these receptor effects and between MsK alkaloids underpin the different effects of kratom at low vs. high doses.

Although kratom was reportedly used to substitute for opiate addiction and cure it (37), the demonstration of their binding by MsK had to await the discovery of opioid receptors (38, 39). Mitragynine and other kratom alkaloids were shown to be possibly allosteric (40) agonists to opioid receptors (41–44), to possess analgesic properties thanks to their binding to brain μ- and δ-opioid receptors, and to induce ileal and vas deferens distention through the same receptors at peripheral sites (43, 45). These properties were long harnessed by traditional healers in the countries where kratom grows. In South-East Asia kratom is used to alleviate muscle aches, and sometimes to heal wounds and cure worm infections, while some users support they assume it to increase resistance to fatigue and to stimulate sexuality (46). Indeed, mitragynine and kratom alkaloids are likely to be associated with "dependence" signs and symptoms which are less severe than those usually associated to opiates and they may be used to alleviate classical opiate withdrawal (47, 48). This is not surprising, since they act as agonists on opioid mu receptors.

Legislations concerning kratom varies across countries. In Europe it is illegal in Denmark, Finland, Ireland, Latvia, Lithuania, Poland, Romania, and Sweden (49), while in the UK it has been included in the Psychoactive Substances Bill 2015 (50), hence it is illegal since March 2016, being regulated through the Psychoactive Substances Act 2016 (51). In Italy, it became illegal in 2016. In Canada and Australia, kratom is illegal, while in New Zealand it is a regulated substance. In the United States it is forbidden in some States and not in other (49). Many US state legislations are likely to change their attitude toward kratom in the near future. Similarly, Thailand, one of kratom's major producers, which prohibits since 1943 the cultivation of new plants and mandates the abatement of the existing ones, while restricting possession and use and establishing sanctions for quantities superior or inferior to 10 Kg, is on the verge of changing its legislation. In Malaysia, Bhutan and Myanmar kratom is illegal, and in Indonesia it will be banned by 2022 (52). Discrepancies among the various legislations internationally, as well as the increase in the use of internet and globalization have resulted in an increased use of kratom for voluptuary purposes (53) indicating the need for international coordination of scientists and legislators (54). That kratom could induce an opioid-like withdrawal syndrome, therefore it can be included among addictive substances, is shown by the fact that it may be present in neonates exposed to the substance due to their mothers' heavy use during pregnancy (55–61). In fact, the World Anti-Doping Agency placed mitragynine on its Monitoring List since 2014, and 1 year later, four cases of mitragynine use among strength sportsmen were detected (62). Kratom use has been also reported in fitness settings (63).

The effects of the use of kratom are variable and may depend on the cultural and genetic background of the user as well as on differences in product composition. Product conservation and transport factors may also be involved, as are co-administered sedative or multisubstance use. In a US-Thailand comparison, for example, symptoms were more severe and mortality higher in the US sample, with drowsiness, irritability-agitation and tachycardia being the most common in order of increasing frequency (64). Kratom may be used according to users' taste and adjusted according to the desired effects, with low doses producing stimulant and activating effects and high doses sedative and tranquilizing effects (65–67), although these dose-related effects were not confirmed in a recent study and was unrelated to the amount and duration of kratom use (68). Many people, especially in South-East Asia, get to use kratom after being addicted to opioids and in the attempt to quit; others are prompted to use kratom due to its anxiolytic and mood enhancing effects (69–71). It is expected that upon discontinuing, rebound mood and anxiety symptoms emerge. In regular users, withdrawal symptoms may occur which are more intense in long-time users or after stopping heavy use, and involve usually moderate anxiety and depression (72), as well as aching and disordered sleep (73).

However, kratom withdrawal syndromes are usually mild and transient (72–74), similar to but milder than those of opiate withdrawal (74, 75), but may be complicated in some users (54).

We here report the case of an adult man who used kratom and developed withdrawal symptoms while trying to quit. He did well on clompipramine just 1 month after initiation and, 9 months later, is currently symptom-free.

CASE REPORT

A 44-year-old man, married to a 44-year-old, currently pregnant woman, with a 5-year-old son, a graduate in economy and employed as a researcher at a University, sought help at a community psychiatric service for symptoms of kratom withdrawal and elevated anxiety.

The patient was collaborative at interview, appropriately dressed and well-oriented in time and space; he showed free-floating and somatic anxiety, with tachycardia, profuse sweating, psychomotor agitation, insomnia, dysphoric mood, and emotional lability. His thoughts were focused on anxious experiences and hopelessness. He reported being treated during the last few months with various benzodiazepines and selective serotonin reuptake inhibitors (SSRIs), first paroxetine 40 mg/Day and then sertraline 200 mg/day, to which he associated cognitive-behavioral therapy, with no clear benefit.

The patient had experienced two important major depressive episodes coinciding with stressful life events, which he overcame through the use of SSRIs and long-term psychotherapy. When he was young, he had engaged in polysubstance use, while in his adult life he first used cannabis and alcohol, but later turned to benzodiazepines, alcohol, and kratom, which he obtained through dark internet sites. The patient has been vague as to when and how he started consumption, and also very unclear regarding dosing. His internet-related kratom sources varied, so we are not in a position to determine the purity of the samples he received. During the last 10 months preceding the visit, he had scheduled daily kratom infusions, but had discontinued quite sharply during the last 2 months. The patient used to continue drinking the infusion until he reached the desired effect. Having realized in the last 2 months he was becoming severely dependent, he decided to quit kratom and to no longer seek it on the internet.

Urinary drug testing was positive for benzodiazepines. Blood chemistry showed no abnormal values. However, kratom could not be quantified due to the unavailability of routine laboratory tests. The electrogram (ECG) showed no abnormalities, with a QTc of 385 ms and a heart rate of 60 beats/min. We established treatment with pregabalin 25 mg b.i.d., gradually tapering off sertraline and substituting it with 150 mg/day bupropion, taken in the morning, and 300 mg controlled-release trazodone, administered in the evening. His next visit was scheduled after 2 weeks.

During the second visit, his clinical conditions were unchanged. The patient was restless, anxious, agitated, insomniac, dysphoric, with frequent cry spells and unstructured ideation of self-harm. He craved for benzodiazepines and alcohol and often abused them. Bupropion was increased to 300 mg/day and pregabalin, 75 mg b.i.d. was initiated.

During his third visit, after further 15 days, the above clinical picture persisted. The patient reported to be able to relax, but observed no symptom improvement. We agreed to add 50 mg/day tramadol in the evening. He noted since the first days of tramadol addition a mild reduction in craving and restlessness, with disappearance of self-harm ideas, while anxiety, which the patient reported as paralyzing, dysphoric mood, cry spells, and avolition remained unchanged. The patient asked for a medical certificate to abstain from work, since he considered teaching at the University a complex and stressful activity. We agreed to increase tramadol to 100 mg b.i.d., gradually introducing clomipramine to a target dose of 75 mg/day, while gradually discontinuing bupropion.

Three months after the first visit and about 1 month after introducing clomipramine, the clinical picture was on the way to resolution; the patient himself asked to discontinue tramadol. Free-floating and somatic anxiety had subsided and craving for all substances, including alcohol, benzodiazepines, and kratom, was significantly attenuated, while mood was stable and in the normal range (euthymic).

In the following months, given the clear clinical improvement and the remission of withdrawal symptoms, it was possible to gradually discontinue both pregabalin and trazodone.

Currently, the clinical picture is stable; the patient continues on clomipramine 75 mg/day and about 9 months after its introduction reports to have resumed normal life.

The patient signed free informed consent for the publication of his case and all treatments received.

DISCUSSION

In this report we presented the case of an adult Italian man in his forties, who deliberately used kratom to soothe his anxiety symptoms. The patient was well-educated and upper socioeconomic class. He had started kratom after engaging in multisubstance use and psychotherapy, while completing steps toward reaching a high social status. He used the internet to obtain kratom, but had no available supplies when he came to our attention, so we could not analyse any kratom specimen he used. After trying several therapeutic strategies, including pharmacotherapy, he was unable to resolve his anxiety symptoms, either during kratom use or during abstinence, and was switched to low-dose clomipramine eventually discontinuing all other psychotherapeutic drugs; 1 month after initiating clomipramine, his symptoms had resolved and so were his anxiety symptoms that had originated psychiatric visits.

There have been several case reports of kratom use toxicity and withdrawal in literature, but clomipramine treatment had not been reported to date. Cases vary in severity and symptom presentation. One of the first described cases of mitragynine toxicity was of severe seizures and come occurring in a 64-year-old man, that resolved soon with symptomatic treatment, that is, intubation to preserve airway integrity (76). In another case,

seizures occurred when a 43-year-old man tried to self-treat his opiate dependence with a kratom-modafinil combination (69); the case resolved with few kratom-related withdrawal symptoms. A further case presenting with seizures occurred in a 18-year old man and treated with antiepileptic drugs. Magnetic resonance imaging showed bilateral alterations in the striatum, cerebral peduncles, and subthalamic nuclei in this chronic kratom user, indicating possible permanent effects of kratom in brain structure (77). Finally, a 27-year-old nab with history of anxiety, attention-deficit/hyperactivity disorder, substance use disorders (benzodiazepines and opioids) developed seizures while using kratom and opioids and recovered with anti-anxiety agents (78). Another 36-year-old man was unresponsive to external stimuli and near comatose, did not respond to naloxone and was treated with respiratory support and symptomatic management (79). Another kratom overdose case occurred in a 38-year-old woman who resented with respiratory depression at the emergency department and resolved with naloxone (80). A 33-year-old male polysubstance user exhibited cardiovascular shock features and high procalcitonin levels promptly treated with vasopressors (81). An otherwise healthy 35-year-old man suffered a cardiac arrest after using kratom alone and was found with small brain infarcts, but recovered spontaneously (82). Finally, a 62-year-old woman who used kratom for the first time to soothe traumatic pain presented at the emergency room with intractable vomiting and nausea that responded to ondansetron, promethazine, and famotidine (83).

Cases of kratom-related deaths are usually linked to simultaneous assumption of kratom with other drugs, as in the above described case. Initial death reports regarded associations, but more recent cases show that people who only take kratom are at risk. One case of death of a 20-year-old man occurred with propylhexedrine and kratom; the latter was not determined to have caused the death, which has been associated to accidental propylhexedrine (84). Nine cases of death occurring in one year were described in Sweden in 2011 with the simultaneous intake of mitragynine and *O*-desmethyltramadol. Decedents' age ranged 22–35; seven were men and two were women (85). The authors concluded that mitragynine-related herbal mixes are not so safe as per internet propaganda. Another death case in which mitragynine was involved, but the death was attributed to quetiapine overdose, has been described in a 27-year-old man succumbing to hyperthermia associated with seizures. One case of a 17-year adolescent male who was trying to quit opioid use by self-medicating with kratom, points to kratom being occasionally toxic; the boy was found dead with pulmonary congestion and oedema, as well as urinary bladder distension, which are typical of opiate intoxication (86). The case was labeled as "probable kratom toxicity." Another case of kratom intoxication-related death was found to be associated with high blood amounts of mitragynine and 7-hydroxymitragynine and unremarkable pathological finding at autopsy in a middle-aged man with psychiatric history and illicit drug use disorder (87). Another report of death related to kratom use was one of a 24-year man with opiate and alcohol use disorders, who was found dead with high peripheral alkaloid concentrations, pulmonary oedema and congestion, and urinary retention, compatible with opioid intoxication; the patient was using several psychiatric medications that were found at therapeutic blood levels (88). Further two cases of young men could not be attributed to the documented kratom use, despite high mitragynine levels in femoral blood (89). One of the patients had attempted suicide just after taking kratom with prescription drugs, while the other took a mix of drugs. Another fatality was due to 3-methoxyphencyclidine, and mitragynine was just one of many other substances the 58-year-old man had taken (90). An emergency case presenting with cardiorespiratory arrest could not be rescued despite the use of intralipid, that nevertheless improved somehow the conditions of a 26-year-old man, but proved ineffective in avoiding exitus, attributed to cardiorespiratory failure and hypoxic brain damage (91). A Canadian 56-year-old woman with chronic obstructive pulmonary disease, after skipping her medication and consuming kratom purchased from Indonesia, died due to respiratory failure (92). Her mitragynine levels in the femoral vein were found to be substantial but sublethal (under the reporting laboratory's threshold of fatality, which was 0.21 mg/L). Another case of multiple drug use ensuing in death has been related to mitragynine due to the very high doses found in inferior cava blood of a 33-year-old man (93). In general, fatality case studies suffer from heterogeneity in kratom alkaloid detection methods and sites.

Cases of chronic kratom used followed by withdrawal symptoms have been reported to resolve with gabapentin in a 26-year-old woman and gabapentin and clonidine in a 27-year-old man (94). A case similar to ours has been described in a 44-year-old man with a history of alcohol use and anxiety; gradually tapered-off dihydrocodeine and lofexidine were followed by rapid withdrawal symptom resolution (95). In our case, the psychiatric symptoms of our patient were more prominent and stubborn, and briefly trialed clonidine in the past had sorted no effect. Hence the need for something more specific for anxiety disorders. Cases of kratom withdrawal in a 47-year-old woman (96) and in a 24-year-old man with an autism spectrum disorder (97) have been treated with clonidine and hydroxyzine, similarly to ordinary opiate withdrawal syndromes. The latter case and four other cases of kratom withdrawal were treated successfully with buprenorphine-naloxone maintenance (98–100). A further withdrawal from combined kratom-tilidine addiction has been successfully treated with retarded morphine (101). Finally, a recent paper reported an unusual presentation of obsessive-compulsive disorder-like syndrome during kratom withdrawal that responded to lorazepam (102). We did not use treatments aimed at treating patient's kratom withdrawal, since the syndrome was mild despite being obstinate, but rather focused on the anxiety disorder, which usually responds to antidepressants. By treating our patient's background psychological symptoms, we were successful in reducing withdrawal symptomatology.

Kratom use has been often linked to liver toxicity. Kratom has been associated with biliary cholangitis and cholestasis in several cases (67, 103–110) and with one case of hepatomegaly (111), but also with acute hepatitis (112). Mitragynine inhibits hepatic and intestinal cytochrome P450 3A activities (113) and

hepatic microsomal CYP2D6 (114), thus increasing blood levels of other concomitantly administered drugs that are metabolized by these isoenzymes, that is, most psychiatric drugs. This may expose to further hepatotoxicity (115, 116). Our patient did not develop liver abnormalities during his kratom use period, despite the fact he was concurrently using alcohol. We did not perform kratom quantification analyses in our patient throughout the treatment period. This was because the patient refused to provide organic specimens or leaves for forensic analyses. There are reliable methods for detecting mitragynine and its derivatives in the urine (117) and in plant and extracts (118) for forensic purposes, but these are not currently routine practice. There is need for standardizing methods of kratom alkaloid detection in reported users.

A limitation of the current review is that the supposed benefits-to-risk ratio of kratom use cannot be currently addressed adequately. There is insufficient epidemiological documentation as to the extent of kratom use worldwide and in specific countries (119), so to estimate how many people use it and how many develop unwanted effects. Besides this, risks may increase, as many kratom users have concurrent other substance use (120), and this is difficult to disentangle. The most recent estimates in indicate kratom use in the adult US population is 0.8% for the past year and 1.3% lifetime (120). The debate on epidemiological issues is strong and ongoing, and points to the evergreen "more studies are needed" (121, 122). The advocates of kratom use to ease opioid dependence and harness its effects on strength and endurance while involved in work activities do not publish in scientific literature, but put forward their uncontrolled views and opinions in sites of their own property. Hence, it is an impervious task to try to respond to the question whether kratom use is relatively safe, but it appears it is not (123). Currently, there is not sufficient evidence to recommend changes in kratom regulation, nor to recommend the use of clomipramine in cases of kratom withdrawal.

Our patient showed while withdrawing from kratom mitigated signs and symptoms typical of opiate withdrawal, which were mixed with other psychiatric symptoms presumably linked to his background psychopathology. Knowing that the withdrawal is generally time-limited and mild, we chose to use an anxiety-specific agent, clomipramine, with preference for serotonin transporter over noradrenaline transporter inhibition, which is a tricyclic antidepressant used in anxiety disorders and obsessive-compulsive disorder and has shown good evidence in these disorders. We used it at 75 mg/day, which is on the lower range of clinical effectiveness for these disorders. Mitragynine counters serotonin 5-HT_{2A} receptors (29) and clomipramine down-regulates the same receptors after chronic treatment (124, 125); furthermore, it has pain supressing effects even at low doses through spinal mechanisms (126). Hence, it is possible that some mitragynine withdrawal symptoms were alleviated concomitantly with clomipramine's anxiety relieving effects. However, this is not the most likely mechanism whereby clomipramine reduced our patient's symptomatology. In fact, clomipramine may obviate for the opiate-like mitragynine withdrawal syndrome through interference with opioid receptors, which it was shown to bind (127); chronic, but not subacute clomipramine administration, induced a mu receptor down-regulation in the rat (128). In this case, clomipramine could reduce the quantity of opioid receptors in the need for occupation, as it occurs in opiate withdrawal. However, the response of human opioid receptors to chronic clomipramine appears to be weak (129). We are unsure about how improvement was obtained, but the timeline appears to match the usual onset of clomipramine antidepressant effects.

CONCLUDING REMARKS

Summarizing the above evidence, we may conclude that kratom may induce addiction, acute toxicity which may be sometimes lethal and, upon discontinuation, it induces a withdrawal syndrome, which may vary in intensity. In many instances that appeared in literature, kratom was regularly used by patients with psychiatric history and/or substance use disorders. Legislations should take very seriously peer-reviewed published evidence and regulate the substance. In parallel, we need to enforce kratom detection methods in consent-providing users for forensic purposes. International drug policies should be coordinated and inform the public about kratom and other novel addictive drugs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The patient signed free informed consent for the publication of his case and all treatments received.

AUTHOR CONTRIBUTIONS

AV, SP, and SD saw the patient and wrote the first draft. FS, FN, and JC supervised the case and the writing of the manuscript. GK wrote the last draft and performed literature searches. All authors saw and approved the final version of the manuscript.

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The Severity of Dependence Scale (SDS) for Codeine: Preliminary Investigation of the Psychometric Properties of the SDS in an Online Sample of Codeine Users From the UK

Paolo Deluca[1], *Michelle Foley*[2], *Jacklyn Dunne*[1] *and Andreas Kimergård*[1]*

[1] National Addiction Centre, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, United Kingdom, [2] School of Health Sciences, Waterford Institute of Technology, Waterford, Ireland

Objective: Investigate the psychometric properties of the Severity of Dependence Scale (SDS) for codeine and its association with aberrant codeine related behaviors.

Design: A voluntary and uncompensated cross-sectional online survey.

Setting: Online population (≥18 years).

Respondents: Two hundred and eighty-six respondents (66% women) who had used codeine containing medicines in the last 3 months and were living in the UK.

Results: Of the respondents (mean age = 35.4 years, SD = 12.5), more than half were employed. Only 3.5% respondents reported no income. The majority of respondents (45.1%) primarily obtained prescription-only codeine from a consultation with a health professional, whilst 40.9% mainly purchased "over-the-counter" codeine containing medicines in a pharmacy without a medical prescription. Principal component analysis indicated a single factor solution accounting for 75% of the variance. Factor loadings ranged from 0.83 to 0.89. Cronbach's Alpha was high (α = 0.92). Several behaviors relating to codeine use were found to significantly predict probable codeine dependence. These included: daily codeine use in the last 3 months (OR = 66.89, 95% CI = 15.8–283.18); tolerance to codeine (OR = 32.14, 95% CI = 13.82–74.75); problems with role responsibility due to intoxication (OR = 9.89, 95% CI = 4.95–19.78); having sought advice on the internet to manage codeine use (OR = 9.56, 95% CI = 4.5–20.31); history of alcohol or drug treatment (OR = 3.73, 95% CI = 1.88–7.43).

Conclusions: The SDS was acceptable and feasible to use to assess probable psychological codeine dependence in an online sample of people using codeine containing medicines. SDS scores were associated with behaviors known to be indicators of codeine dependence. Studies are needed in well-defined populations of people who use codeine to test the different aspects of psychometry of the scale compared against "gold standard" criterion [a diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)].

Keywords: psychometric validation, Severity of Dependence Scale, opioid misuse, codeine, addiction

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***Correspondence:**
Andreas Kimergård
andreas.kimergard@kcl.ac.uk

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STRENGHTS AND LIMITATIONS OF THIS STUDY

- Advances the understanding of the use of screening tools and scales to assess dependence on codeine containing medicines for research purposes.
- The study recruited a broad cross-section of codeine users in the UK, providing an initial investigation of the psychometric properties of the Severity of Dependence Scale for codeine.
- Online purposive samples have unknown population characteristics which must be recognized when interpreting the findings of the present study.
- Studies in well-defined populations of people using codeine are needed to test different aspects of psychometry of the scale compared against independent "gold standard" criterion.

INTRODUCTION

In the UK, the use of codeine containing medicines and the resulting possibility of dependence and severe health outcomes (1) pose a burden on primary and secondary care, specialized addiction treatment (2) and mortality (3). Codeine is used in form of codeine-based Prescription-Only Medicines (POM) or Pharmacy medicines (P), which contain a lower amount of codeine and may be sold under the supervision of a pharmacist without a medical prescription (sold "over-the-counter") (4). Codeine is currently controlled under the Misuse of Drugs Regulations 2001 classified as Schedule 5 (Controlled drugs excepted from the prohibition on importation, exportation and possession) (5).

Many codeine containing medicines include a combination of codeine and a non-opioid analgesic such as ibuprofen or paracetamol (6). In 2014, the UK accounted for nearly one-sixth of the global consumption of codeine (7). Sales of codeine containing "over-the-counter" products in packs of 32 tablets more than doubled in the period of 2006 to 2008 from 5.3 to 11.1 mn (8).

During 2007 to 2016, the number of registered drug-related deaths involving codeine increased from 60 to 131 in England and Wales (9). In Scotland, codeine or a codeine-containing compound was implicated in an average of 19 deaths per year between 2003 and 2007, 27 deaths per year between 2008 and 2012, and 33 deaths per year between 2011 and 2015 (10). The accessibility to codeine is under scrutiny in many countries, including the UK, due to concerns of dependence and severe harm from excessive use and overdose of accompanying paracetamol and ibuprofen (11–13). The recent indicators of an emerging "codeine problem" in the UK expose the need for reliable and accurate instruments to identify and treat early signs of codeine dependence to reduce long-term use, mortality, and the economic burden of addiction treatment.

The Severity of Dependence Scale (SDS) is a simple and practical 5-item, 15-point scale used to assess the degree of psychological dependence across several substance classes (14). In research to date, the psychometric properties of the SDS have been investigated in populations using illicit drugs (14–16), alcohol (17), and nicotine (18). Optimal cut-off scores on the SDS for probable psychological dependence, when measured against the presence of a diagnosis obtained from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), have been determined for amphetamine (19), cocaine (20, 21), benzodiazepines (22), alcohol (23), and cannabis (24). The scale has previously been used to determine the level of probable codeine dependence amongst adults in Australia reporting use of "over-the-counter" codeine (25). Further investigation of the psychometric properties of the SDS for codeine would add understanding and value to the use of the scale for research purposes and possibly in clinical settings.

Using data collected from a cross-sectional, self-completed, online survey of adults who used codeine, the article presents a preliminary investigation of (i) the psychometric properties of the SDS for people living in the UK and (ii) the relation between the scale and behaviors known to be indicators of codeine dependence. Scales to identify people who are codeine dependent which are reliable and simple to administer are currently needed to promote public health.

METHODS

Ethics

The study received ethics approval granted by the Psychiatry, Nursing, and Midwifery Research Ethics Subcommittee (PNM RESC), King's College London. REC Reference Number: PNM/14/15-110.

Recruitment

The survey was advertised on Facebook, Twitter, health and drug related websites and e-mail circulars to include a broad sample of people using codeine resembling the general population. Recruitment lasted between July 2015 and March 2016. The main inclusion criterion was use of codeine containing medicines, prescribed or "over-the-counter," on at least one occasion in the last 3 months. Only respondents over the age of 18 were asked to participate. Participation in the study was voluntary, anonymous and uncompensated. A more detailed account of the survey has previously been published (26).

Sample

The survey was embedded within the CODEMISUSED collaboration aiming to carry out national and international studies to estimate levels of codeine use, misuse and dependence in partner countries (Ireland, South Africa and the UK) (27). For this reason, the online survey was open to respondents from all countries. However, in these re-analyses of the data in the present study, it was decided to only include respondents living the UK for several reasons: (i) There is great disparity between levels of codeine consumption, availability of codeine as "over-the-counter" medicines or POM, the amount of codeine included in codeine containing medicines and regulation of advertising of codeine containing medicines across countries around the world (11, 28–30) which may affect aberrant codeine behavior differently. By limiting the sample to the

UK, respondents completing the SDS were sourcing and using codeine under similar conditions and regulation; (ii) conducting analysis of the SDS according to nationality was not feasible as some nations were represented by very few respondents; and (iii) the survey was only available in English. Limiting the analysis to respondents living in the UK presumably reduces the risk of misunderstanding due to potential language barriers.

Procedure

The online survey was developed in Bristol Online Surveys (BOS) and consisted of 49 questions about demographic information, codeine use, codeine dependence, social factors, treatment history, and other substance use (26).

The SDS was included as part of this larger study questionnaire, with the scale items included as questions 28–32 out of a total of 49 questions. The wording of each item of the scale was adapted to enquire about the use of codeine in the last 3 months. Respondents were asked:

(i) In the last 3 months did you think your use of codeine was out of control? (Responses: "Never/almost never" = 0; "Sometimes" = 1; "Often" = 2; "Always/nearly always" = 3).
(ii) In the last 3 months did the prospect of not taking codeine make you anxious? (Responses: "Never/almost never" = 0; "Sometimes" = 1; "Often" = 2; "Always/nearly always" = 3).
(iii) In the last 3 months did you worry about your use of codeine? (Responses: "Never/almost never" = 0; "Sometimes" = 1; "Often" = 2; "Always/nearly always" = 3).
(iv) In the last 3 months did you wish you could stop taking codeine? (Responses: "Never/almost never" = 0; "Sometimes" = 1; "Often" = 2; "Always/nearly always" = 3).
(v) In the last 3 months how difficult did you find it to stop using codeine? (Responses: "Not difficult" = 0; "Quite difficult" = 1; "Very difficult" = 2; "Impossible" = 3).

Responses were scored from 0 to 3 for a total score between 0 and 15.

Likely indicators of codeine dependence included frequency of use in the last 3 months, reported as a dichotomous variable (daily or non-daily use). Additional questions were asked about tolerance to codeine and withdrawal symptoms after the use of codeine. Respondents were asked to report if they had sought help to control their use of codeine from (i) a community pharmacist, (ii) a general medical practitioner (GP), or (iii) from the internet. Respondents were also asked about past treatment for alcohol and illicit drug use. The survey included items from the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) to investigate problems with role responsibility due to the use of codeine (31). Questions from a scale designed to measure reasons for substance use were included to investigate use of codeine for anxiety (32). Several questions about tampering of codeine containing medicines were developed for the study, including about extraction of codeine (otherwise known as "cold water extraction") (33) and drinking codeine cough syrups mixed with soft drinks or with alcohol. A question about life-time use of illicit drugs, such as cannabis, amphetamines, ecstasy, cocaine, and heroin was included in the survey.

The complete survey was reviewed by experts in codeine misuse and dependence and piloted amongst addiction treatment service users. The survey took between 15 and 20 min to complete.

Data Analysis

Data were downloaded from the online questionnaires and imported to SPSS. All data analyses were conducted using SPSS, version 24. Before undertaking analyses, all respondents living in countries other than the UK were removed from the dataset. Principal Component Analysis (PCA) was conducted for the five SDS items as proposed by Gossop et al. (14). PCA was applied to determine the number of dimensions and item loading structure. The Cronbach's Alpha coefficient was used to assess the internal consistency of the scale. Mono-variate logistic regression analyses were conducted to estimate the associations between the presence of codeine dependence and individual behaviors relating to codeine use. Comparisons were made between a baseline comparison group consisting of non-dependent codeine users and codeine dependent users. For this part of the analysis, a SDS score of five or above indicated probable psychological dependence on codeine, consistent with previous use of the scale to assess dependence to codeine (25, 34). A score of below five indicated non-dependence. Independent variables were demographic characteristics, frequency of codeine use, tolerance, seeking help to manage codeine, past treatment for alcohol or drug use, social problems, codeine use for emotional distress, tampering of codeine containing medicines, and other substance use.

Missing Data

To reduce the amount of missing data, most items were mandatory in the computerized survey and respondents could not proceed to the next question without providing an answer. Missing data was therefore uncommon. However, data was missing for amount of codeine consumed on last occasion of use precluding an analysis of this item in the logistic regression model.

RESULTS

Between July 2015 and March 2016, 472 respondents using codeine in the last 3 months and over the age of 18 completed the survey online. Respondents from outside the UK were removed, leaving a total of 286 respondents in the final analysis. As **Table 1** shows, 66.4% of these were female. The mean age of the sample was 35.4 years (SD = 12.5) with a range of 18–71 years. More than half of the respondents were employed full or part-time (60.5%). The main source of obtaining codeine containing medicines was prescribed following a face-to-face consultation with a doctor (45.1% of respondents). The second most common source was purchased "over-the-counter" in a pharmacy without a medical prescription (40.9% of respondents). In the 3 months prior to completing the survey, 39.2% ($n = 112$) of the respondents had consumed codeine daily. A majority of 219 respondents (76.6%) took less or equal to the maximum recommended daily dose of

TABLE 1 | Respondent characteristics ($n = 286$).

Characteristic	
Age, mean (SD)	35.4 (SD = 12.5)
Gender, *n* (%)[a]	
Female	190 (66.4%)
Male	92 (32.1%)
Income, *n* (%)[b]	
Employment	173 (60.5%)
Student allowance	38 (13.3%)
Dependent on other	17 (5.9%)
Disability allowance	17 (5.9%)
No income	10 (3.5%)
Temporary benefit	8 (2.8%)
Pension	7 (2.4%)
Other	8 (2.8%)
Main type of codeine, *n* (%)	
Prescription codeine	129 (45.1%)
"Over-the-counter" codeine	117 (40.9%)
Other[c]	40 (14%)

SD, Standard Deviation.
[a]*Four respondents did not say (1.4%).*
[b]*Eight respondents did not say (2.8%).*
[c]*Purchased online and obtained from friends and family.*

TABLE 2 | Factor loadings and percentage of variance accounted for.

	Respondents (use of codeine in past 3 months) *n* = 286
SDS score, mean (SD)	2.2 (SD = 3.5)
Range	0–15
Principal components analysis	
Number of factors	1
Factor loadings	
Item 1	0.89
Item 2	0.88
Item 3	0.87
Item 4	0.87
Item 5	0.83
Item % variance accounted for	75
Cronbach's alpha	0.92

codeine (240 mg), 31 (10.8%) took more and 36 (12.6%) did not provide this information or answered the question incorrectly.

Variance and Consistency of the SDS

The respondents answered all required questions for the SDS. The responses to the scale produced a full range of scores from 0 to 15 (Mean score = 2.2, SD = 3.5). Principal component analysis (PCA) was undertaken, indicating a single factor solution which accounted for 75% of the variance in codeine dependence (**Table 2**). The SDS had high internal consistency (Cronbach's alpha = 0.92).

Associations With Aberrant Codeine Use

Mono-variate logistic regression analyses were used to investigate the relation between codeine dependence and aberrant behaviors in themselves indicating codeine dependence. Non-dependent codeine users were the reference category (**Table 3**).

Compared with those who were not dependent on codeine, the group of people with probable codeine dependence were significantly more likely to report daily use of codeine (96.1 vs. 26.8%, $p < 0.01$). In relation to experiences of physical dependence, there was a significantly higher proportion of codeine dependent respondents (58.8%) who reported tolerance to codeine in comparison with non-dependent (4.3%) ($p < 0.01$).

SDS scores were investigated in relation to seeking help to control the use of codeine and specialized addiction treatment history. In the logistic regression model, independent variables that were found to significantly predict probable codeine dependence were having sought help on the Internet (OR = 9.56, 95% CI = 4.5–20.31) and having sought help from a GP (OR = 9.31, 95% CI = 3.21–27.01). Codeine dependent respondents were more likely to have received treatment to manage alcohol and illicit drug use than non-dependent users (35.3% compared to 12.8%, $p < 0.01$).

Those who were dependent on codeine were more likely to report problems with role responsibility, such as missing appointments at work or at home due to intoxication, compared to those who were not dependent (52.9 vs. 10.2%, p < 00.1). SDS scores were investigated in relation to whether a friend or relative or anyone else had expressed concern about the respondents' use of codeine, which was found to significantly predict codeine dependence (OR = 8.74, 95% CI = 4.39–17.38).

Non-medical use of codeine relating to depression and anxiety were found to significantly predict probable codeine dependence, including using codeine to stop worrying about a problem (OR = 6.03, 95% CI = 2.83–12.83) and using codeine to feel better when down or depressed (OR = 5.41, 95% CI = 2.77–10.55).

The group of people with probable codeine dependence had a high proportion of respondents who had consumed codeine cough syrups mixed with soft drinks, juice or alcohol (25.5%) compared to the group of non-dependent respondents reporting this behavior (9.4%) ($p < 0.01$).

There was no significant association between probable codeine dependence and consuming codeine extracted from codeine containing medicines or life-time illicit drug use.

DISCUSSION

This study demonstrates the feasibility of screening 286 respondents to an online cross-sectional survey for probable codeine dependence using the SDS. Pilot testing of the survey indicated that the five SDS items were easy to understand and the assessment easy to complete. The high questionnaire completion rate to the scale (all items of the scale were completed by all 286 respondents) shows that the SDS was acceptable to use as part of a larger survey study. PCA showed a single factor solution accounting for 75% of the variance. The alpha value

TABLE 3 | SDS score and its association with aberrant codeine related behaviors.

	Respondents scoring <5 on the Severity of Dependence Scale (not indicating codeine dependence) (*n* = 235) %	Respondents scoring ≥5 on the Severity of Dependence Scale (indicating probable codeine dependence) (*n* = 51) %	OR (95% CI)
Codeine consumption			
Daily use in last 3 months	26.8%	96.1%**	66.89 (15.8–283.18)
Physical dependence			
Codeine tolerance	4.3%	58.8%**	32.14 (13.82–74.75)
Sought advice to manage the use of codeine			
On the Internet	6.8%	41.2%**	9.56 (4.5–20.31)
From a GP	2.6%	19.6%**	9.31 (3.21–27.01)
Drug addiction treatment			
Received treatment to help control alcohol or drug use	12.8%	35.3%**	3.73 (1.88–7.43)
Impact on social life			
Problems with role responsibility due to codeine	10.2%	52.9%**	9.89 (4.95–19.78)
Others expressed concern about use of codeine	10.6%	51%**	8.74 (4.39–17.38)
Emotional distress			
Used codeine to feel better when down or depressed	13.2%	45.1%**	5.41 (2.77–10.55)
Used codeine to stop worrying about a problem	7.7%	33.3%**	6.03 (2.83–12.83)
Codeine tampering			
Consumed codeine extracted from codeine containing medicines	14.5%	25.5%	1.78 (0.86–3.7)
Drinking codeine cough syrups mixed with soft drink, juice or alcohol	9.4%	25.5%**	3.33 (1.55–7.14)
Illicit drug use			
Life-time substance use	52.8%	64.7%	1.54 (0.85–2.79)

***P < 0.01; OR, odds ratio; CI, confidence interval.*

was high (Cronbach's alpha = 0.92). Using a score of five and above to indicate probable psychological dependence to codeine, the study demonstrated associations between SDS scores and measures in themselves indicating probable codeine dependence, including daily consumption, tolerance, and problems with role responsibility due to codeine intoxication (25, 35). This compares favorably with a previous study using a similar online research design where probable codeine dependence (indicated by a cut-off score ≥5) was associated with past alcohol and drug addiction treatment, chronic pain, and exceeding medical guidance for dose consumption (25). Online purposive samples have unknown population characteristics (36), but have in this study provided useful preliminary data and indication of using the SDS to assess probable codeine dependence.

PCA and Consistency of the Scale

PCA has been used to investigate the dimensionality of the SDS for heroin, cocaine, amphetamine and cannabis (14, 37). In this study, PCA indicated a single factor solution accounting for 75% of the variance, suggesting that the five SDS items are suitable as a single measure of psychological dependence. Previous research on the SDS, comparable to findings presented here, found single factor solutions accounting for a range of 45.5–80% of the variance (14, 17, 37).

Cronbach's alpha was used as a measure of internal consistency. According to previous research, values of ≥0.70 were considered adequate (38). An alpha value of 0.92 in the study is equal to or slightly higher than in previous investigations of the scale (14, 24, 37). In addition to the PCA analyses, a high alpha value is also a necessary condition for unidimensionality (14).

While the conducted analyses, including the PCA, satisfy a number of criteria to account for the SDS as a single measure of psychological dependence on codeine, they do not account for how well the SDS determines if respondents have the condition or not. As such the diagnostic properties of the SDS are unclear until further analyses can be completed comparing SDS scores against indicators of codeine dependence from the DSM-5.

External Validation

Using a cut-off score of five or above, the validity of the SDS score is supported by the association with codeine related behaviors known to be related to the severity of codeine dependence. These include exceeding dose recommendations, daily use, chronic pain, psychological distress, past alcohol and drug addiction treatment, and codeine use to prevent withdrawal symptoms (25, 34, 35). The results obtained in this study show that probable codeine dependence was associated with daily use over the past 3 months, having sought advice and treatment to manage dependence, drinking codeine cough syrup mixed with juice and

alcohol, having experienced that other expressed concern about codeine use and using codeine for emotional distress.

A well-known limitation of the SDS is that it was designed to measure psychological elements of dependence, such as compulsion or craving, whilst excluding components relating to physical dependence like tolerance and withdrawal caused by neuroadaptation (14). It is notable in this respect that respondents who were codeine dependent according to the SDS were significantly more likely to report tolerance to codeine than those who were not codeine dependent, supporting the validity of the SDS by its association with this central component of physical dependence.

Limitations

Whilst, to our knowledge, this is the first study to report on the psychometric properties of the SDS for codeine, the sample size restricts inference of these results to wider populations of people who are using codeine. The sample size is relatively small when considering the time during which the survey was open for recruitment. Lack of data and understanding of codeine dependent populations in the UK impede the construction of a sampling frame and make the representativeness of our sample difficult to measure. Furthermore, it must be noted that online purposive sampling has biases due to unknown characteristics of people who participate in online communities and forums (36). Using online recruitment potentially excludes those with no immediate access to the Internet and may restrict respondents to those with a certain income, social situation and level of education. The differences between levels of codeine dependence and associated problems in online and non-online populations are currently unclear. Missing data precluded an analysis of codeine dose consumption amongst non-dependent and dependent respondents, although dose is a well-known indicator of problematic medicine use (25). Though our findings suggest that a score of 5 and above is an acceptable indicator of probable codeine dependence, the SDS was not designed as a screening tool to decide categorically between non-dependence and dependence (14). Further research is therefore required to compare the adopted cut-off score of 5 against a validated screening tool diagnosing substance dependence. Further research should also explore the use of the SDS compared against a validated diagnostic assessment in different age groups and according to gender.

Implications for Research

Further studies are needed in well-defined populations to test the different aspects of psychometry of the SDS for codeine to determine its feasibility and validity in research settings. Studies should also investigate the validity of the SDS within different settings, such as primary care, community pharmacies and specialized addiction services. The test-retest reliability of the SDS for codeine is not known. Data that provides an indication of the stability of SDS scores across occasions (39) would add additional value to the scale.

Implications in Practice

Previous studies have determined a cut-off point on the SDS that discriminates between the presence and absence of a DSM-5 diagnosis for substance dependence suggesting its implementation and usefulness in clinical settings. These studies found a SDS score of 3 or above optimal for characterizing a DSM-5 diagnosis of alcohol dependence (23), whereas a cut-off score of 7 was found to be the appropriate threshold for dependence to benzodiazepines (22). In this study, several factors relating to aberrant codeine use were associated with probable codeine dependence when using a cut-off score of 5. Research with people attending specialized drug addiction treatment for codeine would enable a comparison between SDS scores and DSM-5 diagnosis, possibly enabling its use in clinical settings as a quick way of determining possible psychological dependence on codeine. Obtaining good assessment amongst people presenting with substance use typically improves care and use of screening, assessment and monitoring tools is recommended (40). This study demonstrated that the SDS is useful as a screening tool for research purposes, which can be included in larger study questionnaires with an excellent response rate presumably due to its short length.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study involving human participants was reviewed, approved and received ethics approval granted by the Psychiatry, Nursing, and Midwifery Research Ethics Subcommittee (PNM RESC), King's College London. REC Reference Number: PNM/14/15-110. The patients/participants provided their written informed consent online to participate in this study.

AUTHOR CONTRIBUTIONS

AK, MF, and PD developed the survey used with people who had recently used codeine. The ongoing monitoring of the survey and recruitment was managed by AK. Data analysis was conducted by AK, MF, and JD. All authors contributed to the writing of the paper, with writing and analyses led by PD and AK.

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Personality to Prescription Drug Misuse in Adolescents: Testing Affect Regulation, Psychological Dysregulation, and Deviance Proneness Pathways

Sherry H. Stewart[1,2]*, *Annie Chinneck*[2], *Kara Thompson*[3], *Mohammad H. Afzali*[4], *Raquel Nogueira-Arjona*[2], *Ioan T. Mahu*[2] *and Patricia J. Conrod*[4]

[1] Department of Psychiatry, Dalhousie University, Halifax, NS, Canada, [2] Department of Psychology & Neuroscience, Dalhousie University, Halifax, NS, Canada, [3] Department of Psychology, St. Francis Xavier University, Antigonish, NS, Canada, [4] Department of Psychiatry, Université de Montréal, Montréal, PQ, Canada

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Fabrizio Schifano,
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University of Hertfordshire,
United Kingdom

***Correspondence:**
Sherry H. Stewart
sstewart@dal.ca

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Background: Fifteen to 25-year-olds are the age group most likely to misuse prescription drugs. Few studies have tested theory-driven models of adolescent risk for prescription drug misuse. Moreover, rarely are distinct pathways to different forms of prescription drug misuse considered.

Methods: We tested mediational paths from personality to mental health symptoms to prescription drug misuse, informed by etiological models of addiction. We specified pathways from particular personality traits to unique forms of prescription drug misuse via specific mental health symptoms. We used semi-longitudinal data collected across two waves of the Co-Venture Trial. Our sample included students from 31 Canadian high schools tested in Grade 9 (n = 3,024) and again in Grade 10 (n = 2,869; 95% retention). Personality (hopelessness, anxiety sensitivity, impulsivity, sensation seeking) was assessed in Grade 9. Mental health symptoms (depression, anxiety, ADHD, conduct disorder) and prescription drug misuse (opioids, sedatives/tranquilizers, stimulants) were assessed at both time points.

Results: Consistent with the negative affect regulation model, hopelessness was specifically associated with opioid misuse via depressive symptoms, and anxiety sensitivity was specifically associated with sedative/tranquilizer misuse via anxiety symptoms. Consistent with positive affect regulation, sensation seeking was directly associated with stimulant misuse. Consistent with the psychological dysregulation model, impulsivity was associated with stimulant misuse via ADHD symptoms. And consistent with the deviance proneness model, impulsivity was also associated with unconstrained (i.e., all three forms of) prescription drug misuse via conduct disorder symptoms.

Conclusions: Screening for adolescents high in hopelessness, anxiety sensitivity, sensation seeking, or impulsivity and providing them with personality-matched

cognitive-behavioral interventions may be helpful in preventing or mitigating prescription drug misuse. Our results point to the specific mental health symptoms that are important to target in each of these personality-matched interventions.

Keywords: adolescents, personality risk, prescription drug misuse, anxiety sensitivity, hopelessness, sensation seeking, impulsivity, mental health symptoms

INTRODUCTION

The National Survey on Drug Use and Mental Health defines prescription drug (PD) misuse as use of PDs "in any way that a doctor did not direct you to use them" including (a) use without a prescription of one's own; (b) use in greater amounts, for longer, or more often than prescribed; or (c) use in any other way that was not prescribed by a physician (1). Many young people consider PDs to be less harmful than illicit drugs (2). Due to their potency, potential for addiction, and overdose potential, however, PD misuse can be injurious or even fatal (3).

Of any age group, 15–25-year-olds are the most likely to misuse PDs (1). After cannabis, PDs are the drugs most commonly misused by North American adolescents (1, 4). One study showed that among adolescents aged 12–17, 5% reported past year PD misuse (5). PDs are readily accessible to adolescents through legitimate medical prescriptions (6), diversion (7, 8), and online pharmacies (9, 10). These trends are concerning for several reasons. First, prescription opiate misuse increases risk for serious injury (11), respiratory depression, and death (12). Moreover, the prevalence of adolescent misuse of sedatives/tranquilizers, including novel designer benzodiazepines, is significantly increasing (13–15), co-use with opioids is common (16), and sedative/tranquilizer-related deaths increased by 137% from 2007 to 2016 (17). Stimulant misuse is associated with adverse short-term (e.g., headaches, sleep problems, academic difficulties) and long-term effects [e.g., decreased likelihood of college graduation; (18)]. Adolescent-onset PD misuse is linked with elevated substance use disorder rates in adulthood (18, 19).

While several risk and protective factors for adolescent PD misuse have been identified [see review by (20)], few studies have tested theoretical models of adolescent risk for PD misuse (21). And although the predictors of PD misuse may vary considerably by drug class (22), little work has examined unique pathways to specific forms of PD misuse. One potential risk factor that may help fill both these identified gaps is personality: specific traits may present risk for particular classes of PD misuse via unique theory-informed pathways.

Personality as a Risk Factor

Personality is a robust predictor of addictive behavior [e.g., (23)]. Internalizing and externalizing traits have been reliably associated with an increased susceptibility for alcohol and illicit substance misuse in adolescence (24). Pihl and Peterson (25) developed a model that delineates four such traits. The first two traits in this model are internalizing. Hopelessness (HOP) involves the trait-like tendency to expect aversive events but not desirable ones (26, 27). Anxiety sensitivity (AS) involves the fear of anxiety-related sensations, due to an unrealistic expectation that such sensations will have catastrophic consequences (28). In adolescents, both HOP and AS are associated with coping motives for substance use (29). Young people high in these traits tend to preferentially misuse depressant drugs (30, 31). In adults, HOP uniquely predicts opioid dependence and AS uniquely predicts anxiolytic dependence (30, 32). The specificity of these paths has yet to be tested in adolescents.

The remaining two traits in Pihl and Peterson's (25) model are externalizing. Impulsivity (IMP), or impulsiveness, is the tendency to act without sufficient forethought (33). IMP has been associated with a pattern of polysubstance use (34, 35). Deficits in response inhibition make high IMP teens more susceptible to early experimentation and to later compulsive substance use (36). Sensation seeking (SS), or novelty seeking (37), involves the desire for novel and intense stimulation (38). High SS substance users are sensitive to the rewarding properties of drugs (39) and tend to specifically misuse stimulants (40) to study, stay awake/alert, "get high," "party," and experiment (41).

Traits from Pihl and Peterson's (25) four-factor personality vulnerability model have proven useful in predicting adolescent alcohol (42) and illicit drug use (43, 44), emerging adult PD use (31, 45), and adult PD use (30). This model has yet to be applied to adolescent PD misuse.

Etiological Models of Addiction

Theoretically, these four traits exert their influence on substance use via negative and positive affect regulation, deviance proneness, and/or psychological dysregulation processes (39). The models most relevant to linking HOP, AS, SS, and IMP with PD misuse are described below (see also **Table 1**). These theoretical models have informed the mediators in the hypothesized paths from personality to PD misuse.

Affect Regulation Models

Affect regulation models theorize that drugs are taken to regulate emotions—either for negative reinforcement (i.e., a drug's ability to relieve negative affect) or positive reinforcement (i.e., a drug's hedonic effects) (31). Negative affect regulation involves PD use to avoid or control negative emotional states whereas positive affect regulation involves PD use to increase positive emotional states. This dichotomy is in keeping with McCabe et al.'s (46) work on PD misuse motives, which suggests that PDs are misused for self-medication (negative affect regulation) or recreation (positive affect regulation).

Negative Affect Regulation

Individuals high in HOP or AS are theoretically most prone to PD misuse for negative affect regulation (29). First, those high in

TABLE 1 | Summary of theories and hypotheses.

Personality trait	Relevant etiological model	Derived hypotheses
HOP, AS	Negative affect regulation	*H1*: HOP → depressive symptoms → opioid misuse *H2*: AS → anxiety symptoms → sedative/tranquilizer misuse
SS	Positive affect regulation	*H3*: SS → stimulant misuse
IMP	Deviance proneness	*H4*: IMP → CD symptoms → opioid misuse IMP → CD symptoms → sedative/tranquilizer misuse IMP → CD symptoms → stimulant misuse
IMP	Psychological dysregulation	*H5*: IMP → ADHD symptoms → stimulant misuse

HOP are thought to misuse opioids to control or avoid symptoms of depression. High HOP adults preferentially misuse opioids over other substances (30–32). HOP also predicts adolescent depression (47), and depression increases risk of PD misuse (21). The negative affect regulation model suggests that depressive symptoms should mediate HOP's specific effect on opioid misuse.

Those high in AS are also theoretically prone to PD misuse for negative affect regulation but through a distinct pathway. Specifically, they are thought to misuse sedatives/tranquilizers to control or avoid anxiety symptoms. High AS adults preferentially misuse anxiolytics over other substances (30, 31). AS incrementally predicts anxiety disorder symptoms in children and adolescents (48, 49) and anxiety disorders are associated with increased risk for sedative/tranquilizer misuse (50). In sum, the negative affect regulation model supports two distinct and specific pathways: HOP to opioid misuse via depressive symptoms vs. AS to sedative/tranquilizer misuse via anxiety symptoms.

Positive Affect Regulation

Stimulants activate mesolimbic dopamine activity and increase positive mood (51). High SS individuals are theoretically most prone to stimulant misuse for positive affect regulation. SS is robustly related to sensitivity to drug reward (39) and to enhancement motivated substance use (31). High SS individuals preferentially misuse stimulants (32, 40). The positive affect regulation model suggests this is because SS underlies sensitivity to stimulant reinforcement (52). The positive affect regulation model suggests a direct pathway from SS to stimulant misuse that is not mediated through mental health symptoms.

Deviance Proneness Model

Another model relevant to understanding PD misuse is the deviance proneness model (53). High IMP individuals are thought to be prone to a broad, unconstrained pattern of PD misuse (opioid, sedative/tranquilizer, and stimulant), occurring amidst other "deviant" or antisocial behaviors. IMP is associated with comorbid addictive and antisocial behaviors (54). IMP in elementary school students is concurrently and prospectively associated with conduct problems (55). Conduct disorder (CD) symptom severity is associated with greater substance involvement (56), including unconstrained PD misuse (57), in adolescence. The deviance proneness model suggests that CD symptoms mediate IMP's effect on unconstrained PD misuse (i.e., all three types of PD misuse).

Psychological Dysregulation Model

The psychological dysregulation model is an alternative model for explaining the specific link of IMP to stimulant misuse. Individuals high in IMP are most prone to PD misuse resulting from an adverse environment triggering a heritable tendency toward psychological dysregulation (58). ADHD is an externalizing disorder characterized by high IMP (59). Individuals with ADHD (60) or high IMP levels (24) are more likely to misuse stimulants. While only 4% of 10–18-year-olds endorse past-month stimulant misuse (61), 14% of 4–17-year-olds with ADHD endorse past-2-week stimulant misuse (62). IMP's effect on stimulant misuse may be attributable, at least in part, to an inability to inhibit pre-potent responses (63). ADHD symptoms are associated with stimulant misuse even after controlling for prescribed use (64). The psychological dysregulation model suggests that symptoms of ADHD mediate IMP's specific effect on stimulant misuse.

Objectives

Nargiso et al. (20) reviewed 50 articles on adolescent PD misuse and identified the following limitations. First, most studies were cross-sectional. Second, non-demographic risk factors (e.g., personality, mental health symptoms) were understudied. Third, there was a lack of specificity regarding predictors of misuse across PD classes. The present study sought to address these limitations by examining predictors of different forms of PD misuse (i.e., opioid, sedative/tranquilizer, stimulant) in a large sample of Canadian adolescents, tested prospectively in Grades 9 and 10 through a "semi-longitudinal design." In this design, one part is longitudinal (i.e., tests of personality to mental health symptoms and personality to PD misuse) and the other part is cross-sectional (i.e., tests of mental health symptoms to PD misuse). We used a broad definition of PD misuse in the present study, involving use of a PD in any way not directed by a physician (1).

See **Table 1** for a summary of our hypotheses. Based on the theories described above, we hypothesized that: in keeping with the negative affect regulation model, (*H1*) Grade 9 HOP would specifically predict Grade 10 opioid misuse via Grade 10 depressive symptoms, and *(H2)* Grade 9 AS would specifically predict Grade 10 sedative/tranquilizer misuse via Grade 10 anxiety symptoms; in keeping with the positive affect regulation model, *(H3)* Grade 9 SS would directly predict Grad 10 stimulant misuse; in keeping with the deviance proneness model, *(H4)* Grade 9 IMP would predict Grade 10 opioid misuse, sedative tranquilizer misuse, and stimulant use, all via Grade 10 CD symptoms; and in keeping with the psychological dysregulation

model, *(H5)* Grade 9 IMP would also predict Grade 10 stimulant misuse via Grade 10 ADHD symptoms.

METHODS

The present study's data was archival. It was collected as part of the Co-Venture Trial (65) examining the longer-term efficacy of personality-targeted substance misuse prevention. Assenting students from 31 high schools (public and private; English and French) in Montreal, Canada participated. Data was collected annually (during the fall and spring terms) beginning in September 2012. A web-based platform (Delosis Ltd., London, U.K.) was used to survey students during regular class times. At baseline, students were in Grade 7. The present study used data collected prospectively in Grade 9 (September 2014-May 2015) and Grade 10 (September 2015-May 2016). Risk increases as adolescents transition from middle to high school (66). In Canada, high school normally runs from Grades 9-12 (67). We therefore excluded Grade 7-8 (i.e., middle school) data. Ethical approval was granted by Sainte-Justine Hospital's Research Ethics Board (approval number = 2012-396, 3427) and by each administrative school board.

Participants

Sample sizes were $n = 3{,}024$ in Grade 9 and $n = 2{,}869$ of these same students in Grade 10 (5% attrition). See **Table 2** for sample characteristics.

Measures

Personality

The 23-item Substance Use Risk Profile Scale (SURPS; 30) was used to assess personality as part of the Co-Venture Trial. The SURPS has four subscales: HOP (7 items; "I feel that I'm a failure"), AS (5 items; "It is frightening to feel dizzy or faint"), SS (6 items; "I like doing things that frighten me a little"), and IMP (5 items; "I usually act without stopping to think"). Participants responded using a 5-point Likert scale (1 *strongly disagree* to 5 *strongly agree*). Following reverse scoring of certain negatively keyed items, subscale scores were generated by summing component items. The SURPS was chosen for use in the large-scale Co-Venture survey given its brevity and its strong psychometric properties in both English (43) and French (73). These include acceptable to good internal consistency, factorial validity, convergent and discriminant validity (e.g., with similar personality measures), and concurrent, predictive, and incremental validity in relation to substance use and substance-related problems in youth [e.g., (31, 43, 74)]. In the present sample, the subscales were internally consistent (see **Table 2**).

Internalizing Symptoms

The 18-item Brief Symptom Inventory-18 [BSI-18; (70)] was used to assess depression and anxiety symptoms. It measures past-week psychological distress. In this study, only the Depression (6 items; "feeling blue") and Anxiety (6 items; "nervousness or shakiness inside") subscales were used. Participants responded using a 5-point Likert Scale (0 *not at all* to 4 *extremely often*). Subscale scores were generated by summing component items. The BSI-18 has strong psychometric properties in both English (75) and French (76). In our sample, the subscales were internally consistent (see **Table 2**).

Externalizing Symptoms

The 25-item Youth Self-Report Strengths and Difficulties Questionnaire (SDQ; 73) was used to assess ADHD and CD symptoms. It measures symptoms over the past 6-months. In this study, only the Hyperactivity/Inattention (5 items; "restless, cannot sit still for long") and Conduct Problems (5 items; "often accused of lying or cheating") subscales were used (77). The remaining subscales were excluded as they pertain instead to prosocial (Prosocial Behavior) and internalizing (Emotional Symptoms, Peer Relationship Problems) behaviors (77). Participants responded using a 3-point Likert Scale (0 *not true* to 2 *certainly true*). Following reverse scoring of certain items, subscale scores were generated by summing component items. The SDQ has strong psychometric properties in both English (78) and French (79). In our sample, the subscales were internally consistent (see **Table 2**).

Prescription Drug Misuse

A modified and validated version of the Detection of Alcohol and Drug Problems in Adolescents (DEP-ADO; 77) assessed lifetime PD misuse for: (1) Opioids: e.g., "Codeine, Demerol, Morphine, Percodan, Methadone, Darvon, Opium, Dilaudid, or Talwin"; (2) sedatives: e.g., "barbiturates, sedatives, downers, or sleeping pills like Seconal and Quaaludes"; (3) tranquilizers: e.g., "Valium, Librium, or Ativan"; and (4) stimulants: e.g., "stimulants, speed, methamphetamine, amphetamine, or Benzedrine." Participants responded using a 6-point frequency scale (0 *never* to 5 *every day*). To deal with zero-inflation, items were scored dichotomously (i.e., 1 = *had used that PD class*, 0 = *had not*). In keeping with our previous research (45), sedatives and tranquilizers were collapsed into a single category. The DEP-ADO has strong psychometrics and is available in both English (69) and French (80). It was developed for and validated with adolescents aged 14-17 years (i.e., Grades 9–11). It has a strong test-retest reliability (r =0.94), acceptable to good internal consistency (Cronbach's alpha =0.61–0.86), and content, convergent, and criterion-related validity (sensitivity =0.84; specificity =0.91) (69).

Alcohol Misuse

Alcohol misuse was also assessed using the modified DEP-ADO (69). This scale includes 10 yes/no items that pertain to lifetime issues with: physical health, psychological health, familial relationships, intimate relationships, academics, finances, delinquency, risky behavior, alcohol tolerance, and treatment seeking, attributable to one's alcohol use. This sole focus on alcohol was a change from the original DEP-ADO which asked these items for alcohol and other drugs combined (69). Items were summed to create a 0–10 total score. Only those indicating a frequency of drinking greater than or equal to "weekends or once or twice during the week" on a previous DEP-ADO item were asked these alcohol misuse items; the others were skipped over these items and automatically assigned an alcohol misuse

TABLE 2 | Frequencies and descriptive statistics.

	Grade 9				Grade 10			
	n	%	*M (SD)*	α	*N*	%	*M (SD)*	α
Age	3,024		14.79 (0.47)		2,869		15.83 (0.42)	
Gender								
Male	1,463	50.7			1,374	50.1		
Female	1.425	49.3			1,371	49.9		
Ethnicity								
Canadian or American	2,535	87.8			2,413	87.9		
European	64	2.2			63	2.3		
African	57	2.0			46	1.7		
Caribbean	28	1.0			26	0.9		
East Asian	81	2.8			82	3.0		
South Asian	17	0.6			17	0.6		
Middle Eastern	21	0.7			21	0.8		
South or Central American	44	1.5			39	1.4		
Other	27	0.9			23	0.8		
Don't know	14	0.5			15	0.5		
Socioeconomic status			5.36 (1.69)				5.37 (1.66)	
Alcohol misuse			0.09 (0.59)	0.79			0.17 (0.79)	0.81
Hopelessness			12.51 (3.92)	0.89			12.73 (3.83)	0.89
Anxiety sensitivity			11.09 (2.95)	0.70			11.02 (2.97)	0.73
Sensation seeking			16.14 (3.63)	0.70			16.37 (3.70)	0.71
Impulsivity			11.66 (2.91)	0.75			11.55 (2.87)	0.75
Depression			5.32 (5.98)	0.90			5.45 (5.93)	0.90
Anxiety			2.81 (4.03)	0.90			2.82 (3.99)	0.89
ADHD			4.12 (2.40)	0.72			4.12 (2.38)	0.74
CD			2.18 (1.64)	0.62			2.09 (1.61)	0.64
Opioids	54	1.8			88	3.1		
Sedatives/tranquilizers	95	3.1			100	3.5		
Stimulants	50	1.7			63	2.2		

Socioeconomic Status was rated using a 10-point Likert scale (68) with higher scores representing greater wealth. Alcohol Misuse was assessed using the DEP-ADO (69); internal consistency values for the DEP-ADO alcohol misuse scale was calculated only among the more frequent drinkers as others were skipped over these items and assigned a score of zero. Personality was assessed using the SURPS (31). Depression and Anxiety were assessed using the BSI-18 (70). ADHD, Attention-Deficit Hyperactivity Disorder; CD, Conduct Disorder. Both were assessed using the SDQ (71). PD misuse was assessed using the DEP-ADO (69) and scored dichotomously. For short scales with 10 items or less, an alpha of ≥ 0.60 is considered acceptable (72).

score of 0. In the present sample, the alcohol misuse scale was internally consistent (see **Table 2**).

Statistical Analyses

Sample descriptive statistics were first calculated in SPSS 20.0. T-tests and chi square tests were used to compare baseline (Grade 9) characteristics of those retained ($n = 2{,}869$) vs. lost to follow-up ($n = 155$) in Grade 10. Correlations were specified between the personality, mental health, and PD misuse variables. The hypothesized model was then run in MPlus 7.11 (81). Because our dependent variables were categorical, a robust weighted least squares approach was used [ESTIMATOR = WLSMV; (82)]. Missing data was handled using pairwise deletion such that only those with data at both timepoints were used in hypothesis testing. We controlled for school and for Grade 9 mental health and PD misuse. Our model therefore accounts for new users. We also controlled for age, sex, ethnicity, and socioeconomic status (68), given their known effects on PD misuse (20, 83). Because high-intensity drinking is associated with PD misuse (84), we controlled for alcohol misuse as assessed on the DEP-ADO. These covariates were regressed onto all the outcome variables.

Standard indices were used to assess model fit. RMSEA $\leq$ 0.05 and CFI/TLI $\geq$0.95 indicate good fit. RSMEA $\leq$ 0.08 and CFI/TLI $\geq$0.90 indicate adequate fit (85). Since chi-square values are often significant when the sample size is large (86), we did not interpret the chi-square as a fit statistic. Instead, we used the χ^2/df ratio where a value < 3.0 indicates good fit. Significant effects were detected at a 95% confidence interval. Bootstrapped confidence intervals were used to determine the significance of indirect effects (i.e., significant if the confidence intervals did not cross zero).

RESULTS

Sociodemographic Features

On average, students were 14.8 ($SD = 0.5$) years of age in Grade 9. There was a relatively equal split of the sample across gender at both waves. Most students were middle class and of Canadian or American descent (see **Table 2**).

Personality

Sample mean scores on the four subscales of the SURPS were relatively consistent with norms on the measure from a previously tested sample of adolescents (31). Scores remained relatively stable from Grade 9 to Grade 10 (see **Table 2**).

Mental Health

Sample mean scores on the BSI-18 measure of internalizing mental health symptoms indicated that levels of anxiety and depression symptoms were both relatively low, on average, in our non-clinical sample at baseline (Grade 9), with depression symptom scores somewhat higher than anxiety symptom scores overall. Sample mean scores on the SDQ measure of externalizing mental health symptoms similarly indicated that levels of ADHD and CD symptoms were both relatively low, on average, in our non-clinical sample at baseline (Grade 9), with ADHD symptom scores somewhat higher than CD symptoms scores overall. Scores remained relatively stable on all four measures of mental health symptoms from Grade 9 to Grade 10 (see **Table 2**).

Substance Misuse

In Grade 10, lifetime PD misuse rates were: 3% for opioids, 4% for sedatives/tranquilizers, and 2% for stimulants (see **Table 2**). Rates of misuse of each type of PD rose between Grade 9 and Grade 10 with the sharpest increase observed for opioid misuse. Levels of alcohol misuse also rose between Grade 9 and Grade 10 (see **Table 2**).

Comparison of Students Retained vs. Lost to Follow-Up

T-tests and chi-square tests suggested that, at baseline (Grade 9), those who were later lost to follow-up (Grade 10) were older, more likely to attend certain schools, and endorsed more personality vulnerability (HOP, SS, IMP), mental health symptoms (depression, CD, ADHD), alcohol misuse, and PD misuse.

Correlations

Bivariate correlations between study variables are displayed in **Table 3**. With respect to correlations between Grade 9 personality and Grade 10 mental health symptoms, HOP was most strongly associated with depressive symptoms, AS was most strongly associated with anxiety symptoms, and IMP and SS were most strongly associated with ADHD and CD symptoms (with IMP showing much stronger associations than SS in this regard). With respect to correlations between Grade 10 mental health symptoms and Grade 10 PD misuse, the strongest correlations were between CD symptoms with all three forms of PD misuse, anxiety and depressive symptoms with sedative/tranquilizer misuse, and ADHD symptoms with stimulant misuse. Grade 9 alcohol misuse was significantly associated with all Grade 9 personality factors save AS, with all four measures of Grade 10 mental health symptoms, and with all three forms of PD misuse in Grade 10, underlining the importance of alcohol misuse as a covariate.

Hypothesis Tests

Our hypothesized model (see **Figure 1**) showed good fit across fit indices: $\chi^2(71) = 158.07$, $p < 0.001$; $\chi^2/df = 2.23$; RMSEA =0.02, 90% CI [0.02, 0.03]; CFI =0.98; TLI =0.96. Indirect effects are reported in **Table 4**.

Grade 9 HOP significantly predicted Grade 10 depressive symptoms which in turn were significantly associated with Grade 10 opioid misuse. Consistent with *H1*, the indirect effect was statistically significant ($p < 0.05$). Grade 9 AS significantly predicted Grade 10 anxiety symptoms which in turn were significantly associated with Grade 10 sedative/tranquilizer misuse. Consistent with *H2*, the indirect effect was statistically significant ($p < 0.01$).

Consistent with *H3*, the direct path from Grade 9 SS to Grade 10 stimulant misuse was statistically significant. Grade 9 IMP significantly predicted Grade 10 CD symptoms which in turn were significantly associated with Grade 10 opioid and sedative/tranquilizer misuse and marginally associated with Grade 10 stimulant misuse ($p = 0.06$). Consistent with *H4*, all three indirect effects were statistically significant ($p < 0.05$ for opioid and stimulant misuse; $p < 0.01$ for sedative/tranquilizer misuse). Grade 9 IMP also significantly predicted Grade 10 ADHD symptoms which were in turn associated with Grade 10 stimulant misuse. Consistent with *H5*, the indirect effect was statistically significant ($p < 0.05$).

Tests of Pathway Specificity

To determine the specificity of the HOP to opioid misuse pathway via depression symptoms [H1] and the AS to sedative/tranquilizer misuse pathway via anxiety symptoms [H2], we examined modification indices (MIs). These indicated that the inclusion of paths from AS to depression (MI: 0.23) and HOP to anxiety (MI: 2.47) did not improve model fit (values > 3.84 indicate that the model would be improved). Thus, for the sake of model parsimony, these were not added to the model.

DISCUSSION

Main Findings

In the present study, we sought to address the limitations of the extant literature on adolescent PD misuse, as outlined by Nargiso et al. (20). We applied the four-factor personality vulnerability model (25) to understanding risk for misuse of specific classes of PDs in adolescents. Moreover, we applied different theoretical models of addiction (39) to understanding specific pathways from personality to adolescents' future PD misuse, as mediated through specific sets of mental health symptoms.

Different personality traits showed effects on specific types of PD misuse through unique sets of mental health symptoms, consistent with different theoretical models of addiction, namely the negative and positive affective regulation,

TABLE 3 | Correlation matrix.

	1	2	3	4	5	6	7	8	9	10	11	12
Grade 9												
1. Hopelessness	1.00	**0.27**	−0.03	**0.32**	**0.11**	**0.46**	**0.35**	**0.33**	**0.22**	**0.07**	**0.11**	**0.09**
2. Anxiety sensitivity		1.00	**−0.12**	**0.19**	0.02	**0.23**	**0.33**	**0.14**	**0.05**	−0.03	−0.01	−0.01
3. Sensation seeking			1.00	**0.25**	**0.14**	−0.01	−0.02	**0.12**	**0.16**	**0.13**	**0.11**	**0.11**
4. Impulsivity				1.00	**0.11**	**0.22**	**0.18**	**0.45**	**0.41**	**0.11**	**0.11**	**0.12**
5. Alcohol harms					1.00	**0.08**	**0.06**	**0.08**	**0.13**	**0.12**	**0.17**	**0.20**
Grade 10												
6. Depression						1.00	**0.73**	**0.29**	**0.24**	**0.07**	**0.16**	**0.10**
7. Anxiety							1.00	**0.29**	**0.20**	**0.06**	**0.11**	**0.07**
8. ADHD								1.00	**0.40**	**0.09**	**0.09**	**0.10**
9. CD									1.00	**0.14**	**0.14**	**0.14**
10. Opioids										1.00	**0.21**	**0.30**
11. Sedatives/tranquilizers											1.00	**0.17**
12. Stimulants												1.00

ADHD is attention-deficit hyperactivity disorder; CD is conduct disorder. Bold correlations are significant at $p < 0.05$.

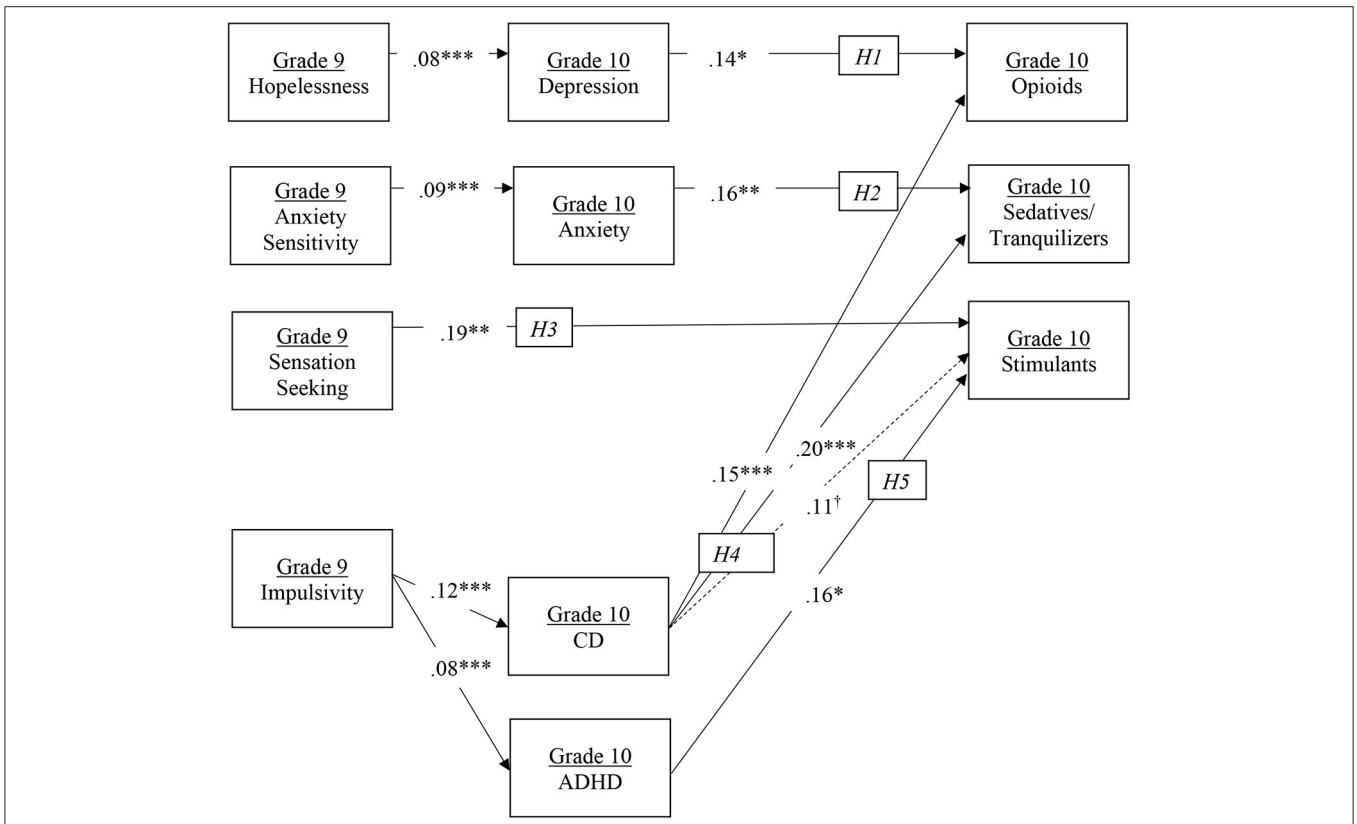

FIGURE 1 | Model results. *H1-H5* represent numbered hypotheses. Solid arrows represent statistically significant hypothesized pathways; dotted arrows represent hypothesized but non-significant pathways. Numbers represent standardized coefficients. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. † represents marginal significance at $p = 0.06$.

deviance proneness, and psychological dysregulation models. Two internalizing personality traits (HOP and AS) followed a negative affect regulation model for predicting specific PD misuse, while SS (an externalizing trait) followed a positive affect regulation model. First, depressive symptoms mediated the relationship between HOP and future opiate misuse. Second, anxiety symptoms mediated the relationship between AS and future tranquilizer misuse. While both these paths are

TABLE 4 | Tests of hypothesized indirect effects.

Hypothesis	Predictor	Mediator	Outcome	Indirect effect	95% confidence interval
H1	Hopelessness	Depression	Opioids	0.003	[0.000, 0.007]*
H2	Anxiety sensitivity	Anxiety	Sedatives/tranquilizers	0.005	[0.002, 0.012]**
H4	Impulsivity	CD	Opioids	0.005	[0.001, 0.010]*
	Impulsivity	CD	Sedatives/tranquilizers	0.008	[0.004, 0.014]**
	Impulsivity	CD	Stimulants	0.005	[0.000, 0.014]*
H5	Impulsivity	ADHD	Stimulants	0.005	[0.000, 0.012]*

*ADHD is attention-deficit hyperactivity disorder; CD is conduct disorder. *p < 0.05, **p < 0.01.*

consistent with negative affect regulation, they suggest that high HOP adolescents may be using opiates to self-medicate their depressive symptoms—while high AS teens may be using tranquilizers to self-medicate their anxiety symptoms. Third, SS was predictive of future stimulant misuse suggesting high SS adolescents may be using stimulants to enhance positive affect. This suggests that adolescents high in HOP and AS are prone to PD misuse via negative affect regulation pathways while those high in SS are prone to PD misuse via a positive affect regulation pathway. Fourth, CD symptoms mediated the relationship between IMP and future opiate, sedative/tranquilizer, and stimulant misuse, consistent with a deviance proneness pathway. Unlike the other three traits, IMP therefore seems to be a more general predictor of PD misuse, rather than a specific predictor of a particular form of PD misuse. Higher IMP adolescents appear to more prone to misusing PDs indiscriminately—in the same way that they are prone to engaging in broadband antisocial behaviors. Finally, ADHD symptoms also mediated IMP's effect in the case of future stimulant misuse. We have suggested that this unique personality-to-PD misuse pathway may represent self-medication of psychological dysregulation. In the next section, we look at each of these main findings in relation to the extant literature.

Comparison With the Literature

H1 predicted that HOP would specifically predict future opioid misuse via depressive symptoms. This hypothesis, informed by the negative affect regulation model, was supported through a significant indirect effect from Grade 9 HOP to Grade 10 opioid misuse 1 year later as mediated through Grade 10 depressive symptoms. Depression has been identified as the mental health issue most strongly related to opioid misuse (odds ratios from 1.2 to 4.3) (87). Zullig and Divin (88) found that students who endorsed HOP, depression, and suicidality were 1.18–1.43 times more likely to misuse opioids. Opioids possess psychic pain-numbing properties (89), which may make them particularly attractive to high HOP adolescents—who are prone to depression and may be looking to dull their psychological pain. Our mediational findings are consistent with a mechanism where HOP confers risk for opioid misuse in adolescence via negative affect regulation. More specifically, high HOP adolescents may be self-medicating their depressive symptoms by misusing opioids. Given that opioids are prescribed for the management of physical pain (89) but not for the management of depression (90), any use of opioids for depression self-medication would be considered opioid misuse since it would involve taking the medication for a non-prescribed purpose (91). To help establish the specificity of this HOP risk pathway to opioid use, we tested an additional personality to PD misuse pathway informed by the negative affect regulation model involving AS (i.e., *H2*).

H2 predicted that AS would specifically predict future sedative/tranquilizer misuse via anxiety symptoms. This hypothesis, also informed by the negative affect regulation model, was supported through a significant indirect effect from Grade 9 AS to Grade 10 sedative/tranquilizer misuse 1 year later as mediated through Grade 10 anxiety symptoms. While sedatives/tranquilizers are commonly prescribed for anxiety (92), the relevant DEP-ADO items (69) specify use "without a prescription," suggesting that high AS adolescents may be taking non-prescribed sedatives/tranquilizers that they have obtained from family, friends, dealers, or online pharmacies (15) to self-medicate their anxiety symptoms. Taken together, support for *H1-2* suggests that there are two distinct negative affect regulation paths from personality to PD misuse. The first is specific to opioid misuse through HOP and the self-medication of depression, and the second specific to sedative/tranquilizer misuse through AS and the self-medication of anxiety. Furthermore, modification indices indicated that the inclusion of paths from AS-to-depression and HOP-to-anxiety did not improve model fit, providing further evidence of the specificity of these pathways.

Informed by the positive affect regulation model, *H3* predicted that SS would lead to future stimulant misuse. This hypothesis was supported through a direct path from Grade 9 SS to Grade 10 stimulant misuse. SS is strongly related to sensitivity to positive reinforcement and enhancement motives (31). It predicts substance misuse (93) that is driven by a need for positive affect and psycho-stimulation (29). Previously, we found that SS predicted undergraduate stimulant misuse (45). Other studies also support a robust association between SS and adolescent alcohol misuse (74). Finn et al. (94) found that SS was both directly linked to alcohol problems as well as indirectly linked through alcohol use and positive alcohol expectancies. Castellanos-Ryan et al. (95) concluded that SS's effect on binge drinking was mediated by a reward response bias. Thus, SS likely confers risk for adolescent stimulant misuse as well as excessive drinking via a positive affect regulation pathway. Taken together, the support for *H1-H3* suggests that three distinct

affect regulation paths predict PD misuse in adolescence: two involving negative affect regulation (i.e., HOP to depression to opioid misuse and AS to anxiety to sedative/tranquilizer misuse) and one involving positive affect regulation (i.e., SS to stimulant misuse).

Unlike the specific associations of each of HOP, AS and SS with particular forms of PD misuse, we expected IMP to have a more general association with PD misuse, including future opioid, sedative/tranquilizer, and stimulant misuse. *H4* predicted that Grade 9 IMP would be associated with all three forms of PD misuse in Grade 10 via Grade 10 CD symptoms. These hypotheses, informed by the deviance proneness model, and IMP's centrality as a characteristic of CD (59, 96), were all supported in tests of indirect effects. This pattern is in keeping with previous research with other substances. Mackie et al. (93), for instance, found that IMP predicted adolescent alcohol use via CD symptoms. This result also replicates and extends prior research linking CD symptoms to unconstrained PD misuse in adolescents, including misuse of opioids (97) and stimulants (64). IMP's relationship with substance misuse is motivationally undefined (31) in that it is more reflective of a general inability to inhibit behavior (98). IMP is associated with deficits in response execution and inhibition (95). Poor response inhibition is a risk factor for both CD (99) and substance misuse (100). Paths from IMP to both CD and alcohol problems are also partially mediated by deficient response inhibition (94, 95). In sum, we know that high IMP adolescents struggle to regulate and inhibit their impulses. This makes them more vulnerable to deviance (including CD and PD misuse). Our results are consistent with the idea that IMP confers risk for broadband PD misuse (including all three types of PD misuse) via a general proneness toward deviance in adolescence.

In addition to these general IMP to CD symptoms to PD misuse pathways, *H5* predicted a second indirect pathway specifically linking IMP to later stimulant misuse via ADHD symptoms. This hypothesis, informed by the psychological dysregulation model, was supported by a significant indirect effect from Grade 9 IMP to Grade 10 stimulant misuse via Grade 10 ADHD symptoms. IMP is a prominent symptom of ADHD (101) for which stimulants are prescribed (102). Previously, we showed that IMP was concurrently associated with both medically sanctioned stimulant use and stimulant misuse in university students (45). Prescription stimulants are classified as Schedule III under the Canadian Controlled Drugs and Substances Act (S.C. 1996, C. 19) due to their high potential for misuse (103). Their use is legal only when prescribed by a licensed practitioner and taken by the person for whom they were prescribed. For those high in IMP, availability is the best motivational predictor of misuse (34). Adolescents who report symptoms of ADHD are more likely to have stimulant prescriptions, which they can then misuse [e.g., by taking their stimulants in greater amounts or more often than prescribed, via non-intended routes, for non-prescribed reasons, and/or with contraindicated substances; (91)]. While rates of stimulant misuse are relatively low in general adolescent samples, rates are much higher among adolescents who: have symptoms of ADHD, have ADHD diagnoses, are receiving treatment for ADHD, or have stimulant prescriptions (104). Interestingly, some research suggests that the young people most likely to misuse prescription stimulants are those with markers of a possible mental health disorder (e.g., ADHD) but without a formal diagnosis or prescription (105). Our results suggest that some young people may misuse stimulants to cope with their ADHD-related disorganization, poor time management, forgetfulness, and distractibility (64). Thus, in adolescence, IMP may confer risk for stimulant misuse, in part, via self-medication of psychological dysregulation—a form of self-medication that is theoretically distinct from the self-medication of negative affect pathways described above for AS and HOP.

Strengths and Limitations

Our study has several important strengths. These include the large sample size, inclusion of both French- and English-speaking students, the longitudinal component (personality to mental health symptoms and personality to PD misuse paths) over a 1-year follow-up across the developmentally challenging transition to high school, the excellent retention rate (95%), the control of baseline levels of mediators and outcomes in all models, and the theoretically driven hypotheses. Moreover, the topic of the paper is likely to be of interest to both a general and specialty audience of mental health professionals, particularly those that work with youth.

These findings should be interpreted in the context of several potential study limitations. First, we measured personality in Grade 9—and mental health symptoms *and* PD misuse in Grade 10. As such, the final pathways in our semi-longitudinal model (from mental health symptoms to PD misuse) were cross-sectional. Methodologically, we set up our semi-longitudinal model in this manner because *H1-H3* pertain to self-medication. We considered assessing PD misuse in Grade 11, in a three-wave design, but this would have meant testing whether students misused PDs to cope with the mental health symptoms they had reported a year earlier. We wanted to measure mental health symptoms and PD misuse in closer proximity. Self-medication models posit that the mental health-to-PD misuse relationship is unidirectional (50). There are data, however, that suggest that it may be bidirectional. PD misuse, for example, has been shown to exacerbate students' mental health symptoms (106). Our data do not allow us to compare these possibilities and our model does not allow for causal inference. Nonetheless, mediation analyses with even partially cross-sectional data can be a useful starting point (107) and our model had the advantage of being semi-longitudinal (i.e., where part of the design was longitudinal—specifically personality to mental health symptoms and personality to PD misuse). To demonstrate reliability and address these limitations, however, our model should be replicated in a fully longitudinal design that uses shorter (e.g., 6 month) lags between waves. Future research could also use ecological momentary assessment to examine these relationships day-to-day [e.g., (108)].

A second potential limitation pertains to our measure of PD misuse. The DEP-ADO was chosen because it is standardized, has been demonstrated reliable and valid in the measurement of Canadian high school students' substance use (69), and

can be use with both English- and French-speaking Québécois adolescents (73). Despite these strengths, the DEP-ADO has some shortcomings. For example, we assessed each type of PD misuse with a single item, introducing measurement error. It also provides little information about students' means of access (e.g., diversion sources, online pharmacies), administration routes, or motives for use. Moreover, different definitions of PD misuse abound (109), and it has been suggested that none of the instruments published to date can adequately assess PD misuse (110). When improved PD misuse measurement tools become available, our model should be replicated. This would reduce measurement error, allowing for a more accurate and refined test of personality's effects on PD misuse generally and on specific classes of PD misuse specifically.

Third, our sampling was limited. While our study was bolstered by its large sample size, this increases the likelihood that small effects will be statistically significant. And some of our effects were relatively small in magnitude, calling for evaluation of their clinical significance (see below). In addition, the students who did not complete our Grade 10 measures were more likely to report Grade 9 personality vulnerability, mental health symptoms, and alcohol and PD misuse, and were more likely to come from specific schools. Some of these results are in keeping with previous studies, in which adolescents lost to follow up were more likely to be involved in drug use and other deviant behavior (111–113). Moreover, we controlled effects of school in our analyses. It still bears noting, however, as samples and findings can be biased when the individuals who drop out differ substantially from those who are retained (114).

Finally, while the use of our brief personality measure [SURPS; (31)] allowed for brevity in the context of a large-scale survey, it did not allow for nuanced assessment of the components of each of our traits. For example, the longer Childhood Anxiety Sensitivity Index (115) would have allowed for examination of the relative contributions of the AS Physical, Social/Control, and Psychological concerns dimensions (116) to the anxiety symptom mediated pathway to sedative/tranquilizer misuse observed in the present study. Similarly, the longer Barratt Impulsiveness Scale (117) would have allowed for examination of the relative contributions of the Attentional, Motor, and Non-planning Impulsiveness components (118) to the CD and ADHD symptom mediated pathways to PD misuse observed in the present study.

Future Research Directions

The present study focused on the mediating effects of mental health symptoms. Motives for PD misuse were not assessed. Bennett and Holloway (119) have concluded that opioids, sedatives/tranquilizers, and stimulants tend to be misused in one of two ways. PDs are misused for self-medication of mental health (e.g., more sleep, less anxiety) or physical health (e.g., to manage a pre-existing illness) problems. They are also misused for pleasure (e.g., to party, get high, or experiment). Boyd et al. (22) and McCabe et al. (46) have published measures of motives for PD misuse. Negatively and positively reinforcing motives are both associated with increased PD misuse frequency (120). Follow-up studies might test whether personality predicts specific motives for PD misuse just as personality predicts specific motives for alcohol use (121). Previously, in the alcohol field, we found chained mediation from personality to mental health symptoms, to drinking motives, to alcohol outcomes (122). The results of the present study suggest that a four-variable chained mediational model might be equally applicable to PD misuse. For example, HOP may predict opioid misuse via symptoms of depression and in turn self-medication motives.

There are also several other areas of future research that are worthy of investigation in the field of personality and PD misuse risk more broadly. First, given that online marketplaces are an accessible source of PDs for young people [e.g., largely uncontrolled, not requiring a prescription, allowing for anonymous access; (123, 124)], and thus a significant public health concern, we need more information on the types of adolescents who are accessing PDs via these sites. While the demographic characteristics of the typical customers of such online marketplaces have been identified [i.e., young, male, Caucasian; (125)], we have not yet identified their personality or mental health characteristics, which would be helpful for targeting prevention efforts. Second, given the well-established role of social influence in young people's drug misuse [e.g., (126)] and emerging data concerning online drug forums and social networking sites where those experimenting with psychotropics, including PDs, share drug-related information (9), it would be interesting to study whether involvement in such communities might be related to personality. For example, are these experimenters or "psychonauts" higher in sensation seeking? Finally, personality and mental health factors may be relevant when it comes to pre-marketing assessment trials of the abuse liability of new prescription drugs. Current practices in this regard have been criticized for excluding those with a previous history of drug misuse or addiction [e.g., (8)]. Given the present findings of significant links of four factor personality model traits and mental health symptoms to different forms of PD misuse, there could be utility to testing a new compound's abuse potential using these more substance-misuse prone individuals in pre-marketing assessment trials to get at the compound's truer abuse liability.

Clinical Implications

Our model suggests that treatment of opioid misuse in adolescents might benefit from a specific targeting of HOP and IMP youth. Cognitive-behavioral therapy (CBT) could benefit teens high in HOP, by teaching them to better cope with their symptoms of depression (127). Motivational approaches could benefit antisocial teens high in IMP, by increasing their future-oriented thinking and teaching them to weigh the short vs. long term consequences of their behavior (128). Because we substantiated paths from IMP to CD symptoms, to opioid, sedative/tranquilizer, and stimulant misuse—a focus on this personality factor would theoretically reduce misuse of a variety of types of PDs. The results of our specificity tests further suggest that treatments of sedative/tranquilizer misuse be targeted toward youth high in AS and include techniques drawn from CBT for anxiety (128). To treat stimulant misuse, our model suggests we should be targeting adolescents high in externalizing traits. Those

high in SS could be encouraged to pursue other stimulating yet prosocial activities (129). "Alternate rebellions" including hair dyeing, getting a tattoo, or getting a piercing (130) are safer activities that might meet these adolescents' need for excitement. In contrast, psychologically dysregulated, high-IMP teens could be trained in behavioral ADHD-management techniques (131).

Treating PD misuse is, of course, important. But, given the ongoing PD crisis in North America (132), preventing it is *critical*. Adolescent overdoses from prescription opioids rose 95% from 1999 to 2016 (133). The likelihood of reporting PD misuse during adolescence, increases with age (83), as we saw across each PD type from Grade 9 to 10 in our sample. Research has shown that PD misuse rates rise consistently between Grade 8–12 and ages 12–17 (134). Thus, prevention efforts geared toward at-risk youth are especially vital. Our results suggest that identifying high personality-risk adolescents (i.e., those high in HOP, AS, SS, or IMP) would benefit both early intervention and targeted prevention strategies for PD misuse.

Personality-matched interventions have effectively reduced illicit drug use in adolescence (135) and PD misuse in adulthood (136). The present study was embedded within a larger trial, which evaluated the longer-term efficacy of the Preventure Program (65). This personality-matched prevention program targets teens with elevated four-factor trait scores (25). It is rooted in the cognitive-behavioral model and incorporates psycho-educational and motivational interviewing components. When applied to alcohol and illicit drug use, the Preventure Program has resulted in delayed onset and reduced escalation of misuse (65). Our study suggests that personality is related to PD misuse in a similar manner to its relations with alcohol and illicit drug use, through mental health symptoms. Thus, personality-matched interventions may have the potential to reduce PD misuse and even prevent PD uptake, if administered prior to PD misuse onset. Our results suggest that the Preventure Program should next be investigated in relation to its utility in targeting adolescent PD misuse.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical approval was granted by Sainte-Justine Hospital's Research Ethics Board and each administrative school board. The consent process varied across schools. Some schools opted for active consent where written informed consent to participate in the study was provided by the participants' legal guardian/next of kin. Other schools opted for a passive consent procedure where legal guardians/next of kin were fully informed about the study and they declined if they did not consent for their adolescent to participate. All adolescents provided their assent prior to participating.

AUTHOR CONTRIBUTIONS

SS and AC wrote the manuscript with input from all co-authors. KT ran the statistical analyses. MA assisted with database management. The data collection was coordinated by PC as part of the CoVenture trial. All authors assisted with conceptualization of the model and interpretation of the results.

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Non-medical Use of Prescription Gabapentinoids (Gabapentin and Pregabalin) in Five European Countries

Francina Fonseca[1,2,3†], William Lenahan[4†], Richard C. Dart[4], Esther Papaseit[5,6], Paul I. Dargan[7,8], David M. Wood[7,8], Marilena Guareschi[9], Icro Maremmani[10], Marc Auriacombe[11,12,13], Magí Farré[5,6‡], Norbert Scherbaum[14‡] and Marta Torrens[1,2,3‡]*

[1] Hospital del Mar, Institut de Neuropsiquiatria i Addiccions (INAD), Barcelona, Spain, [2] Grup de Recerca en Addiccions, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain, [3] Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona (UAB), Cerdanyola del Vallès, Spain, [4] Rocky Mountain Poison and Drug Safety, Denver Health and Hospital Authority, Denver, CO, United States, [5] Clinical Pharmacology Unit, Hospital Universitari Germans Trias i Pujol (HUGTP-Germans Trias i Pujol Research Institute), Badalona, Spain, [6] Department of Pharmacology, Therapeutics and Toxicology, Universitat Autònoma de Barcelona (UAB), Cerdanyola del Vallès, Spain, [7] Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [8] Clinical Toxicology, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom, [9] Association for the Application of Neuroscientific Knowledge to Social Aims (AU-CNS), Lucca, Italy, [10] Vincent P. Dole Research Group, Santa Chiara University Hospital, University of Pisa, Pisa, Italy, [11] Addiction Psychiatry Department, University of Bordeaux, Bordeaux, France, [12] Addiction Team, Sanpsy Centre National de la Recherche Scientifique (CNRS) USR 3413, Bordeaux, France, [13] Pôle Addictologie et Filière Régionale, Centre Hospitalier (CH) Charles Perrens and Centre Hospitalier Universitaire (CHU) de Bordeaux, Bordeaux, France, [14] LVR-Hospital Essen, Department of Psychiatry and Psychotherapy, Medical Faculty, University of Duisburg-Essen, Essen, Germany

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Fabrizio Schifano, University of Hertfordshire, United Kingdom

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***Correspondence:**
Marta Torrens
mtorrens@imim.es

[†]These authors have contributed equally to this work and share first authorship

[‡]These authors share senior authorship

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Background: Non-medical use (NMU) of prescription GABA analogs (pregabalin and gabapentin) has been reported especially in opiate dependent persons. However, by now the prevalence of NMU of gabapentinoids in the general population has not been sufficiently evaluated. The aim of this research paper is to determine the prevalence of prescription GABA analog NMU and associated demographics in five European countries with special detail of Spain.

Methods: The RADARS Survey of Non-Medical Use of Prescription Drugs Program (NMURx) is a harmonized series of contemporaneous cross-sectional surveys of adults conducted in multiple countries. NMURx collects data from the general population in each participating country about NMU of prescription drugs, illicit drugs, and associated demographics. NMU was defined as "using a medication without a doctor's prescription or for any reason other than what was recommended by their doctor." Responses from Spain (4Q2017, n=10,062) were analyzed in detail. Comparative data were available from France, Germany, Italy, and UK. Responses were collected using non-probability quota sampling and post-stratification population weighting was applied to reflect the national distributions of adults, based on age, gender, and census region. Rates of NMU and associated demographics were reported as rate of past 90-day NMU per 100,000 adult population with 95% confidence intervals.

Results: Germany (1,197 per 100,000 adult population [95% CI: 1,004.3–1,379.1]) and United Kingdom (1,067 per 100,000 adult population [95% CI: 851.3–1,283.2]) presented the highest prevalence of gabapentinoids NMU. In Spain the prevalence

of past 90 days GABA analog NMU was: 344.4, 95% (CI 204.8–484.0), with male predominance. Those who non-medically use GABA analogs had a higher prevalence of lifetime chronic pain, lifetime illicit drug use, and previous substance abuse treatment. In Spain, 20% of respondents who ever have used gabapentinoids, reported a lifetime NMU; the prevalence was higher for pregabalin 624 (6.2%) than for gabapentin 444 (4.4%). The main reasons for use were to self-treat pain and other medical conditions.

Conclusions: The risk of NMU of gabapentinoids should not be neglected. Subjects with a history of chronic pain and lifetime substance use disorders had an increased risk of NMU of gabapentinoids.

Keywords: gabapentin, pregabalin, non-medical use, prescription drugs, misuse

INTRODUCTION

Gabapentinoids, pregabalin and gabapentin, are widely used for the treatment of neuropathic pain and epileptic disorders according to the United States (US) Food and Drug Administration (FDA). Both gabapentin and pregabalin have been approved by the European Medicine Agency (EMA) for neuropathic pain and generalized anxiety disorder, respectively. Additionally, some off-label uses of gabapentinoids include treatment for chronic lower back pain, insomnia, migraine, social phobia, panic disorder, mania, bipolar disorder, and alcohol withdrawal (1, 2).

Gabapentinoids are now among the most commonly prescribed medications in most countries (3). For instance, the overall rate of pregabalin prescriptions use increased from 1.0 per 1,000 individuals in 2013 to 22.0 per 1,000 individuals in 2014 in Ontario, Canada (4). Also, there has been a progressive increase in the reported cases of misuse and dependence to the European Medicines Agency's EudraVigilance database, specifically in subjects with previous history of substance use disorders (3).

At the pharmacological level, gabapentinoids selectively bind to the α2δ-subunit of voltage-gated calcium channels in central nervous system neuronal tissues. This in turn increases the GABA levels and decreases other excitatory neurotransmitters (5). This mechanism is associated with their antinociceptive, anticonvulsant, anxiolytic, and sleep-modulating effects (6). Gabapentinoids have significant risks despite their reputation as safe drugs. Sedation, dizziness, gait instability, and feeling of intoxication are quite common side effects; as many as one in three patients taking therapeutic doses experience dizziness or somnolence (7). Although, both substances share some mechanisms of action, they also have some pharmacokinetic differences that could explain differences in their abuse potential; for instance, pregabalin is absorbed more rapidly by oral route, with maximum plasma concentrations attained within 1 h, whereas, maximum plasma concentrations of gabapentin are detected 3–4 h after oral administration. Pregabalin absorption is linear, and gabapentin absorption is saturable (non-linear –zero-order- process) with less predictable pharmacokinetics. Bioavailability is also different; pregabalin has a 90% bioavailability independently from the dosage, but gabapentin bioavailability changes with dosage, from 60% at 900 mg/day to 33% at 3,600 mg/day. On the other hand, similarities in pharmacokinetics are: both can be given without regard of meals, they do not bind to plasma proteins and both are excreted renally with an elimination half-live of 6 h (7). The linear pharmacokinetics of pregabalin and its greater potency explains its steep dose-response relationship and differences in abuse potential and severe adverse events as respiratory depression.

Evidence regarding misuse and diversion of gabapentinoids has grown in recent years (8–10). The first description of their misuse and abuse were published in 2010 (11). Prevalence of misuse and abuse in the general population is an estimated 2.5% (12) but, the rates in people suffering a substance use disorder (SUD) is higher (pregabalin: 3–68%; gabapentin: 15–22%) (1). In a systematic review aimed to evaluate the abuse liability of gabapentin and pregabalin, the authors found that pregabalin had a greater potential for addiction than gabapentin based on the magnitude of behavioral dependence symptoms, transitions from prescription to self-administration, and the durability of the self-administrations (8).

Current research suggests that the addictive potential of gabapentinoids is primarily a concern among patients with other substance use disorders, especially opioid use disorder (8). The reasons that motivate gabapentinoid misuse and abuse are not clearly described. Also, the subjective effects described by people who report non-medical use are multiple: self-treatment of pain and other medical conditions, pursuit of changes in states of consciousness, and "to get high" (1, 13). According to a recent systematic review (13), one of the most predictive factors associated with gabapentinoid use was the concomitant use of opioids.

The neurobiological mechanism involved in the abuse liability of gabapentinoids has not been yet clearly investigated. The usual increase in the dopamine levels at the mesolimbic brain circuits has not been proved in preclinical studies (14, 15). Gabapentinoids have been reported to produce alcohol/gamma hydroxybutyrate (GHB)/benzodiazepine-type effects mixed with euphoria. Rates of euphoria have been reported at between 1 and 12% but this has been for therapeutic doses. Other reported effects include dissociative feeling, improved sociability, relaxation and sense of calm, and psychedelic effects (10, 16).

On the other hand, however, there are studies indicating that gabapentin could be an useful treatment for alcohol use disorder. For instance, a recent randomized controlled trial showed efficacy of gabapentin in the treatment of alcohol use disorder, improving the alcohol withdrawal syndrome, reducing the heavy drinking days and more total abstinence in the group treated with 1,200 mg of gabapentin (17). Also, in a meta-analysis of seven studies, gabapentin showed efficacy in the treatment of alcohol use disorder, reducing the number of heavy drinking days (18).

In countries as United Kingdom gabapentinoids have been reclassified as Class C controlled drugs under the Misuse of Drugs Act, from 1 April 2019 (19). That means that it is illegal to dispense them without a signed prescription, but that they do not require safe custody in controlled drug cabinets. In Spain, Italy, Germany, and France, gabapentin and pregabalin are available both only under a medical prescription. Alternatively, in the USA, the Drug Enforcement Administration (DEA) classifies pregabalin as a Schedule V controlled substance, or the lowest abuse potential among controlled substances, and gabapentin as a non-controlled substance (20).

The aim of this study is to determine the prevalence of prescription gabapentinoids non-medical use and associated demographics in five European countries (France, Germany, Italy, Spain, and the United Kingdom) and to evaluate the main factors related with its misuse in Spain.

MATERIALS AND METHODS

Design and Participants

The data were obtained from the Researched, Abuse, Diversion and Addiction Related Surveillance (RADARS®) System Survey of Non-Medical Use of Prescription Drugs (NMURx) Program that collects data on respondent demographics and the prevalence, reasons of use, routes of administration, and method of drug acquisition for NMU of prescription drugs across multiple countries. The methodology and the validity of this program is explained in its validation study (21, 22).

The whole program collects information from France, Germany, Italy, Spain, and the United Kingdom. Recruitment and data collection are delivered to country-based members through a global survey panel company, in the native language of the country where the survey is undertaken and in English. Each launch has a "soft launch" of around 500 participants to ensure proper data collection. The surveys were available during the following timeframes: In France: from 2017 December 13 to 2018, January, 7: in Germany: from 2017 December 12 to 2018, January, 16; in Italy: 2017, from December 14 to December 26; in Spain: From 2017 December 12 to 2018, January, 4; and in UK: 2017, from September 28 to December 1.

The inclusion criteria were: agree to be included and give informed consent at the beginning of the survey; adult age that was defined as ages 15–110 years in Spain, 16–110 years in the United Kingdom, and 18–110 in France, Germany, and Italy; in order to reflect the geographical and gender distribution of the country, surveys from different countries and regions have been included if region/sex sampling strata that has not yet met its sampling quota; and have completed the survey in its entirety. Respondents and/or surveys were excluded from the analysis if the respondent met criteria for careless response as defined by the validation study (21).

Calibration weights were applied to the survey population to be representative of the distribution of the adult population of each of the countries included in the study based on geographic region, age, sex, limitations in daily activities, and smoking status (21). National data utilized for this weighting scheme was calculated from estimates from Eurostat and the European Social Survey; NMURx was approved by the Colorado Multiple Institutional Review Board (Protocol Number: 13-2394) and locally by the Parc de Salut Mar Ethics Committee (Protocol Number: 2017/7331/I). Data used in this analysis is from the surveys launched in the second half of 2017 (17Q4).

Measures

Respondents were asked if they had ever used prescription gabapentin or pregabalin for any reason in their lifetime; a "yes" response classified lifetime use. If respondents reported lifetime use, they were asked about last 12- month use and last 12-month NMU, where NMU was defined as "in a way not directed by your healthcare provider."

Basic demographics (age and gender) were collated together with data on prevalence of last 12-month gabapentin/pregabalin use and NMU.

Analyses

The weighted proportion and 95% confidence intervals (CIs) of select demographic and respondent characteristics were calculated to describe the population. Weighted prevalence estimates and 95% CIs were calculated for last 12-month use and NMU of prescription gabapentin only, pregabalin only, and pregabalin and gabapentin. The prevalence of prescription or NMU in the last 12 months was estimated by gender and age. Differences in prevalence of prescription and were compared by gender and age range (18–24, 25–34, 35–44, 45–54, 55–64, 65+ years). Analyses were conducted in SPSS Version 25.0 (Armonk, NY).

RESULTS

Survey Termination and Completion for the Five Countries

In the last quarter of 2017, approximately 63,450 French panelists were invited to participate in the survey. Of the 16,903 who initiated the survey, the inclusion and exclusion criteria below were applied and a total of 10,072 respondents were included in the analysis (5,058 (50.2%) females, 46.8±15.17 years).

In Germany, ∼64,982 German panelists were invited to participate in the survey. Of the 21,977 who initiated the survey, 15,051 completed it and fulfilled the inclusion criteria (7,531 (50.0%) female, mean age 46.8 ± 14.24 years).

In Italy, 41,167 Italian panelists were invited to participate in the survey. Of the 12,766 who initiated the survey, the inclusion and exclusion criteria below were applied and 10,019 surveys were included (5,019 females (50.1%), mean age 43.5 ± 13.72 years).

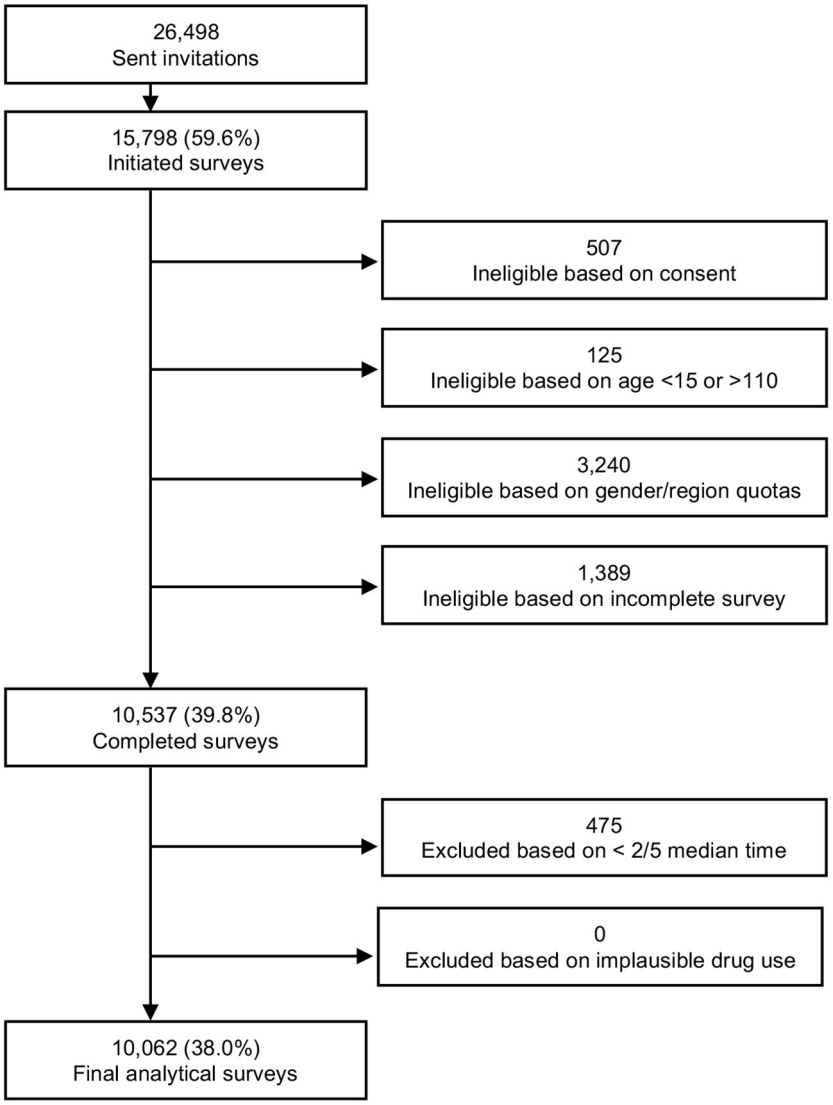

FIGURE 1 | Final analytic sample flowchart.

In Spain, 26,498 panelists were invited to participate in the survey. Of the 15,798 who initiated the survey, the inclusion and exclusion criteria below were applied (**Figure 1**). Finally, 10,062 people completed the survey (5,030 (50.0%) female, mean age: 41.6 ± 12.74 years).

In the United Kingdom, there were 108,633 panelists invited to participate in the survey, of which 13,036 initiated the survey and 10,004 were included in the analysis (5,003 (50.0%) females, mean age 51.6 ± 15.33 years).

Comparison of Five Countries

Prevalence of past 90 day GABA analog NMU was highest in Germany (1,191.7 per 100,000 population, 95% CI 1,004.3–1,379.1) and the UK (1,067.2, 95% CI 851.3–1,283.2), and lowest in Spain (344.4, 95% CI 204.8–484.0) and Italy (366.2, 95% CI 207.7–524.6) (**Table 1**).

NMU was evenly distributed between genders except in Spain which showed a male predominance (**Table 2**). Those who non-medically use GABA analogs were estimated to have higher incidence of lifetime chronic pain, lifetime illicit drug use, and previous substance abuse therapy (**Table 2**).

Spanish Respondents Characteristics

Approximately 26,498 Spanish panelists were invited to participate in the survey. Of the 15,798 who initiated the survey, the inclusion and exclusion criteria below were applied (**Figure 1**). Finally, 10,062 people completed the survey (5,030 (50.0%) female, mean age: 41.6 + 12.74 years). The main characteristics (unweighted and weighted) of the respondents are described in **Table 3**. The responses are weighted to represent the population above 15 years old in Spain by region, gender and age.

A total of 1,003 (10.0%) respondents referred a lifetime use of gabapentinoids; after weighting the responses a 9.9% (95% CI: 9.2–10.6) (**Table 4**).

From the total Spanish sample, 444 (4.4%) respondents have ever used gabapentin and 624 (6.2%) pregabalin. Out of them, 84 (18.9%), and 126 (20.6%) reported non-medical use of gabapentin and pregabalin, respectively (cave: according to **Table 4** the % of respondents with NMU of gabapentinoids should be something higher >>2.9 out of 9.9.% = 29.3%. The others respondents were not sure (40 (9.0%) for gabapentin and 33 (5.3%) for pregabalin) about their NMU (that means, that they were not sure whether they followed the recommendations of the prescriber) or answered that they do not use for NMU (320 (72.1%) for gabapentin and 465 (74.5%) for pregabalin).

Characteristics of Non-medical Use in Spain

The main reasons for non-medical use were to self-treat pain and other medical condition different from pain (**Table 5**).

Respondents who declare NMU of gabapentinoids, usually used the oral route of administration (either swallowed or chewed and then swallowed). Those of them who used to get high, reported to inject gabapentin (41%) and pregabalin (14.3%) (**Table 6**).

TABLE 1 | Last 90 day non-medical use of GABA analogs by country.

	France	Germany	Italy	Spain	UK
Rate (95% CI) per 100,000 Adult Population[a]	574.2 (424.4, 724.0)	1191.7 (1004.3, 1379.1)	366.2 (207.7, 524.6)	344.4 (204.8, 484.0)	1067.2 (851.3, 1283.2)
Rate (95% CI) per 100,000 Standard Units[b]	216.8 (160.2, 273.4)	470.4 (396.5, 544.4)	242.6 (137.6, 347.6)	105.9 (63.0, 148.9)	174.0 (138.8, 209.2)

[a] *Rates based on the weighted estimated number of adults who reported NMU of each drug class in the last 90 days per 100,000 adult population.*

[b] *Rates are based on the weighted estimated number of adults who reported NMU of each drug class in the last 90 days per 100,000 standard units sold.*

Respondents said that they main method of drug acquisition in Spain was by a prescription of a doctor/dentist (61.3% for gabapentin and 69.8% for pregabalin), however, they used several methods to acquire them including family or friends (either bought or given), taken from family, friends and other people, bought outside the country, by internet or to a dealer (**Table 7**).

Finally, in **Table 8**, is described the last purchase of gabapentin and pregabalin where respondents said that they have obtained the substances from a dealer of bought in internet. The median price paid for both was similar (10 €).

DISCUSSION

The main finding of this study is that it confirms the potential abuse liability and then non-medical use of the gabapentinoids gabapentin and pregabalin. When comparing the five European countries, those who non-medically use gabapentinoids were estimated to have a higher likelihood of chronic pain, use of illicit substances, and history of substance abuse treatment compared to the general population. These results are in concordance with country surveys, reviews and metanalyses published previously (8, 23, 24).

There are differences in the rate per 100,000 people among the five countries, with Germany and UK the countries having a higher rate compared to France, Italy and Spain. Reasons for these differences could be related to the availability of other sedative type substances in those countries. According to the European Drug Report of the same year that the information of this study was recorded (25), the prevalence of cannabis use in France, Italy, and Spain was higher than 15%, whereas, in Germany and United Kingdom the prevalence was lower than 15%. We can hypothesize that some reasons for using cannabis and gabapentinoids could be similar: to treat pain and anxiety symptoms; in countries with higher availability of cannabinoids and opioids, subjects could prefer them to gabapentinoids. Also, in some countries, gabapentinoids might replace partially benzodiazepines; in Spain, a general population survey performed every 2 years, showed data on life-time NMU of benzodiazepines about 3.0% in male and 3.1% in female (26).

TABLE 2 | Demographics of those who have non-medically used GABA Analogs in the last 90 days vs. the general adult population demographics.

	France		Germany		Italy		Spain		UK	
	GABA analog NMU	**General population**	**GABA analog NMU**	**General population**	**GABA analog NMU**	**General population**	**GABA analog NMU**	**General population**	**GABA analog NMU**	**General population**
Male	56.8% (48.19, 65.36)	47.6% (46.59, 48.68)	54.0% (48.13, 59.90)	48.6% (47.79, 49.49)	45.0% (33.54, 56.38)	49.1% (47.89, 50.21)	65.7% (53.60, 77.79)	48.6% (47.47, 49.79)	46.8% (39.82, 53.83)	48.8% (47.61, 49.94)
Chronic pain during lifetime	72.1% (64.39, 79.88)	33.0% (32.03, 34.05)	77.6% (72.26, 82.46)	39.2% (38.41, 40.09)	68.6% (57.86, 79.26)	29.4% (28.29, 30.47)	63.1% (51.92, 74.37)	30.9% (29.82, 32.05)	70.3% (63.79, 76.72)	38.9% (37.84, 40.04)
Lifetime illicit drug use	33.9% (25.71, 42.05)	18.2 (17.39, 18.94)	28.7% (23.42, 34.05)	25.4% (24.70, 26.17)	37.8% (26.47, 49.04)	20.5% (19.64, 21.38)	42.0% (30.86, 53.20)	24.4% (23.45, 25.32)	48.0% (40.95, 54.98)	27.3% (26.22, 28.31)
Previous substance abuse treatment	11.5% (6.04, 16.89)	1.7% (1.46, 1.97)	7.7% (4.56, 10.91)	1.8% (1.59, 2.05)	3.8% (0.00, 8.40)	0.6% (0.47, 0.80)	13.3% (6.45, 20.21)	2.2% (1.92, 2.55%)	19.3% (13.35, 25.21)	1.7% (1.41, 2.02)

TABLE 3 | Spanish survey respondents' demographics ($N = 10,062$).

Variable	Unweighted *N* (%)	Weighted[a] % (95% CI)
Gender		
Male	5,032 (50.0%)	48.8 (47.6, 49.9)
Age (years)		
Mean (STD)	41.6 (12.74)	45.7 (0.2)
Median (IQR)	41.0 (32.0, 50.0)	46.0 (33.6, 56.9)
Range	(15.0, 90.0)	(15.0, 90.0)
Age categories (years)		
15–24	1,008 (10.0%)	0 (0.0, 0.0)
25–34	2,021 (20.1%)	0 (0.0, 0.0)
35–44	2,999 (29.8%)	14.4 (13.8, 15.0)
45–54	2,391 (23.8%)	19.8 (19.0, 20.5)
55+	1,643 (16.3%)	18.2 (17.5, 19.0)
Territory of residence		
Andalucía	1,813 (18.0%)	18.0 (17.1, 18.9)
Aragón	570 (5.7%)	5.7 (5.2, 6.3)
Canarias	467 (4.6%)	4.7 (4.2, 5.1)
Cantabria	51 (0.5%)	0.5 (0.3, 0.7)
Castilla y León	617 (6.1%)	6.1 (5.5, 6.7)
Castilla-La Mancha	424 (4.2%)	4.1 (3.6, 4.6)
Cataluña	1,673 (16.6%)	17.1 (16.3, 18.0)
Ciudad Autónoma de Ceuta	2 (0.0%)	0.0 (0.0, 0.0)
Ciudad Autónoma de Melilla	10 (0.1%)	0.2 (0.1, 0.3)
Comunidad de Madrid	1,380 (13.7%)	13.7 (12.9, 14.5)
Comunidad Foral de Navarra	65 (0.6%)	0.6 (0.5, 0.8)
Comunidad Valenciana	1,105 (11.0%)	10.4 (9.8, 11.1)
Extremadura	188 (1.9%)	1.9 (1.5, 2.2)
Galicia	643 (6.4%)	6.2 (5.6, 6.7)
Illes Balears	131 (1.3%)	1.3 (1.1, 1.6)
La Rioja	39 (0.4%)	0.4 (0.2, 0.5)
País Vasco	290 (2.9%)	2.9 (2.5, 3.3)
Principado de Asturias	283 (2.8%)	3.0 (2.6, 3.5)
Región de Murcia	311 (3.1%)	3.1 (2.7, 3.5)
Region of residence		
Noroeste	977 (9.7%)	9.7 (9.0, 10.5)
Noreste	964 (9.6%)	9.6 (9.0, 10.3)
Comunidad de Madrid	1,380 (13.7%)	13.7 (12.9, 14.5)
Centro	1,229 (12.2%)	12.1 (11.3, 12.9)
Este	2,909 (28.9%)	28.9 (27.9, 29.9)
Sur	2,136 (21.2%)	21.3 (20.3, 22.2)
Canarias	467 (4.6%)	4.7 (4.2, 5.1)
Net monthly household income		
Under €499	404 (4.0%)	4.0 (3.5, 4.4)
Between €500 and €799	430 (4.3%)	4.6 (4.1, 5.1)
Between €800 and €999	588 (5.8%)	5.9 (5.3, 6.4)
Between €1.000 and €1.499	2,145 (21.3%)	20.5 (19.6, 21.4)
Between €1.500 and €1.999	1,723 (17.1%)	16.6 (15.8, 17.5)
Between €2.000 and €2.499	1,472 (14.6%)	14.4 (13.5, 15.2)
Between €2.500 and €2.999	1,105 (11.0%)	11.1 (10.4, 11.9)
Between €3.000 and €4.999	1,116 (11.1%)	11.5 (10.7, 12.2)
Between €5.000 and €6.999	204 (2.0%)	2.1 (1.8, 2.5)
€7.000 or more	92 (0.9%)	0.8 (0.7, 1.0)
Prefer not to say	783 (7.8%)	8.5 (7.8, 9.2)
Marital status		
Single	3,709 (36.9%)	32.3 (31.3, 33.3)
Married	5,463 (54.3%)	55.5 (54.3, 56.6)
Separated/divorced	760 (7.6%)	9.5 (8.7, 10.3)
Widowed	130 (1.3%)	2.7 (2.2, 3.2)
Education achieved		
No studies or incomplete primary studies	25 (0.2%)	0.3 (0.2, 0.5)
Comprehensive primary education	174 (1.7%)	2.3 (1.9, 2.7)
Secondary studies 1st stage	1,481 (14.7%)	15.8 (14.9, 16.7)
Secondary studies 2nd stage	3,544 (35.2%)	35.9 (34.8, 37.0)
Middle University studies	2,274 (22.6%)	22.0 (21.0, 22.9)
Higher University studies	2,564 (25.5%)	23.7 (22.7, 24.6)
Student within the last 3 months		
Yes	1,403 (13.9%)	13.6 (12.8, 14.3)
No	8,659 (86.1%)	86.4 (85.7, 87.2)
A member or former member of the armed forces		
Yes	479 (4.8%)	4.6 (4.2, 5.1)
No	9,583 (95.2%)	95.4 (94.9, 95.8)
Currently a healthcare professional		
Yes	615 (6.1%)	5.6 (5.1, 6.1)
No	9,447 (93.9%)	94.4 (93.9, 94.9)
Pregnancy status[b]		
Yes	250 (5.0%)	3.3 (2.9, 3.8)
No	4,780 (95.0%)	96.7 (96.2, 97.1)
Gestation[c] (months)		
Mean (STD)	4.8 (2.08)	4.8 (0.1)
Median (IQR)	5.0 (3.0,6.0)	4.4 (2.6,5.9)
Range	(1.0, 9.0)	(1.0, 9.0)
Survey language		
English	197 (2.0%)	2.1 (1.8, 2.5)
Spanish	9,865 (98.0%)	97.9 (97.5, 98.2)

CI, Confidence Interval; STD, Standard deviation; IQR, Interquartile range.
[a] Responses are weighted to represent the distribution of adults (ages 15+) in Spain by region, gender, and age.
[b] Among females only ($n = 5,030$).
[c] Among pregnant females only ($n = 250$).

Some studies have tried to analyze the possible usefulness of pregabalin and gabapentin in the treatment of benzodiazepine use disorder, but there are no clear results regarding this (27, 28).

When evaluating the rates by drug, as described before, pregabalin has more endorsements than gabapentin, for example, in a recent paper describing data from addictovigilance monitoring for gabapentinoids (24). Some publications have described a higher abuse liability for pregabalin compared to gabapentin. One of the explanations of this difference could be the higher prevalence of euphoria in pregabalin compared to gabapentin. The studies that have described this effect reported that this is a dose-dependent effect and it is not related to treatment indication, nor previous abuse of substances; its

prevalence varies among different studies from 1 to 40% (10, 29). The theory of people taking pregabalin to experience euphoria and to get high it is not completely explained by our results, as the majority of the respondents used pregabalin as self-treatment. The differences between the two substances could also be explained by the different pharmacokinetic characteristics of both molecules; pregabalin has more rapid absorption than gabapentin; also, the peak plasma concentration is more rapidly achieved with pregabalin (1 h compared to 4–5 h) and has a longer half-life (7).

In the subsample of Spanish population evaluated, about 20% of all persons ever using gabapentinoids report on NMU of these substances. A risk for NMU that should not be neglected. The main reason for non-medical use was in both medications for self-treat any pain, followed to treat other medical conditions; few respondents used them to get high or to come down; also, there were a percentage of people using them to prevent withdrawal symptoms. Another article, based on data of pharmavigilance (24), found that the use of pregabalin was not only related to the objective to get high, but also, to prevent withdrawal symptoms, as a substitute of other substances and to potentiate the effect of other drugs (mainly benzodiazepines and opioids). In our sample, the inhaled and intravenous route were mainly reported for those who use pregabalin and gabapentin to prevent withdrawal syndrome, to come down and to get high. It is important to consider the possibility of using the intravenous route, and asking patients about it to prevent the transmission of blood borne infections (Hepatitis B and C, and HIV).

TABLE 4 | Respondents that reported use of gabapentinoids (from total survey respondents $n = 10{,}062$).

	Unweighted *N* (%)	Weighted[a] % (95% CI)
Lifetime use	1,003 (10.0%)	9.9 (9.2, 10.6)
Lifetime non-medical use	323 (3.2%)	2.9 (2.6, 3.3)
Last 12 month non-medical use	169 (1.7%)	1.5 (1.2, 1.7)
Last 90 day non-medical use	45 (0.4%)	0.4 (0.3, 0.6)
Last 30 day non-medical use	42 (0.4%)	0.4 (0.3, 0.6)
Last 7 day non-medical use	35 (0.3%)	0.4 (0.2, 0.5)

CI, Confidence Interval.
[a]*Responses are weighted to represent the distribution of adults (ages 15+) in Spain by region, gender, and age.*

Another aspect to take into account may be the polymedication risk. Pregabalin and gabapentin are usually prescribed with other pain medications, mainly with opioids; among 50–70% were reported in a recent paper (23). This combination could increase the risk for overdose death (30). Otherwise, the usefulness of the combination of pregabalin and opioids for the treatment of some kind of pain is not clear, as some researchers have described that pregabalin plus opioids was associated with more pain severity and higher oral doses of opioids; furthermore, pregabalin use was not associated with improvements on mental health symptoms (31).

When prescribing these medications it is important to be aware and monitor for signs of misuse and overdosification, mainly in patients with risk factors for NMU (previous history of substance use disorder and chronic pain). It is important to remark that, although NMU of gabapentinoids is more frequent in patients with previous substance use disorder, there are described cases of a primary abuse in people without any of the known risk factors (24), for this reason, it is important to monitor for signs of NMU in all patients in treatment with gabapentinoids. The detection of NMU could be complicated as these medications are not detected in routine toxicology urine controls. Furthermore, prescribers should be aware of the risk of NMU, when patients request for specific drugs of higher doses, when they obtain medications from different sources (doctor shopping), when the medications are lost or stolen frequently or they ask for new prescriptions too early (1).

The NMURx survey methodology is useful to identify under-documented use and misuse of medication and can detect changes in trends of substance use and misuse; also, it permits to make comparisons among different countries. The large sample size and post-stratification weighting applied creates estimates that are representative of general populations. However, there are some limitations related to online surveys, in first place the reliance of participants to provide honest responses; also, another limitation of the study is that respondents who have acquired a gabapentinoid product from a family member, friend, or dealer may not be aware whether it was initially obtained with a prescription or from another source. However, these limitations will apply to all surveys so still allow for comparison across countries.

In conclusion, in spite of the risk of NMU, gabapentinoids are useful medications in the treatment of neuropathic pain, generalized anxiety disorder, and some forms of epilepsy.

TABLE 5 | Reasons for non-medical use in the Spanish sample.

	N[a]	To self-treat my pain *N* (%)	To treat a medical condition, other than pain *N* (%)	For enjoyment to get high *N* (%)	To come down *N* (%)	To prevent or treat withdrawal symptoms *N* (%)	Other reason *N* (%)
Gabapentin	124	65 (52.4%)	40 (32.3%)	12 (9.7%)	10 (8.1%)	13 (10.5%)	20 (16.1%)
Pregabalin	159	76 (47.8%)	45 (28.3%)	14 (8.8%)	9 (5.7%)	9 (5.7%)	28 (17.6%)

[a]*Includes all survey respondents who report non-medical use of the product.*
Respondents may check multiple options, percentages may not sum to 100.

TABLE 6 | Route of administration by reason for non-medical use in Spain.

Reason for NMU	*N*[a]	Swallowed *N* (%)	Chewed and then swallowed *N* (%)	Dissolved in mouth (e.g., between cheek and gum, under tongue) *N* (%)	Inhaled (snorted or smoked) *N* (%)	Injected (shot it up) *N* (%)	Other route *N* (%)
Gabapentin (e.g., Gabatur, Neurontin®, or generic), tablets/capsules							
To self-treat my pain	65	47 (72.3%)	24 (36.9%)	19 (29.2%)	13 (20.0%)	12 (18.5%)	10 (15.4%)
To treat a medical condition, other than pain	40	27 (67.5%)	13 (32.5%)	14 (35.0%)	7 (17.5%)	9 (22.5%)	3 (7.5%)
For enjoyment/to get high	12	4 (33.3%)	5 (41.7%)	3 (25.0%)	1 (8.3%)	5 (41.7%)	2 (16.7%)
To come down	10	3 (30.0%)	5 (50.0%)	6 (60.0%)	1 (10.0%)	3 (30.0%)	0 (0.0%)
To prevent or treat withdrawal symptoms	13	5 (38.5%)	6 (46.2%)	7 (53.8%)	6 (46.2%)	4 (30.8%)	4 (30.8%)
Other reason	20	10 (50.0%)	6 (30.0%)	5 (25.0%)	6 (30.0%)	3 (15.0%)	5 (25.0%)
Pregabalin (e.g., Lyrica® or generic), tablets/capsules							
To self-treat my pain	76	53 (69.7%)	19 (25.0%)	13 (17.1%)	12 (15.8%)	8 (10.5%)	5 (6.6%)
To treat a medical condition, other than pain	45	30 (66.7%)	21 (46.7%)	8 (17.8%)	4 (8.9%)	5 (11.1%)	1 (2.2%)
For enjoyment/to get high	14	2 (14.3%)	6 (42.9%)	8 (57.1%)	4 (28.6%)	2 (14.3%)	1 (7.1%)
To come down	9	1 (11.1%)	7 (77.8%)	3 (33.3%)	3 (33.3%)	2 (22.2%)	1 (11.1%)
To prevent or treat withdrawal symptoms	9	5 (55.6%)	6 (66.7%)	4 (44.4%)	4 (44.4%)	3 (33.3%)	1 (11.1%)
Other reason	28	17 (60.7%)	9 (32.1%)	7 (25.0%)	5 (17.9%)	4 (14.3%)	10 (35.7%)

[a]*Includes all survey respondents who report each reason for non-medical use of the product.*
Respondents may check multiple options, percentages may not sum to 100.

TABLE 7 | Reported method of drug acquisition in Spain.

	N[a]	Was prescribed it by a doctor or dentist *N* (%)	Bought it or was given it by friends or family members *N* (%)	Took it from friends or family members without their knowledge *N* (%)	Took it from someone other than friends/ family without their knowledge *N* (%)	Bought it abroad (outside Spain) without a Rx *N* (%)	Bought it on the internet without a Rx *N* (%)	Bought it from a dealer *N* (%)
Gabapentin	124	76 (61.3%)	35 (28.2%)	30 (24.2%)	39 (31.5%)	33 (26.6%)	32 (25.8%)	38 (30.6%)
Pregabalin	159	111 (69.8%)	51 (32.1%)	40 (25.2%)	33 (20.8%)	41 (25.8%)	39 (24.5%)	46 (28.9%)

[a]*Includes all survey respondents who report non-medical use of the product.*
Respondents may check multiple options, percentages may not sum to 100.

TABLE 8 | Last purchase characteristics in Spain.

	N[a]	Number/volume purchased	Strength[b]	Total price paid (€)
Gabapentin	45	N: 45 Mean (STD): 5.8 (8.53) Median (IQR): 2.0 (1.0, 6.0) Range: (0.0, 33.0)	N: 12 Mean (STD): 38.9 (49.44) Median (IQR): 8.0 (2.0, 100.0) Range: (1.0, 120.0)	N: 45 Mean (STD): 14.4 (15.42) Median (IQR): 10.0 (2.0, 20.0) Range: (0.0, 55.0)
Pregabalin	52	N: 52 Mean (STD): 5.4 (7.65) Median (IQR): 2.0 (1.0, 6.0) Range: (0.0, 35.0)	N: 16 Mean (STD): 26.3 (61.40) Median (IQR): 3.5 (2.0, 27.0) Range: (1.0, 250.0)	N: 52 Mean (STD): 185,204.8 (1,302,466.10) Median (IQR): 10.0 (2.0, 32.0) Range: (0.0, 9,393,939.0)

STD, Standard deviation; IQR, Interquartile Range.
[a]*Includes all survey respondents who report non-medical use of the product and "Bought it from a dealer" or "Bought it on the internet".*
[b]*Strength: MG per tablet/capsule, MCG/h per patch, MG per oral film, MG/ML per liquid, MCG per lollipop, MCG per lozenge, MG per suppository; All non-numeric entries were excluded.*
Respondents have option to check 'I'm not sure' under strength.

Professionals prescribing these medications should be aware and actively search for signs of misuse and diversion.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Colorado Multiple Review Board (Protocol Number: 13-2394) and locally by the Parc de Salut Mar Ethics Committee (Protocol Number: 2017/7331/I). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FF, PD, DW, NS, MG, IM, MA, and RD were responsible to prepare and adapt the country protocols. MG and RD were

responsible for the project concept and study design. FF, WL, EP, and MF contributed to drafting the manuscript. MF, NS, and MT were responsible for the final revision. All authors have read and approved the final submitted manuscript.

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SYSTEMATIC REVIEW
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Focus on Over-the-Counter Drugs' Misuse: A Systematic Review on Antihistamines, Cough Medicines, and Decongestants

Fabrizio Schifano[1], *Stefania Chiappini*[1,2]*, *Andrea Miuli*[2], *Alessio Mosca*[2], *Maria Chiara Santovito*[2], *John M. Corkery*[1], *Amira Guirguis*[3], *Mauro Pettorruso*[2], *Massimo Di Giannantonio*[2] *and Giovanni Martinotti*[2]

[1] Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom, [2] Department of Neuroscience, Imaging and Clinical Sciences, "G. D'Annunzio" University, Chieti, Italy, [3] Swansea University Medical School, Institute of Life Sciences 2, Swansea University, Swansea, United Kingdom

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Institut National de la Santé et de la Recherche Médicale (INSERM), France

***Correspondence:**
Stefania Chiappini
stefaniachiappini9@gmail.com

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Background: Over the past 20 years or so, the drug misuse scenario has seen the emergence of both prescription-only and over-the-counter (OTC) medications being reported as ingested for recreational purposes. OTC drugs such as antihistamines, cough/cold medications, and decongestants are reportedly the most popular in being diverted and misused.

Objective: While the current related knowledge is limited, the aim here was to examine the published clinical data on OTC misuse, focusing on antihistamines (e.g., diphenhydramine, promethazine, chlorpheniramine, and dimenhydrinate), dextromethorphan (DXM)- and codeine-based cough medicines, and the nasal decongestant pseudoephedrine.

Methods: A systematic literature review was carried out with the help of Scopus, Web of Science databases, and the related gray literature. For data gathering purposes, both the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and PROSPERO guidelines were followed (PROSPERO identification code CRD42020209261).

Results: After completion of the selection, eligibility, and screening phases, some 92 articles were here taken into consideration; case reports, surveys, and retrospective case series analyses were included. Findings were organized according to the specific OTC recorded. Most articles focused here on DXM ($n = 54$) and diphenhydramine ($n = 12$). When specified, dosages, route(s) of administration, toxicity symptoms (including both physical and psychiatric ones), and outcomes were here reported.

Conclusion: Results from the systematic review showed that the OTC misusing issues are both widespread worldwide and popular; vulnerable categories include adolescents

and young adults, although real prevalence figures remain unknown, due to a lack of appropriate monitoring systems. Considering the potential, and at times serious, adverse effects associated with OTC misusing issues, healthcare professionals should be vigilant, and *ad hoc* preventative actions should be designed and implemented.

Keywords: drug abuse, drug misuse, prescription drug misuse, pharming, drug diversion, over the counter drug misuse, addiction, OTC

INTRODUCTION

Since generally being considered safe, over-the-counter (OTC) medicines are available without a prescription and can be purchased directly from related pharmacies/stores (1, 2). OTC medicines are meant to treat a variety of illnesses and symptoms, including pain, coughs and colds, diarrhea, nausea, etc. OTC availability, while encouraging self-care, has contributed to a public perception of safety and a lack of awareness relating to their potential for misuse, dependence, and harm (3–6). Indeed, some OTC medicines have active ingredients possessing a misusing potential at higher-than-recommended dosages (7) and are becoming increasingly popular for the possibility of their diversion in order to reach central psychoactive effects (8–11). Currently, there is minimal information about the prevalence of OTC misuse, abuse, and dependence (8–10, 12). Indeed, current lack of knowledge may partly be due to poor sales' monitoring because of OTCs' favorable legal status. However, the so-called "pharming" phenomenon (13–15) has been requiring attention at different levels because of increased treatment admissions, dangerous behavior, more emergency room visits, drug-related deaths, and overdoses (11, 16, 17). Most implicated drugs include certain cough suppressants, sleep aids, and antihistamines, which can at times be ingested in combination with remaining recreational psychotropics and/or prescription drugs and/or alcohol (17, 18). Overall, the misuse of OTC drugs is considered as more socially acceptable, less stigmatizing, and safer than the intake of illicit substances, also due to their likely lack of detection in standard drug screens (16). OTC drugs' intake may involve snorting or injecting the crushed tablets' powder to amplify the effects of a drug or ingesting these molecules for a purpose different from the therapeutic one. This may be the case for dextromethorphan (DXM) and codeine-based cough mixtures, being possibly misused at high dosages for recreational or euphoric effects; conversely, loperamide is at times being ingested for self-medicating withdrawal symptoms (7, 16, 18–20). OTC misuse has also been associated with notable drug interactions, physical and mental health effects, individual variation in responses, and significant socioeconomic impact for the users, their family, and the wider community (13–15). Currently, most OTC misusing data are obtained through clinical records (e.g., case reports and case series) and surveys.

Aims of the Study

Thus, the current review aimed at (i) examining the current literature on the misuse of OTC drugs, focusing on the following OTCs: among antihistamines, diphenhydramine (DPH), promethazine, chlorpheniramine, and dimenhydrinate (DH); DXM- and codeine-based cough medicines; and the nasal decongestant pseudoephedrine; (ii) illustrating patterns of OTCs' misuse, psychopathological effects, and harms associated; and (iii) better understanding the psychotropic molecular mechanisms underlying their recreational use.

METHODS

Systematic Review Procedures

A systematic electronic search was conducted from October 2020 to December 2020 and was set without a timeframe on the following scientific search engines: PubMed, Scopus, and Web of Science (WoS). The gray literature was also checked for relevant information. The following search strategies were used, respectively, in PubMed: ("diphenhydramine" OR "promethazine" OR "chlorpheniramine" OR "dimenhydrinate" OR "dextromethorphan" OR "pseudoephedrine" OR codeine-based cough medicines) AND ("abuse" OR "misuse" OR "craving" OR "addiction") NOT review NOT (animal OR rat OR mouse) NOT "*in vitro*;" in Scopus: [TITLE-ABS-KEY ("Diphenhydramine") OR TITLE-ABS-KEY ("Promethazine") OR TITLE-ABS-KEY ("Chlorpheniramine") OR TITLE-ABS-KEY ("Dimenhydrinate") OR TITLE-ABS-KEY ("Dextromethorphan") OR TITLE-ABS-KEY ("Pseudoephedrine") OR TITLE-ABS-KEY (codeine-based cough medicines) AND TITLE-ABS-KEY ("Abuse") OR TITLE-ABS-KEY ("Misuse") OR TITLE-ABS-KEY ("Craving") OR TITLE-ABS-KEY ("Addiction") AND NOT TITLE-ABS-KEY (Review) AND NOT TITLE-ABS-KEY (animal) OR TITLE-ABS-KEY (rat) OR TITLE-ABS-KEY (mouse) AND NOT TITLE-ABS-KEY ("*in vitro*")]; and WoS: ("diphenhydramine" OR "promethazine" OR "chlorpheniramine" OR "dimenhydrinate" OR "dextromethorphan" OR "pseudoephedrine" OR codeine-based cough medicines) AND ("abuse" OR "misuse" OR "craving" OR "addiction") NOT Review NOT (animal OR rat OR mouse) NOT "*in vitro*." The systematic review was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (21) and PROSPERO guidelines (22). All data collected were tabulated on an Excel sheet to enable easy comparison and analysis.

Data Synthesis Strategy

The selection and eligibility phase of the articles was carried out by three independent reviewers (AM, AMo, and MCS), who screened articles based on title and abstract; the first screening was followed by full text reviews, using predetermined criteria for inclusion and exclusion. Eligible articles were

considered if the published studies met all the following criteria: (i) original articles (open-label or double-blind trials, prospective or retrospective observational studies, case series and case reports); (ii) studies involving all age individuals misusing the OTC drugs selected. There were no other restrictions on the type of study population or publication time period. Exclusion criteria were as follows: (i) nonoriginal research articles (e.g., review, letter, commentary, editorial, book chapter, professional or clients' opinions); (ii) non full-text articles (e.g., meeting/conference abstracts); (iii) languages other than English; (iv) animal/*in vitro* studies; (v) articles mentioning OTC drugs only as an example in the context of OTC drugs misuse; and (vi) articles not dealing with the misuse of the OTC drugs selected (e.g., DPH, promethazine, chlorpheniramine, and DH; DXM- and codeine-based cough medicines; and pseudoephedrine). Individual studies were also manually searched to identify additional citations. A final, between reviewers, cross-check was carried out, supervised by SC and MP, with both doubtful cases and possible inclusion/exclusion disagreements resolved through discussion with GM, MDG, and FS.

Protocol and Registration

Current research methods were approved by PROSPERO (identification code CRD42020209261).

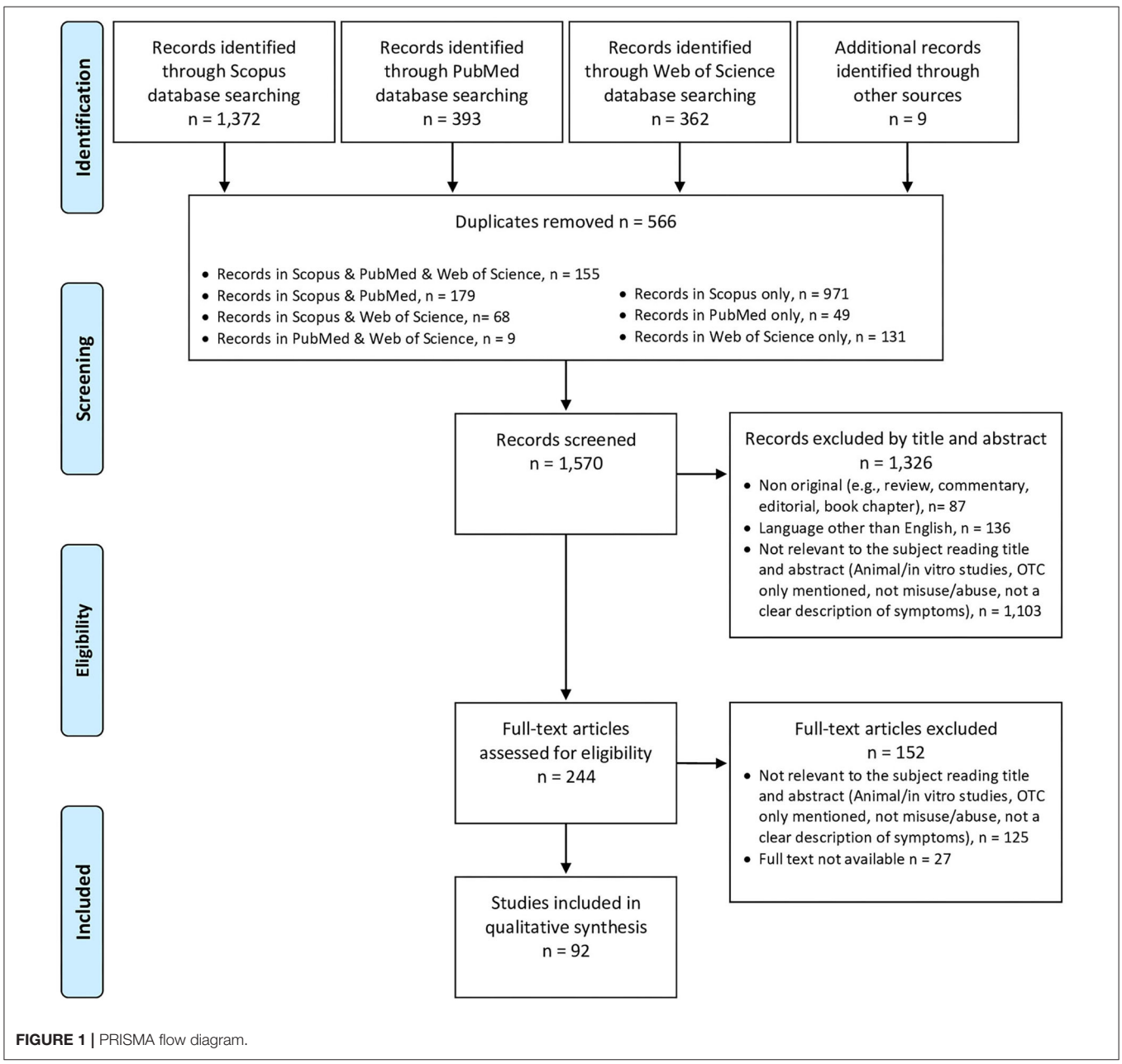

FIGURE 1 | PRISMA flow diagram.

Risk of Bias

The assessment of risk of bias was made in accordance with the Cochrane risk of bias 2 (RoB 2) tool (23).

RESULTS

In removing duplicate articles ($n = 566$) from a total of 2,136 papers (PubMed = 393; Scopus = 1,372; WoS = 362; additional sources = 9), some 15,70 records resulted to be relevant for screening. Those considered not relevant to the subject while considering both the title and the abstract ($n = 1{,}103$; e.g., animal/*in vitro* studies; articles only mentioning OTC drugs, or not regarding OTC misuse/abuse, or not giving a clear description of related symptoms), those not written in English ($n = 136$), and those that were non-original articles ($n = 87$) were eliminated. Out of the 244 remaining full-text articles assessed for eligibility, some 125 papers did not match the inclusion criteria and 27 were not available. Hence, 92 articles were taken into consideration and properly analyzed (**Figure 1**). Findings were organized according to the specific OTC recorded, reported in alphabetical order in **Supplementary Table 1**; conversely, the most relevant characteristics of the misusing potential of the range of OTC drugs commented are summarized in **Table 1**.

Dextrometorphan

DXM resulted to be the most reported misused drug, with $n = 54$ related papers having been here identified (**Supplementary Table 1**). Indeed, it was recorded in two retrospective studies (24, 25), in 10 case series (26–35), and in several case reports (24, 25, 36–77). Most represented users were male adolescent and young adults; DXM was mostly used alone (28, 36, 37, 40, 44, 45, 54, 57, 66) or in DXM-containing cough mixtures (26, 29, 30, 39, 41, 42, 47, 50, 52, 53, 62, 64, 68, 71, 72, 74, 76). Concomitant drugs included both licit and illicit substances, such as alcohol (25, 30, 31, 35, 52, 53, 55, 60, 71, 76); cannabis (25, 31, 35, 48, 60); sedatives drugs, e.g., benzodiazepines (35); diethylamide lysergic acid (LSD) (35); opioids, e.g., morphine, heroin (25, 35, 54); ecstasy (35); cocaine (35); and phencyclidine/ketamine (34, 35). Dosages varied among cases, up to super-high dosages (up to 4,920 mg) (31, 35, 36, 61). The only route of administration (ROA) here recorded was the oral one. Autonomic (e.g., mydriasis, tachycardia, palpitations) (30, 33, 35, 42, 44, 46, 47, 51, 67, 70, 71), gastrointestinal (32, 35, 42, 47), neurological [e.g., amnesia, nystagmus, ataxia, seizures, and dystonia; (24, 26, 29, 30, 32, 34, 35, 39, 43–46, 49, 51–53, 56, 59, 67)], and psychiatric symptoms, such as euphoria, agitation/irritability, confusion, hallucinations, and delusions, have been recorded (24, 25, 27–31, 33–38, 40–50, 52–54, 56, 58, 60, 61, 63, 66, 67, 70–74, 76). DXM misusers' psychiatric history frequently included alcohol and substance use disorders (SUD) (25–27, 29, 31, 32, 34–37, 40, 43, 45–48, 50, 53, 55–62, 64–67, 69, 76), mood disorders (29, 31, 32, 35, 37, 38, 41, 46, 56–65, 67, 68, 71), and schizophrenia (37, 53, 69). Regarding the outcome, most cases required hospitalization with supportive treatments and antipsychotics [e.g., haloperidol (43, 47, 71, 73, 75)], risperidone (74), and olanzapine (54, 61) administration. A DXM-related suicide has been recorded (31).

Chlorpheniramine and Codeine

Chlorpheniramine and codeine were recorded as having been misused in two papers (respectively, 68 and 69), as constituents of BRON, a Japanese codeine-based cough suppressant, together with methyl-ephedrine and caffeine (78, 79). BRON abuse has been associated with both psychotic/affective symptoms and dependence/withdrawal issues (78). Moreover, a case of severe intoxication of a codeine-based cough mixture determining a respiratory acidosis and requiring hospitalization was recorded (80) (**Supplementary Table 1**).

Dimenhydrinate

DH misuse was described in eight articles (**Supplementary Table 1**), including five case reports (81–85) and three case series (86–88), mostly involving adults or adolescents (88). Most important psychiatric comorbidities described were represented by mood disorders (82, 84), SUD (83–87), and schizophrenia (85, 87). Massive dosages, up to 5,000 mg, of DH have been recorded in a few cases (84, 85, 87). DH administration was always oral, except for one case where the molecule was administered intramuscularly in association with opiates and benzodiazepines (83). The symptoms recorded ranged from recreational stimulating effects (87) to emotional lability, agitation, anxiety, and drug-induced delirium with paranoia, thought incoherence, and visual/auditory hallucinations (81, 86). The physical effects reported were mild and included mydriasis, tachycardia, hypertension, flushing, restlessness, dystonic reactions, and ataxia (81, 82, 84–86, 88), while one case reported generalized seizures (87). Withdrawal symptoms have been recorded after the abrupt interruption of chronic use and included irritability, anxiety, and craving (82, 84, 87). When reported, treatment was almost supportive (81–83, 85, 88); in two cases, benztropine was required to treat dyskinesia and related movement, muscle control, and balance symptoms (81, 84).

Diphenhydramine

DPH misuse was reported in 12 articles, including 10 case reports (17, 89–97); the remaining two included, respectively, a case series (98) and a retrospective review study (99) (**Supplementary Table 1**). Apart from the retrospective review study focusing on all Mandrax® (DPH + Methaqualone) abuse cases ($n = 67$, male) retrieved from the United States (US) Army during January–June 1972, users were here mostly represented by female (F/M, 9/6). A high number of users were adolescents, aged between 13 and 18 years (17, 94, 96–98). Reported psychiatric comorbidities mostly included SUD (17, 89–92, 95), schizophrenia/psychotic symptoms (89, 91, 92), and mood disorders (17, 90, 91). DPH was taken in most cases orally, but both intramuscular (IM) (90) and intravenous (IV) (96–98) administrations were reported as well. Super-high dosages were recorded, up to 2,000 mg daily (91–93, 98). In a few cases, DPH was misused together with alcohol (91, 99), lorazepam (98), and cannabis (99).

TABLE 1 | 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, and sometimes bradycardia and hypotension. The triad of coma, pinpoint pupils, and respiratory depression is strongly suggestive of opiate poisoning. In severe overdosage, death may occur • CHRONIC EFFECTS: dependence	• 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
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 min of ingestion and persist for approximately 6 h • They are dose-related, starting from a mild to moderate stimulation with restlessness and euphoria (100–200 mg), to a state characterized by hallucinations, paranoia, perceptual distortions, delusional beliefs, ataxia, and out-of-body experiences (>1,000 mg) • ACUTE EFFECTS: (i) *psychiatric effects*: euphoria, altered mental status, mania, mood lability, 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 chronic abusers of DXM (neurotoxic effects, resulting in somnolence, psychosis, seizures, and delirium	• Although DXM is not thought to have addictive properties, its chronic use might determine addiction due to GABAergic/antiglutamatergic mechanisms, including substance-taking compulsive behaviors, 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®

(Continued)

TABLE 1 | Continued

Drug/drug classification	Administration path	Mechanism of action	Effects	Does it cause dependence?	Street names and brand names
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 diarrhea. 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 beta2-adrenergic receptors	• ACUTE EFFECTS: stimulant effects, e.g., euphoria, insomnia, diminished sense of fatigue, anorexia, and accelerated thinking; psychotic symptoms with auditory and visual hallucinations, persecutory delusions, fear, disorganized behavior might develop after high-dose consumption • CHRONIC EFFECTS: dependence	• Dependence might be developed after long-term use • Withdrawal symptoms include: dysphoria, restlessness, abnormal perceptions • 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	"Chalk," "Crank," "Meth," "Speed"; 'Russian Cocktail' includes pseudoephedrine consumed together with 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.

A polydrug overdose (e.g., DH together with bupropion, citalopram, acetaminophen, omeprazole, and naproxen) was recorded (94). DPH recreational use was associated with relaxation, calmness, and sleep improvement (90, 92, 96, 98, 99). Acute intoxication was associated with psychotic symptoms, psychomotor agitation, restlessness, and disorientation (89, 92–96, 98, 99). Withdrawal, consisting in both physical (e.g., bowel and bladder incontinence, hypertension, hypertonia, and extrapyramidal symptoms) and psychological (e.g., anxiety, irritability, rebound insomnia, and craving) symptoms have been recorded (17, 89, 90, 92, 95, 98, 99). DPH-induced intoxication was associated with signs and symptoms of anticholinergic toxicity, such as fever, mydriasis, flushed skin, dry mouth, dry eyes, decreased sweating, urinary retention, and dyskinesia (92–94, 98). A severe toxicity case was associated with cardiac conduction abnormalities and increased QT interval (90). On-drug cases of violent behavior, including suicide, have been reported (97, 99). Treatment required hospitalization and supportive care; drugs used were antipsychotics, such as fluphenazine and quetiapine, benzodiazepines, and benztropine (89, 90, 92, 93).

Promethazine

A few papers recorded here the misuse of promethazine; a retrospective analysis of data from the American Association of Poison Control Centres (AAPCC) National Poison Data System (NPDS) from January 2002 to December 2012 reported 354 promethazine intentional misuse/abuse cases (100) (**Supplementary Table 1**). All cases involved adolescents and young adults who misused promethazine orally. In most cases ($n = 259$) promethazine abuse was associated with other substances, such as DXM, codeine, phenylephrine, pseudoephedrine, caffeine, etc. Intoxication symptoms ranged from mild to severe effects, up to seizures and coma, but no fatalities have been reported. Agitation, confusion, slurred speech, and hallucinations were described as well. Promethazine-alone abuse cases were mostly managed in healthcare facilities, while promethazine in coformulation mostly required emergency department (ED) care management (100). Moreover, further cases of nonmedical use of promethazine were here identified from (i) the Danish Poison and Information Centre (DPIC) and related registers used within the State Serum Institute of Denmark (SSI) (101); (ii) a prospective database of poisoning admissions (January 1987-May 2007) to a UK regional toxicology service (102); and (iii) a prospective study regarding patterns of misuse of heroin injectors (103). Drug-induced delirium was the most represented psychiatric effects; this was managed with antipsychotics and benzodiazepines (101, 102). Interestingly, the use of promethazine injection in opioid users was reported as a substitute for heroin or to increase the effects of an inadequate heroin dosing (103). A case of drug-induced delirium deriving from the coingestion of high-dose promethazine, cyproheptadine, and fluvoxamine in a young girl was recorded (104). Finally, a case of promethazine dependence and withdrawal after 2-year continuing use of a promethazine–cough mixture was described (105).

Pseudoephedrine

Seven articles, including six case reports (106–111) and one case series (112), described the misuse of pseudoephedrine (**Supplementary Table 1**). Cases mostly involved male adults (age range, 18–45 years) (F/M, 3/7) suffering from mood disorders (107, 109–111). One paper recorded an SUD [e.g., alcohol, cannabis, and heroin; (112)]. Massive dosages [e.g., 3,000–4,500 mg of pseudoephedrine/day; (107)] and IV administrations (108, 111, 112) have been associated with the misuse of pseudoephedrine. Physical symptoms associated with pseudoephedrine high dosage ingestion included stimulating effects such as decreased appetite, dry mouth, palpitations (106, 107, 112), and motor symptoms [e.g., gait and balance disorder, postural instability, generalized dystonia, hypokinesia, bradykinesia, psychomotor retardation; (106–108, 112)]. Pseudoephedrine effects were dose dependent and ranged from euphoria, insomnia, diminished sense of fatigue, and accelerated thinking, to psychotic symptoms with auditory and visual hallucinations, persecutory delusions, fear, and disorganized behavior (106, 109–111). Withdrawal symptoms have been recorded after the abrupt interruption of the long-term use (106, 107). Some cases required hospitalization and treatment with antipsychotics, e.g., haloperidol (106, 109–111); benzodiazepines (108); and antidepressants, e.g., amitriptyline (106, 108). No fatalities have been recorded.

DISCUSSION

This systematic review has illustrated a range of both themes and data regarding the misuse/abuse of some selected OTC drugs, including DXM, DPH, DH, codeine-based cough syrups, promethazine, and pseudoephedrine. Their misuse potential may be particularly significant in adolescents and young adults (10, 12, 113). OTC recreational intake appeared to be associated with high/very high dosages (17, 27, 30, 31, 35, 36, 40, 42, 45, 46, 55, 58, 61, 66, 76, 79, 84, 85, 88, 90–93, 104, 107, 114); idiosyncratic routes of administration (e.g., snorting; IM; IV; 39, 69, 88–90, 100, 103); and associated with ingestion of both licit [e.g., alcohol, prescription opioids, benzodiazepines, other OTCs; (25, 35, 49, 52–55, 60, 61, 72, 76, 83, 91, 94, 99, 101, 102)] and illicit (e.g., cannabis, cocaine, ketamine, etc.) drugs (30, 31, 34, 35, 48, 58, 60, 61, 88, 99). OTC drugs were obtained by various means (8–11), including family and friends (63), multiple doctor prescriptions (27, 36, 63, 90, 93), illegal online pharmacies/shops (36, 42, 70, 77), and theft/burglary from hospitals, residences, and pharmacies (27, 105, 110). DXM pills named "Snurf" were also reported to have been acquired online and in having been marketed as a legal high (70).

Overall, two main populations of OTC misusers were identified (11): (a) patients already suffering from a health condition and/or a psychiatric disorder who became dependent on their prescription/OTC drugs due to prolonged/high-dosage use (115), e.g., DXM-based cough mixtures started for sinusitis, cough, nasal congestion, and then continued for years at higher dosages (27, 58). Other examples have included DH prescribed for emesis in pregnancy and then continued for

12 years at a higher dosage without a prescription (82), DPH use initiated to assist with initial insomnia and then continued for 6 months up to 1,600 mg daily (92), and pseudoephedrine self-administered to lose weight then causing addiction (106); (b) individuals, including substance abusers, not in treatment for a medical disorder or illness who may have started to misuse/abuse with OTC medications for recreational purposes (36, 40, 43, 45, 70, 116).

Out of a total of $n = 185$ OTC misusers described in case reports/series surveys (24, 25, 77, 78, 99–103), male subjects were the most represented (F/M = 51/134), with an SUD 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 (e.g., bulimia; $N = 1$), and personality disorders (e.g., dependent disorder; $N = 1$). Regarding the outcome, most cases recorded were associated with a full recovery after hospitalization, with treatment having been either supportive (32, 44–46, 65) or symptomatic, with the latter consisting of benzodiazepines and antipsychotics (25, 27, 28, 43, 47, 49, 51, 54, 61, 67, 68, 71, 73–75, 79, 111, 115). A full detoxification procedure was recorded in cases of dependence and withdrawal (17, 82, 92, 95, 98, 105, 107, 109, 115); examples included buprenorphine 2 mg/day to treat a sudden opiate (codeine) withdrawal symptoms (114), naltrexone as a relapse prevention agent for DXM dependence (63), and topiramate for DXM craving (56). Some cases required specific actions in the Emergency Unit (80). Finally, it has been suggested here that drug use treatment would benefit from counseling, behavioral therapies support, and rehabilitation treatment to better overcome drug craving (11, 18, 27, 28, 34, 36, 46, 48, 53, 59, 60, 78, 84, 110, 117). OTC-related fatalities were here related to either cases characterized by unusually high dosages (24, 31, 96) or to suicide/self-aggression (31).

The cough-suppressant DXM resulted here to be the most popular OTC being misused (**Supplementary Table 1**) due to its dose-dependent sedative, dissociative, and stimulant properties (16, 118–120). Indeed, DXM psychotropic effects are mostly related to its active metabolite dextrorphan, which, if used in large dosages, is able to antagonizes N-methyl-D-aspartate (NMDA) receptors, hence modulating the excitatory neurotransmission; this results in the production of specific dissociative, ketamine-like, experiences (19, 25, 31, 56, 118–121) (**Supplementary Table 1** and **Table 1**). The effects depend upon several factors, such as an individual's CYP2D6 subtype, body weight, as well as the degree of tolerance to DXM, and the concomitant use of other CYP2D6 substrates, including antidepressants (fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine), antipsychotics (clozapine, haloperidol, risperidone, thioridazine), β-blockers (atenolol, metoprolol, propranolol), antiarrhythmics, and opioid analgesics (codeine, tramadol, and methadone), which may decrease the rate of DXM metabolism, resulting in a DXM intoxication (13, 19, 47, 121, 122). Due to DXM catabolism by repeated demethylation, which may lead to abnormal folate demands for methyl group transfer, a folate deficiency has been described in association with chronic DXM use (26, 39, 122). In addition, dental caries cases were associated with the high syrup content of cough mixtures (26). Although DXM is not thought to have addictive properties, with chronic use, vulnerable individuals may rapidly develop tolerance, dependence, and withdrawal (35, 36, 56, 58, 63, 66, 76). Interactions with other substances can often produce synergistic effects; in fact, OTC cough formulations frequently contain, in addition to DXM, other pharmaceutical agents such as chlorpheniramine, acetaminophen, or pseudoephedrine, exhibiting different effects. Indeed, individuals abusing with chlorpheniramine-containing DXM formulations may also exhibit anticholinergic signs and symptoms (25, 31, 42, 47, 49, 73, 74, 123). Conversely, the antipyretic and analgesic acetaminophen produces delayed hepatic injury (29, 62). Finally, interactions between DXM and selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitor (MAOI) might further increase the risk of a serotoninergic syndrome occurrence (67, 68, 121, 124).

Although widely used and generally considered safe, cases of antihistamine abuse and dependence have been recorded (125). These molecules were originally marketed for their antiallergy properties and are now made available as sleeping aids. Antihistamines' toxicity appears to be clinically related to both central and peripheral acetylcholine antagonism. In addition, specifically due to multiple potential mechanisms of action, DPH (e.g., the antihistamine moiety of DH) can acutely block the cell membrane pump mechanism of central 5-hydroxytryptophane and peripheral noradrenaline neurons, causing the euphoria reported by some users (**Table 1**). At high dosages, and taken together with other drugs (e.g., alcohol, cannabis, and stimulants), DPH and DH might be used to achieve a stimulant effect (87, 91, 92, 126, 127). Reported cases of DPH dependence have resulted from long-term usage of large doses (often over 1,000 mg/day). Gradual tapering has been described to alleviate withdrawal symptoms (17, 125). Conversely, promethazine is used in cough syrups for its antihistaminic, antiemetic, and sedative effects, available with codeine in common cough suppressants (128); its abuse potential appears related to its calming and sedating effect and enhancement of other coingested substances (**Table 1**). A recreational use of promethazine mixed with a soft drink and/or alcohol ("purple drank") is currently popular among young people for its euphoric effects and easy accessibility (19, 20, 129–131). Promethazine has been reported in SUD clients and is 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) (13, 19, 20, 103, 129, 130, 132, 133). Overdose of promethazine is associated with an antimuscarinic delirium, agitation, and neuroleptic malignant syndrome (100, 102, 104, 133). Scott et al. (104) recorded a promethazine-induced delirium treated with physostigmine intravenously, which reversed both central and peripheral anticholinergic effects, similarly to a polydrug overdose due to the ingestion

of DPH (94). Chlorpheniramine is used as a cheap sleep aid and/or as an anxiolytic due to its antimuscarinic properties; its abuse has been related to pleasurable feelings, which reinforces the repetitive use and the possibility of developing drug dependence (**Table 1**). It may, however, be associated with psychotic symptoms in predisposed individuals [e.g., people with mental illnesses or individuals concomitantly abusing other drugs; (42, 43, 114, 115)].

Codeine was reported within the misusing scenario of codeine-based cough and cold medicines and/or coingested with other substances, e.g., DXM, DPH, ephedrine, pseudoephedrine, methyl ephedrine, chlorpheniramine, promethazine, caffeine (26, 27, 34, 78–80, 100, 114, 134). Codeine is a natural isomer of methylated morphine and, similarly to DXM, is a prodrug, requiring metabolic activation by O-demethylation to morphine by CYP2D6. Thus, codeine-related effects are associated with CYP2D6 metabolism, e.g., ultrarapid CYP2D6 metabolizers produce an unexpectedly large amount of morphine, with resulting life-threatening opioid toxicity. Its recreational use is related to the agonism at mu receptors and the subjective effects of euphoria, elation, analgesia, and "liking" (114, 121). Codeine toxicity is characterized by respiratory depression and extreme somnolence progressing to stupor or coma (79); in severe overdosage cases, death may occur (121) (**Supplementary Table 1** and **Table 1**). 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) to be then injected. Regular use of codeine is described here together with the development of both tolerance (135) and dependence (80, 114).

Decongestants, here recorded as being abused, both alone and with coingestants, were ephedrine and its stereoisomer pseudoephedrine (78, 79, 106–109, 111, 112), which are sympathomimetic agents (136, 137) exerting a stimulating action on both alpha- and beta-adrenergic receptors (136, 137) (**Supplementary Table 1** and **Table 1**). Indeed, ephedrine has been reported to obtain weight loss or to enhance athletic performance; both pseudoephedrine and ephedrine have been recorded as used illicitly in the production of methamphetamine (136, 138). The abuse was here associated with high dosage (106–109) and IV administration (108, 111, 112). Dependence issues have been recorded (106–109).

LIMITATIONS

One of the difficulties regarding the literature on prescription drug misuse is both its heterogeneity and the issues in identifying misusing practices; interpretation was easier for both those cases reported by healthcare professionals, whose intervention was needed, National/Regional Poison Data System information (100, 101), etc. According to UNODC, the misuse of medicines is defined as "the problematic consumption outside of acceptable medical practice or medical guidelines, when self-medicating at higher doses and for longer than is advisable, for intoxicating purposes and when risks and adverse consequences outweigh the benefit" (8–11). However, levels of terminology variability and inconsistency to describe the OTC phenomenon were identified as well; this use was referred to as non-medical use, problem use, harmful use, recreational use, self-medication, or inappropriate use, which calls into question whether there is a consensus on the negative consequences (i.e., problem, harm) of OTC use. Indeed, some of these terms may not even necessarily refer to the same issue (8).

CONCLUSIONS

The current systematic review showed that OTC misuse is an increasingly relevant health issue associated with potential harms, including drug-related toxicity, addiction, and fatalities. Nowadays, the CoViD-19 pandemic has likely facilitated the occurrence of these misusing practices, as more users turned from street drugs to prescription/OTC products (14, 15). Indeed, OTC drugs are both widely accessible and perceived because of their favorable legal status as relatively safe, hence accepted in a "pill-popping culture" (11). There is the need of both drafting *ad hoc* treatment guidelines and planning preventative measures. These measures should revolve around the implementation of a range of associated issues, including scheduling amendments, proper surveillance, enhanced detection of misuse in clinical and pharmacy practice, and promotion of public health awareness initiatives (9, 11, 16, 139–141). As an example, due to the recent rise in opioid abuse and related overdose deaths worldwide, efforts are focusing on strengthening public health surveillance and limiting opioid prescribing (142, 143). Specifically, as codeine-containing products misusing levels might be hampered by their widespread and easy availability, upscheduling and pharmacy-based interventions targeting users might limit the purchase of codeine products without a prescription. The recent introduction of new OTC combinations with non-opioid agents may provide a safer alternative to these widely misused products (144). In the case of the antidiarrheal loperamide, found to be misused at high dosages and associated with cardiotoxicity, to support its safe use, the Food and Drug Administration (FDA) approved changes to the packaging for tablet and capsule forms limiting each carton to no more than 48 mg of loperamide and requiring the tablets and capsules to be packaged in individual doses (145). A range of professionals should be involved in tackling the OTC misusing issues, including (i) physicians, especially general practitioners (GP), who can help OTC misusers in early recognizing a drug-related problem and refer them to the appropriate service (e.g., mental or addiction services); they should also take note of rapid increases in the amount of medication needed or frequent, unscheduled refill requests and uncovering possible "doctor shopping" practices. Physicians will continue to have a role in educating users to ensure that they use medications appropriately, following the prescribed directions, while being aware of potential interactions with other licit/illicit drugs (11, 16, 18, 116, 135, 141). Conversely, pharmacists should be watchful for prescription falsifications or alterations, being at the frontline in recognizing prescription drug abuse issues. Moreover, prescription drug monitoring programs could

assist healthcare professionals in identifying patients who are getting prescriptions from multiple sources (11, 13, 16–18, 141, 144, 146). Finally, abuse prevention campaigns might provide valuable resources on raising awareness and preventing medicine abuse [https://stopmedicineabuse.org/; (144)].

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

FS, SC, and GM conceived the idea of this paper. AM, MCS, and AMo extracted the data. FS, MP, GM, AG, and MDG supervised all stages of the process and were consulted to resolve any possible disagreement. SC, AM, and JMC drafted the first version and revised it after contributions from FS, AG, and GM. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.657397/full#supplementary-material

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REVIEW
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Early Detection of Prescription Drug Abuse Using Doctor Shopping Monitoring From Claims Databases: Illustration From the Experience of the French Addictovigilance Network

Thomas Soeiro[1†], Clémence Lacroix[1], Vincent Pradel[1†], Maryse Lapeyre-Mestre[2†] and Joëlle Micallef[1†]*

[1] Aix-Marseille Université, Inserm, UMR 1106, Hôpitaux Universitaires de Marseille, Service de Pharmacologie Clinique, Centre d'évaluation et d'information sur la Pharmacodépendance – Addictovigilance, Marseille, France, [2] Université Paul Sabatier, Inserm, CIC 1436, Centre Hospitalier Universitaire de Toulouse, Service de Pharmacologie Clinique, Centre d'évaluation et d'information sur la Pharmacodépendance – Addictovigilance, Toulouse, France

Opioid analgesics and maintenance treatments, benzodiazepines and z-drugs, and other sedatives and stimulants are increasingly being abused to induce psychoactive effects or alter the effects of other drugs, eventually leading to dependence. Awareness of prescription drug abuse has been increasing in the last two decades, and organizations such as the International Narcotics Control Board has predicted that, worldwide, prescription drug abuse may exceed the use of illicit drugs. Assessment of prescription drug abuse tackles an issue that is hidden by nature, which therefore requires a specific monitoring. The current best practice is to use multiple detection systems to assess prescription drug abuse by various populations in a timely, sensitive, and specific manner. In the early 2000's, we designed a method to detect and quantify doctor shopping for prescription drugs from the French National Health Data System, which is one of the world's largest claims database, and a first-class data source for pharmacoepidemiological studies. Doctor shopping is a well-known behavior that involves overlapping prescriptions from multiple prescribers for the same drug, to obtain higher doses than those prescribed by each prescriber on an individual basis. In addition, doctor shopping may play an important role in supplying the black market. The paper aims to review how doctor shopping monitoring can improve the early detection of prescription drug abuse within a multidimensional monitoring. The paper provides an in-depth overview of two decades of development and validation of the method as a complementary component of the multidimensional monitoring conducted by the French Addictovigilance Network. The process accounted for the relevant determinants of prescription drug abuse, such as pharmacological data (e.g., formulations and doses), chronological and geographical data (e.g., impact of measures and comparison

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***Correspondence:**
Joëlle Micallef
joelle.micallef@ap-hm.fr

†ORCID:
Thomas Soeiro
orcid.org/0000-0003-2604-9673
Vincent Pradel
orcid.org/0000-0003-2619-4432
Maryse Lapeyre-Mestre
orcid.org/0000-0002-5494-5873
Joëlle Micallef
orcid.org/0000-0002-7172-7835

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between regions), and epidemiological and outcome data (e.g., profiles of patients and trajectories of care) for several pharmacological classes (e.g., opioids, benzodiazepines, antidepressants, and methylphenidate).

Keywords: doctor shopping, prescription drug abuse, claims database, signals detection, addictovigilance, opioids, benzodiazepines, methylphenidate

INTRODUCTION

Opioid analgesics and maintenance treatments, benzodiazepines and z-drugs, and other sedatives and stimulants are increasingly being abused to induce psychoactive effects or alter the effects of other drugs, eventually leading to dependence (1). Awareness of prescription drug abuse has been increasing in the last two decades, and organizations such as the International Narcotics Control Board has predicted that, worldwide, prescription drug abuse may exceed the use of illicit drugs (2). Prescription drug abuse is now qualified as an epidemic in economically developed countries, particularly in North America (1, 3, 4).

Many studies pointed out an increasing trend of prescription drug abuse across European countries, highlighting the need for a specific monitoring (5–9). Several factors may explain this trend, such as a greater ease in obtaining prescription drugs than illicit drugs, a lower risk of arrest for trafficking, a higher social acceptability of their abuse, their higher purity, and their more predictable doses (6).

Assessment of prescription drug abuse tackles an issue that is hidden by nature, which therefore requires a specific monitoring. A single data source is rarely enough to assess such a complex phenomenon (10). The current best practice is to use multiple detection systems to assess prescription drug abuse by various populations in a timely, sensitive, and specific manner (11). By using various tools to mine epidemiological data, assess the pharmacological properties of the drugs, and assess the social contexts where the drugs are used, these systems demonstrated their usefulness to detect emerging trends earlier and intervene more quickly to protect the public from associated risks (12). Among these tools, assessing doctor shopping through overlapping prescriptions, multiple prescribers, or pharmacy shopping was implemented in several countries (13–19). Therefore, the paper aims to review how doctor shopping monitoring can improve the early detection of prescription drug abuse within a multidimensional monitoring. The paper provides an in-depth overview of two decades of development and validation of the method as a complementary component of the multidimensional monitoring conducted by the French Addictovigilance Network.

RELEVANCE OF DOCTOR SHOPPING AS A PROXY FOR PRESCRIPTION DRUG ABUSE

Drug-abusing patients may develop drug-seeking behavior to meet their need. Among them, doctor shopping has long been described, in several countries (e.g., North America, Europe, Asia, and Oceania) and for several pharmacological classes (e.g., opioids, stimulants, and benzodiazepines) (13–19). Doctor shopping involves overlapping prescriptions from multiple prescribers for the same drug, to obtain higher doses than those prescribed by each prescriber on an individual basis. Doctor shopping is based on circumventing the optimal one-to-one patient-prescriber relationship, and therefore on a lack of medical management, because one given prescriber does not know that other prescribers are also prescribing the same drug. The lack of medical management in addition to high doses increase the risks for adverse outcomes, such as high-risk use, overdose, and death (13, 20–24).

Among many diverted means for obtaining prescription drugs (e.g., friends or relatives, black market, or internet), doctor shopping is reported as one of the most frequent ones (25–27). In addition, obtaining prescription drugs from a dealer raises the question of how dealers obtain the prescription drugs they sell (28). Although the question is difficult to answer with a strong evidence, field studies suggest that doctor shopping may play an important role in supplying the black market (29–32). Notably, without regard to the final consumer (i.e., whether the patient himself or a subsequent purchaser), the concern for the lack of medical management remains, along with the risks associated with it.

HOW TO QUANTIFY DOCTOR SHOPPING?

Doctor shopping is difficult to monitor because the patient often attempts to hide the abuse and the prescribers may not even realize that they have been deceived. These observations underline the limitations of interviewing the prescribers or patients, and therefore, highlight the added value of claims databases to quantify doctor shopping objectively. Several teams from different countries have developed methods to detect doctor shopping in claims databases (13–19). The methods face two main challenges: a proper design of the method to accurately detect drug-abusing patients and the use of a data source that is representative of the population of interest.

First Challenge: The Design of the Method

The method must be both specific (i.e., must not red flag non-abusing patients) and sensible (i.e., must not miss real drug-abusing patients). Nevertheless, there is no standard definition of doctor shopping, and therefore, no gold standard method. Most studies assessing doctor shopping rely on the number of prescribers or pharmacies visited, without regard to successive and overlapping prescriptions (33). Such methods may overestimate abuse, because successive prescriptions from different prescribers may be legitimately needed, particularly in cancer and palliative care (34), or in similar situations when a

general practitioner refers a regular patient to a specialist (35). Other situations involving successive prescribers may not be related to abuse or restricted to psychoactive prescription drugs, but rather related to prescriber factors (e.g., inconvenient hours or locations, long waiting times, or personal characteristics of the prescriber), illness factors (e.g., persistence of symptoms, lack of understanding, or lack of confidence in diagnosis or treatment), or psychological factors (e.g., anxiety leading to dose stockpiling) (36, 37).

Conversely, overlapping prescription is at the core of the safety concern, because it is the reason for the lack of medical management. Interestingly, a study compared the diagnostic odds ratios for opioid overdose of nine definitions of pharmacy shopping, using a multistate Medicaid claims database in the USA (38). The overdose rate was higher in patients with overlapping prescriptions than in patients with only pharmacy shopping. In addition, another study quantified episodes of multiple prescriber for benzodiazepines using a two-year cohort in Japan. Consecutive overlapping prescriptions had the best accuracy to detect patients with potentially questionable prescribed quantities, and predict patients with episodes of multiple prescriber in the subsequent year (19).

In the early 2000's, we designed a method to detect and quantify doctor shopping for prescription drugs, accounting for overlapping prescriptions (14, 39–45) (**Figure 1**). To detect overlapping prescriptions, the method relies on periods of prescriptions, defined as the period between the first and last dispensing for each prescriber of each patient (i.e., the period during which a patient consults a prescriber). If there is a longer delay than a predefined threshold between two consecutive dispensings, the period of prescriptions is interrupted. During an interruption, a prescription from another prescriber is not considered as overlapping to avoid the overestimation of doctor shopping. If there are overlapping periods of prescriptions, there is a lack of medical management, and a share of the drug prescribed is considered to be obtained by doctor shopping. The method provides aggregated drug-level indicators (e.g., total quantity and proportion obtained by doctor shopping) and population-level indicators (e.g., number and proportion of patients with doctor shopping behavior), and individual patient-level indicators (e.g., individual quantity obtained by doctor shopping) (**Figure 2**). Taken together, these complementary indicators enable to assess the extent of abuse and abuse potential of prescription drugs, and characterize profiles of patients with doctor shopping behavior and their trajectories of care.

Notably, the method deliberately relies on a strict design to specifically detect overlapping prescriptions rather than the number of prescribers or pharmacies visited. In addition, the quantity obtained by doctor shopping is not the entire quantity received by a patient with doctor shopping behavior, but only the quantity received in addition to what is dispensed with only one prescriber. The underlying reason for this design is that the patient may legitimately need the drug for a medical use at the quantity prescribed by one prescriber. This design helps to rule out the hypothesis of pseudoaddiction [i.e., doctor shopping driven by insufficient dosing (46)], because it enables to discriminate patients who receive high doses in addition to a treatment considered legitimate (14, 45).

Second Challenge: A Representative Data Source

To enable an accurate quantification of doctor shopping, the database must be representative of the population of interest. In addition, the database must identify each health professional and health care consumer by a consistent pseudonym over time and across geography. Given that claims databases were initially designed for medicoadministrative purposes, it is far from trivial in practice. For example, in the USA, health insurance plans only cover residents by states or focus on a specific subset of the population (e.g., Medicaid covers low-income populations, while private insurances are employment-based). Notably, the use of a non-representative population may bias the results, because socioeconomic status is associated with abuse (47–49). In addition, some regulation [e.g., the 42 CFR part 2 in the USA, which aims to ensure confidentiality of records from federally funded drug and alcohol treatment centers (50)] may further complicate the use of claims databases.

In this regard, the French National Health Data System is a first-class data source for pharmacoepidemiological studies, as one of the world's largest claims database, whose representativeness is almost perfect (51–53). The National

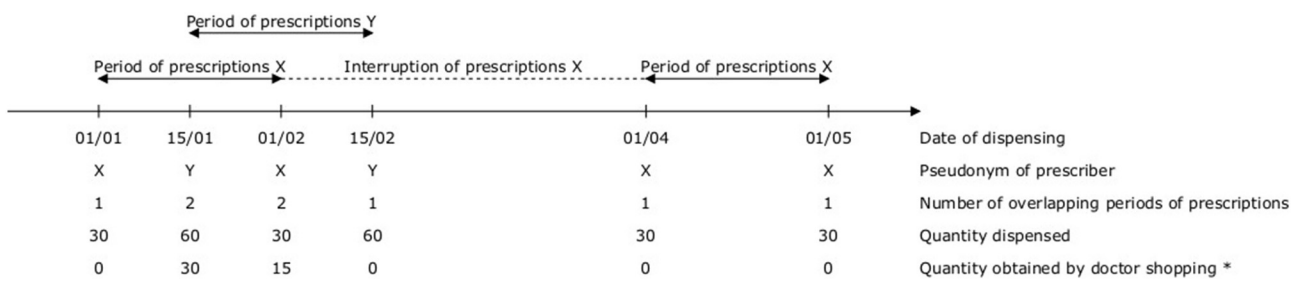

FIGURE 1 | Method to detect and quantify doctor shopping for prescription drugs, accounting for overlapping prescriptions. *The quantity obtained by doctor shopping is calculated as Qd–Qd/n, where Qd is the quantity dispensed, n is the number of overlapping periods of prescriptions, and Qd/n is the quantity that would have been dispensed with only one prescriber.

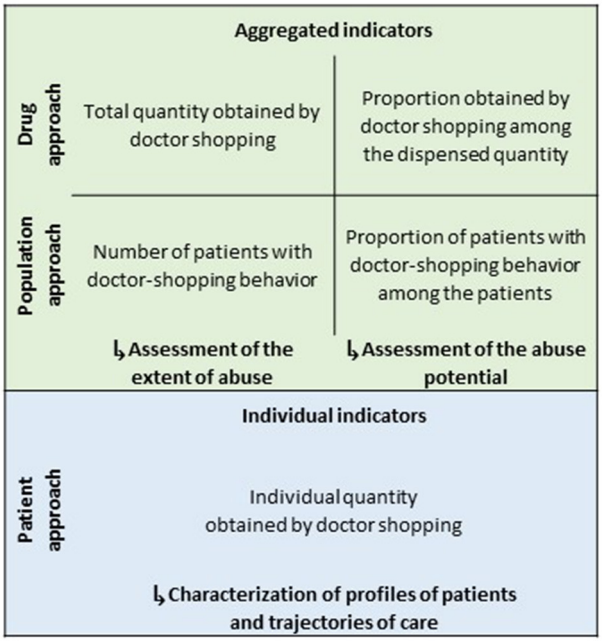

FIGURE 2 | Complementary indicators provided by the method.

Health Data System prospectively merges pseudonymized records of claims from all the French health insurance plans, the national hospital-discharge database, and the national death registry (54). Because the coverage by a health insurance plan is mandatory in France, the French National Health Data System covers almost 100% of the 67 million inhabitants, from birth to death, independently of the socioeconomic status and region of residence. In addition, each health professional and health care consumer is identified by a consistent pseudonym over time and across geography. As a result, the French National Health Data System enables a nationwide and exhaustive quantification of doctor shopping.

In the last two decades, the French National Health Data System has been extensively used for pharmacoepidemiological research, including some large-scale studies that have led to major public health interventions (55, 56). Among them, many studies have focused on psychoactive prescription drugs (57–63).

VALIDATION OF DOCTOR SHOPPING AS A PHARMACOLOGICAL TOOL

Before using doctor shopping as a proxy for prescription drug abuse, there is a need for an in-depth customized validation process within the health system of interest. The lack of a gold standard method makes a classical statistical validation process impossible (i.e., sensitivity, specificity, and predictive values). Therefore, an empirical approach is required to assess the external validity of the proxy in a given health system for several pharmacological classes. Such a process should rely on linking doctor shopping to relevant determinants of prescription drug abuse, such as pharmacological data (e.g., formulations and doses), chronological and geographical data (e.g., impact of measures and comparison between regions), and epidemiological and outcome data (e.g., profiles of patients and trajectories of care).

In the last two decades, we have conducted such an empirical validation of our method (14, 39–45) (**Table 1**). The process has provided solid evidence that the method is a relevant proxy for prescription drug abuse within the French health system, because it has always demonstrated an excellent external validity. In particular, the method demonstrated to be a useful pharmacological tool, able to provide detailed results by discriminating drugs, formulations, and doses.

Detecting Prescription Drugs With a High Abuse Potential

The method was first developed for buprenorphine maintenance treatment (14, 39), which was expected to have a high abuse potential in the real-life setting. In France, a wide access to maintenance treatments is ensured by an office-based setting for the majority of patients (64, 65). In parallel of a marked decrease in lethal heroin overdoses, a concern emerged along with observations of abuse (e.g., injection of crushed tablets, snorting, association with benzodiazepines such as flunitrazepam, and deaths) and an increasing buprenorphine black market (14). Interestingly, evidence of multiple prescribers for buprenorphine maintenance treatment was also described, but without quantifying the buprenorphine maintenance treatment involved, nor accounting for overlapping prescriptions (66).

A study was conducted among the 3,259 patients who received buprenorphine maintenance treatment in a population of two million inhabitants in South East France in 1999 and 2000. The method found that 225,351 defined daily doses (DDD) were obtained by doctor shopping, corresponding to 18.7% of the quantity dispensed (14). Doctor shopping was highly concentrated on a minority of patients (i.e., 8.5% of patients accounted for 45.4% of the quantity obtained by doctor shopping).

As a result, the health insurance implemented a prescription monitoring program for opioid maintenance therapies in 2004, for both public health and economic concerns. Patients who received >32 mg/day of buprenorphine maintenance treatment (i.e., twice the maximum recommended dose) were proposed a contract of care, including the choice of a single prescriber and pharmacist for buprenorphine maintenance treatment. Patients with particularly high doses who did not respond to the convocation, or did not respect their contract of care, could be prosecuted, or excluded from the health insurance plan. A second assessment of doctor shopping from 2000 to 2005 in the same population found that the prescription monitoring program led to a decrease in doctor shopping, without decreasing the access to buprenorphine maintenance treatment (39).

TABLE 1 | Empirical validation of the method accounting for overlapping prescription, in the last two decades, in France.

References	Date	Setting	Prescription drugs under study	Number of patients included	Main findings
Pradel et al. (14)	1999 and 2000	Two million inhabitants in South East France	Buprenorphine maintenance treatment	3,259	225,351 DDD were obtained by doctor shopping, corresponding to 18.7% of the quantity dispensed. Doctor shopping was highly concentrated on a minority of patients (i.e., 8.5% of patients accounted for 45.4% of the quantity obtained by doctor shopping).
Pradel et al. (39)	2000 to 2005	Two million inhabitants in South East France	Buprenorphine maintenance treatment	>2,600 each semester	Doctor shopping increased from 2000 (i.e., 14.9% of the quantity dispensed) to 2004 (i.e., 21.7% of the quantity dispensed), and decreased in 2005 (i.e., 16.9% of the quantity dispensed) following the implementation of a prescription monitoring program. The number of patients remained stable from 2000 to 2005.
Pradel et al. (40)	2003	One million inhabitants in South West France	Benzodiazepines	128,230	Benzodiazepines were ranked according to their abuse potential in real-life setting. The proportion obtained by doctor shopping was the highest for flunitrazepam 1 mg (i.e., 42.8% of the quantity dispensed), then for diazepam 10 mg (i.e., 3.2% of the quantity dispensed), and clorazepate 50 mg (i.e., 2.7% of the quantity dispensed).
Rouby et al. (41)	2005	Five million inhabitants in South East France	Antidepressants and benzodiazepines as comparator	410,525	Tianeptine ranked first among antidepressants for the proportion obtained by doctor shopping (i.e., 2.0% of the quantity dispensed), and was close to benzodiazepines with a well-known abuse potential in real-life setting.
Nordmann et al. (42)	2008	14 million inhabitants in three regions in South France (i.e., Provence-Alpes-Côte d'Azur, Rhône-Alpes, and Midi-Pyrénées)	Opioids	885,941 in Provence-Alpes-Côte d'Azur 945,102 in Rhône-Alpes 386,834 in Midi-Pyrénées	The quantity obtained by doctor shopping in Provence-Alpes-Côte d'Azur (i.e., 213 DDD/1,000 inhabitants) was two-fold higher than in Rhône-Alpes (i.e., 115 DDD/1,000 inhabitants) and in Midi-Pyrénées (i.e., 106 DDD/1,000 inhabitants). A signal emerged for oxycodone in Midi-Pyrénées.
Ponté et al. (43)	2013	14 million inhabitants in South France	Opioids and benzodiazepines as comparator	1,257,246	The proportion obtained by doctor shopping was the highest for the highest doses of morphine (i.e., 8.4% of the quantity dispensed for morphine 200 mg) and oxycodone (i.e., 2.8% of the quantity dispensed for oxycodone 80 mg), and for nasal and transmucosal fentanyl (i.e., respectively 4.1 and 3.3% of the quantity dispensed).
Soeiro et al. (44)	2010 and 2016	67 million inhabitants in France	Oxycodone	67,838 in 2010 212,753 in 2016	There was a three-fold increase in doctor shopping in line with population exposure. The quantity obtained by doctor shopping increased with the dose for both immediate-release and extended-release tablets.
Soeiro et al. (45)	2016	67 million inhabitants in France	Methylphenidate	63,739	Patients with heavy doctor shopping behavior were older, received more concomitant dispensing of antipsychotics and opioid maintenance treatments, and had more prescribers.

DDD, defined daily dose.

Ranking Prescription Drugs Within a Pharmacological Class Known for Abuse

The method demonstrated its ability to rank prescription drugs according to their abuse potential in the real-life setting. A study was conducted among the 128,230 patients who received benzodiazepine in a population of one million inhabitants in South West France in 2003. The method found a much higher proportion obtained by doctor shopping for flunitrazepam 1 mg (i.e., 42.8% of the quantity dispensed), then for diazepam 10 mg (i.e., 3.2% of the quantity dispensed), and clorazepate 50 mg (i.e., 2.7% of the quantity dispensed) (40) (**Figure 3**).

Interestingly, although flunitrazepam has pharmacological characteristics prone to abuse [e.g., rapid onset of action, liposolubility, and additive effects with alcohol (67, 68)], there is no evidence of any important experimental difference for its abuse potential compared to other benzodiazepines

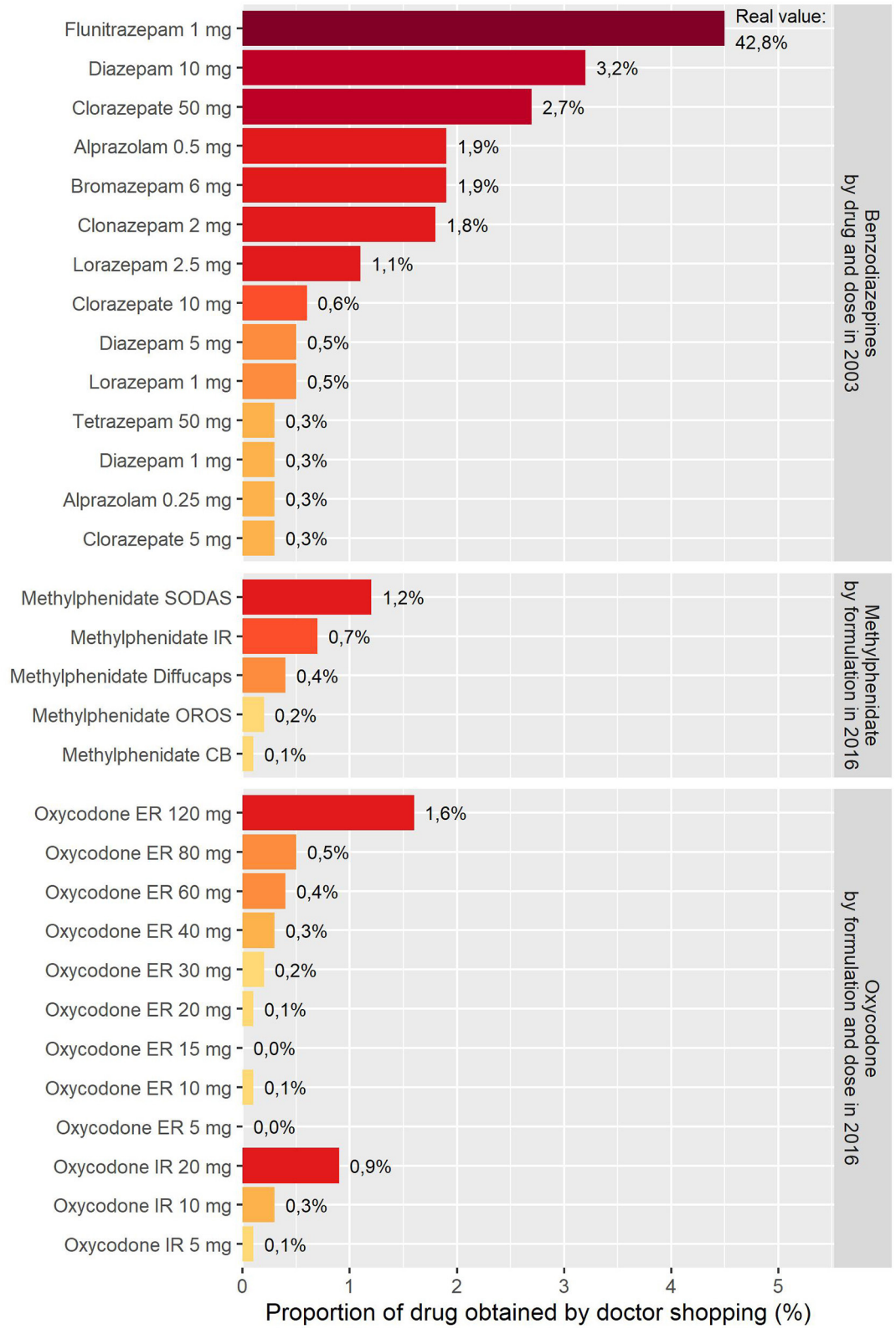

FIGURE 3 | Validation of doctor shopping as a pharmacological tool through its ability to rank prescription drugs within a pharmacological class known for abuse (e.g., benzodiazepines) and recover pharmacological determinants of abuse (e.g., formulation for methylphenidate and dose for oxycodone). SODAS: Spheroidal Oral Drug Absorption System; IR: Immediate-release; OROS: Osmotic-Controlled Release Oral Delivery System; CB: Coated beads. See Table 1 in Soeiro et al. (45) for details on formulations.

(69). Nevertheless, a review of the literature found that the two benzodiazepines with the highest abuse potential are flunitrazepam and diazepam (70), particularly in opioid-abusing patients, many of whom reported a preference for flunitrazepam over other benzodiazepines (69).

Discriminating Prescription Drugs Within a Pharmacological Class Not Known for Abuse

The method also demonstrated its ability to discriminate prescription drugs by specifically detecting tianeptine among antidepressants (41). Back then, tianeptine was thought to have no abuse potential, as mentioned in the French summary of product characteristics before 2005, because there was no evidence of such a risk on the data available before approval (71). Nevertheless, the first reports of abuse with tianeptine emerged in the literature (72–75).

A study was conducted among the 410,525 patients who received an antidepressant in a population of five million inhabitants in South East France in 2005. Tianeptine ranked first among the antidepressants for the proportion obtained by doctor shopping (i.e., 2.0% of the quantity dispensed), and was close to benzodiazepines with a well-known abuse potential in the real-life setting (41). In addition to reports from other data sources, these findings led to a stricter regulation of tianeptine in France.

Interestingly, tianeptine is a selective serotonin reuptake enhancer and an opioid agonist (76), with a chemical structure close to amineptine, which was withdrawn in several countries because of the abuse associated with hepatitis (77, 78). In addition, psychostimulant effects of tianeptine appear at high doses (75). These pharmacological properties makes tianeptine an atypical antidepressant, and may account for its abuse potential.

Recovering Pharmacological Determinants of Abuse

The method finally demonstrated its ability to recover pharmacological determinants of abuse, such as a preference for specific formulations and high doses for several pharmacological classes (e.g., benzodiazepines, opioids, and methylphenidate) (40, 42–45).

The effect of formulation is especially notable for methylphenidate, which was available in five formulations, using different extended-release technologies and ratio of immediate-release/extended-release methylphenidate in France in 2016. On the same year, a study was conducted among the 63,739 patients who received methylphenidate in the 67 million inhabitants in France. Patients with doctor shopping behavior preferred formulations with a higher ratio of immediate-release/extended-release methylphenidate (e.g., methylphenidate with Spheroidal Oral Drug Absorption System and methylphenidate immediate-release) over methylphenidate with Osmotic-Controlled Release Oral Delivery System (OROS) (45) (**Figure 3**). Given that the use of intravenous route for methylphenidate is frequent in France (79–81), this pattern also suggests that a part of methylphenidate obtained by doctor shopping may be used by intravenous route, because methylphenidate OROS is the least preferred drug for intravenous route in drug-abusing patients (82). Interestingly, OROS increases the time for preparing due to the viscosity of the preparation, which may be the reason for this preference (83).

Similarly, the effect of dose is especially notable for oxycodone, which was available in 12 doses from 5 to 120 mg in France in 2016. A study was conducted in 2016 among the 212,753 patients who received oxycodone in the 67 million inhabitants in France. There was a dose-response-like relationship between dose and doctor shopping (i.e., the quantity obtained by doctor shopping increased with the dose for both immediate- and extended-release tablets) (44) (**Figure 3**). Interestingly, as soon as 2008, the method detected a first signal for oxycodone, particularly in one region (81), although no oxycodone abuse had been detected in France back then. This finding underlines the usefulness of local monitoring to assess the geographical specificities of abuse, which may help to target public health interventions (84).

ADDED VALUE OF DOCTOR SHOPPING MONITORING TO IMPROVE THE EARLY DETECTION OF PRESCRIPTION DRUG ABUSE WITHIN A MULTIDIMENSIONAL MONITORING

In order to face the challenges of monitoring prescription drug abuse, several authors and health authorities advocate for a multidimensional proactive post-marketing monitoring (10–12). Such a multidimensional monitoring is already operational in France through the French Addictovigilance Network (85–90). In addition to a spontaneous notification by health professionals and pharmacoepidemiological studies from claims databases (91, 92), multiple *ad hoc* studies have been conducted nationwide, such as: the OSIAP program, to detect forged prescription (93, 94); the OPPIDUM program, to detect psychoactive drug use in drug-abusing patients (95, 96); the DRAMES program, to detect deaths related to psychoactive drugs; the DTA program, to detect deaths related to analgesic prescription drugs; or the chemical submission program, to detect psychoactive drugs administered without the victim's knowledge (97).

The multidimensional monitoring conducted by the French Addictovigilance Network enables the detection of signals by crossing complementary data sources, which overcomes the limitation of each data source taken individually (**Figure 4**). In addition to the already existing programs of the French Addictovigilance Network, the added value of doctor shopping monitoring is its ability to exhaustively detect drug-abusing patients in the general population, and for all the marketed prescription drugs. This ability in not only theoretical, as demonstrated by a nationwide quantification of doctor shopping recently conducted in France for 220 psychoactive prescription drugs from many pharmacological classes (e.g., opioids, benzodiazepines, stimulants, antihistamines, gabapentinoids, antidepressants, and antipsychotics) (98). Given its automatic nature, the method can be implemented routinely, with minimal costs and limited workforce. Interestingly, doctor shopping monitoring is not impaired by under-declaration. Such features

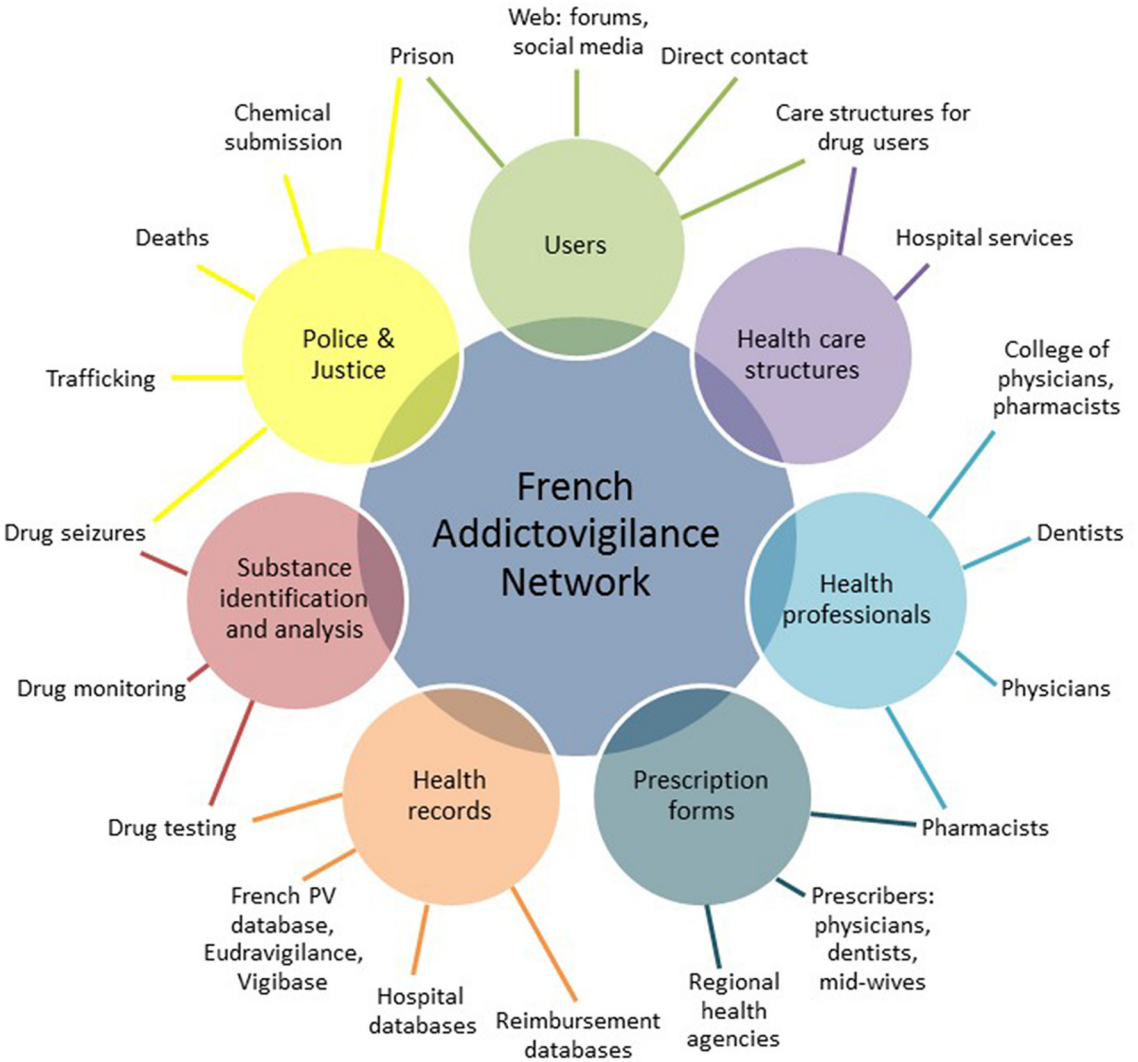

FIGURE 4 | Multidimensional monitoring conducted by the French Addictovigilance Network to detect signals by crossing complementary data sources.

make doctor shopping monitoring a complementary tool, which is even more topical in the big-data era to assess prescription drug abuse and detect emerging trends in the field of addictovigilance as early as possible (99).

For example, the monitoring of tramadol conducted by the French Addictovigilance Network detected an increasing abuse (100, 101). Beside a regular increase in spontaneous reports, tramadol has been used in combination or in alternation with other opioids in drug-abusing patients according to the OPPIDUM program; has ranked first among analgesics for deaths in the DTA program; and has increased for falsified prescriptions in OSIAP. These converging data are further strengthened and complemented by the nationwide quantification of doctor shopping in France (98). Notably, tramadol ranked ninth among 220 psychoactive prescription drugs for the quantity obtained by doctor shopping (i.e., 755,333 DDD). From 2010 to 2016, tramadol was one of the few opioids for which both quantity and proportion obtained by doctor shopping increased (i.e., +12% and +5%, respectively). In the population approach, tramadol ranked first for the number of patients with doctor shopping behavior (i.e., 44,088 patients). Interestingly, tramadol is an atypical opioid analgesic that also inhibits the reuptake of serotonin and norepinephrine (102). In addition, O-desmethyltramadol, which is produced by the polymorphic cytochrome P450 2D6, has a 200 to 500 higher affinity for μ-opioid receptor than tramadol (103). In light of the pharmacological properties of tramadol and international data (104–106), these increasing trends are strong signals in the French context.

DISCUSSION

The paper aims to review how doctor shopping monitoring can improve the early detection of prescription drug abuse within a

multidimensional monitoring. The paper provides an in-depth overview of two decades of development and validation of the method as a complementary component of the multidimensional monitoring conducted by the French Addictovigilance Network. In this context, doctor shopping monitoring has demonstrated its added value to improve the early detection of prescription drug abuse. Notably, the monitoring must also include a strong pharmacological expertise, which is essential to both analyze signals and interpret pharmacoepidemiological data.

While the method has been developed and validated in France, the rationale is transposable in other health systems with available claims databases. In practice, given the increasing availability of claims databases in several countries, the main issue is to integrate doctor shopping monitoring within a multidimensional monitoring. In addition, the method must undergo an in-depth customized validation process, accounting for the specificities of the targeted health system (e.g., availability of prescription drugs and illicit alternatives, cost of prescription drugs and visits, prescription and control methods, and risks involved for fraud).

Such pharmacoepidemiological monitoring is intended to develop in the big-data era. Interestingly, it is nowadays technically possible to implement a real-time doctor shopping monitoring, assuming that a quick access to data is available, which is currently the bottleneck.

Finally, as a public health mission, monitoring prescription drug abuse must rely on free from conflict-of-interest organizations to prevent private interest from interfering, as it was the case in the opioid crisis (107, 108). This is even more necessary given that such monitoring may lead to the reconsideration of the safety of some prescription drugs in the real-life setting, and trigger regulatory measures. Among them, prescription monitoring programs are efficient to mitigate doctor shopping and its consequences (39, 109, 110). Nevertheless, the consequences of such regulatory measures must be globally assessed, because hardening the access to prescription drugs may lead to switching to illicit drugs. The challenge is to develop methods that maximize the detection and prevention of prescription drug abuse, while minimizing any adverse impact on legitimate medical treatments.

CONCLUSION

To conclude, doctor shopping monitoring is a useful component for an efficient multidimensional monitoring to improve the early detection of prescription drug abuse in the field of addictovigilance.

AUTHOR CONTRIBUTIONS

TS wrote the manuscript. CL, VP, ML-M, and JM reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Assessment of the Safety Signal for the Abuse Potential of Pregabalin and Gabapentin Using the FAERS Database and Big Data Search Analytics

Georgios Papazisis[1], Dimitrios Spachos[2], Spyridon Siafis[1], Niki Pandria[2], Eleni Deligianni[1], Ioannis Tsakiridis[3] and Antonios Goulas[4]*

[1] Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece, [2] Laboratory of Medical Physics, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece, [3] Department of Obstetrics and Gynaecology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece, [4] First Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

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***Correspondence:**
Georgios Papazisis
papazisg@auth.gr
orcid.org/0000-0003-1641-9095

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Introduction: The latest decade, an emerging issue has been the abuse potential of the gabapentinoids pregabalin and gabapentin. The aim of our study was to assess this safety signal combining two different methods of surveillance: search analytics big data and the FDA spontaneous reporting system database.

Methods: Analysis of big data and the FAERS was used to detect pregabalin's and gabapentin's abuse potential in comparison with two controls, clonazepam and levetiracetam, and further, the correlation between these domains was investigated. Data from the United States between 2007 and 2020Q2 were analyzed.

Results: The FAERS analysis revealed the following pattern of signals: clonazepam > pregabalin ≥ gabapentin > levetiracetam, for both the primary term "drug abuse and dependence" and the secondary terms (withdrawal, tolerance, overdose). The Google domain pattern was slightly different: clonazepam ≥ gabapentin ≥ pregabalin≥ levetiracetam. A monotonic correlation was found between FAERS and Google searches for gabapentin ($r = 0.558$; $p < 0.001$), pregabalin ($r = 0.587$; $p < 0.001$), and clonazepam ($r = 0.295$; $p = 0.030$).

Conclusion: Our results revealed that there is preliminary evidence of a safety signal for the abuse potential of pregabalin and gabapentin. Analysis of the FAERS database, supplemented by big data search analytics, suggests that there is potential of using these methods as a supplementary tool to detect drug abuse-related safety signals in pharmacovigilance.

Keywords: pregabalin, gabapentin, big data, Google search analytics, disproportionality analysis, abuse potential, safety signal, FAERS database

INTRODUCTION

Gabapentinoids (pregabalin and gabapentin) are a class of drugs that have been widely used-prescribed for neuropathic pain, epilepsy, anxiety, and other psychiatric disorders, while pregabalin showed promise as a treatment for alcohol dependence (1, 2). Gabapentin and pregabalin have a similar structure and are derivatives of the inhibitory neurotransmitter GABA. Their proposed mechanism of action is the inhibition of calcium currents via high-voltage-activated channels containing the a2d-1 subunit (3). Since their first approval, both gabapentinoids are widely prescribed medications in the United States (4, 5).

The latest decade, an emerging issue has been the abuse potential of both pregabalin and gabapentin. An increase in non-medical use of gabapentinoids for recreational purposes has been reported, especially in Europe (6, 7). Higher doses of gabapentinoids use have been characterized by causing euphoria effects and a range of experiences such as relaxation, improved sociability, and sedative and psychedelic-like effects (8). From the EudraVigilance database review on gabapentinoids, fatalities were also reported associated with pregabalin and gabapentin use and in most of the cases in combination with opioids (9). Pharmacovigilance data from the Food and Drug Administration Adverse Event Reporting System (FAERS) have shown adverse drug events from gabapentinoid abuse with a higher prevalence in young and male individuals (10). Both pregabalin and gabapentin from 1st April 2019 have been classified as Schedule 3 controlled drugs under the Misuse of Drugs Regulations 2001, and Class C of the Misuse of Drugs Act 1971 in the UK. On the other hand, in the US, pregabalin is a Schedule 5 controlled substance while gabapentin is a controlled substance only in some States. In Australia, pregabalin and gabapentin are classified as Schedule 4 (prescription only) medications; therefore there are no special control measures on supply or possession yet (11).

Considering the abovementioned data on the relative well-established abuse potential profile of the gabapentinoids, the aim of our study was (i). to detect pregabalin's and gabapentin's abuse potential in comparison with two controls, clonazepam and levetiracetam and (ii). to investigate the correlation between the search analytics and the FAERS domain. Our group has recently published the methodology of combining these pharmacovigilance domains in order to detect safety signals (12, 13).

METHODS

Data Sources

Following the methodology of our previous analysis that investigated mirtazapine's abuse liability (12), herein, we investigated the abuse liability of the gabapentinoids combining pharmacovigilance and search analytics data from the United States between 2007 and 2020Q2. Clonazepam, a frequently used benzodiazepine with a well-known abuse potential profile, was used as a positive control (12, 14), while levetiracetam (a well-known antiepileptic with a low abuse potential) (15) served as negative control.

TABLE 1 | Drug names and drug abuse-related terms.

	Google	FAERS
Drugs	• Clonazepam, Klonopin • Gabapentin, Neurontin • Pregabalin, Lyrica • Levetiracetam, Kepra	• Clonazepam • Gabapentin • Pregabalin • Levetiracetam
Drug abuse-related terms	{Abuse, dependence}	Drug abuse and dependence (SMQ narrow scope)
	{Withdrawal}	Drug withdrawal (SMQ narrow scope)
	{Overdose}	Tolerance [drug tolerance (PT) and drug tolerance increased (PT)]
	{Tolerance}	Overdose [overdose (PT) and intentional overdose (PT)]
	{High}	Euphoria [euphoric mood (PT), feeling abnormal (PT), feeling drunk (PT), feeling of relaxation (PT), dizziness (PT), thinking abnormal (PT), hallucination (PT), inappropriate affect (PT)]

In the FAERS database, the drugs are registered with their generic names; in Google search analytics, a brand name was also used. Drug-abuse-related MedDRA terms were selected in FAERS, and similar abuse-related search terms in the search analytics domain (SMQ, standardized MedDRA query; PT, preferred term).

FAERS

The pharmacovigilance database of the FAERS consists of individual safety reports originated mainly from the United States. The structure and data mining algorithms of FAERS have been described elsewhere (16). Briefly, reports can be submitted by patients, the pharmaceutical industry, and healthcare professionals, while adverse events are classified with MedDRA terminology (16, 17). The freely available pharmacovigilance tool OpenVigil-2.1-MedDRA (available at http://openvigil.sourceforge.net/) was used in order to access cleaned FAERS data, by removing duplicates and normalizing drug names to the generic name of the drug (18). Similar to our previous analysis, higher level terms were used, whenever possible, to classify reports with drug-abuse-related adverse events (12). The narrow scope of the Standardized MedDRA Query (SMQ) "drug abuse and dependence" was used as the primary term, and other terms related to drug abuse, including overdose, tolerance, withdrawal, and euphoria-related events, were used as secondary terms (**Table 1**) (12, 19). Disproportionality analysis was conducted for the aggregated period of 2007–2020Q2 for both the primary and secondary terms, while correlation analyses were conducted using quarterly data of the primary term.

Google Analytics

The Google search engine receives more than 5 billion of queries per day (20). Although it does not provide detailed analytics,

some indicators, such as the interest over time, are publicly accessible. Usually, search queries contain terms related to the generic and brand names of the drug, combined together with some additional terms (e.g., "Can you get high of…?"). We combined analytics data retrieved using both the generic name and a common brand name of each drug (**Table 1**).

An important aspect for retrieving analytics data from the Google search engine is the context. We can define the search context by limiting the returned results per category. The widest category is the "general search term," where Google returns analytics from searches in all categories. However, since we were studying a very specific area of interest, we could also restrict our results in a more specific category (e.g., "medication"). Google is using search semantics to classify each search query and is expected that the more specific category will provide more accurate results. However, depending on the search popularity of some terms, there may not be enough results inside the category context, because Google returns only results that can be considered as big data volumes. In our study, we used only the "prescription drug" category for the extraction of our data.

Next, we defined a set of six abuse-related search terms, similar to the MedDRA abuse-related terms: {"abuse," "dependence," "overdose," "withdrawal," "tolerance," and "high"}. **Table 1** indicates the relationship of the terms between the FAERS and the Google domains. We used the term "high" as the corresponding term of "euphoria," as the second did not have enough data.

By default, Google does not return results for searches with terms and queries made by a few people. Moreover special characters (i.e., queries with apostrophes) were filtered—this is a way of normalization that is also made by default. It is also important that Google's tools eliminate repeated searches from the same person over a short period of time. We identified queries containing combinations of the drug names and the abuse-related terms from the set we defined in a previous step. Finally, we filtered the results manually, by dropping out queries unrelated to abuse. For example, while the search query "clonazepam and high blood pressure" contains both the terms "clonazepam" and "high," it is not related to abuse. Instead, the query "can you get high of pregabalin" is related to abuse and, thus, included to our search results.

Statistical Analysis

The search interest over time is measured by the search popularity score (SPS) in the Google domain. We used the SPS score to collect metrics related to abuse liability. In the FAERS domain, we used the reporting odds ratio (ROR) for abuse-related adverse events. This methodology of analysis was recently published from our group (12).

Search Interest Over Time

Google reports top searches for every search query. These are terms (queries) that are most frequently searched with the main term in the same search session and within the selected category, country, or region (21).

The most popular queries are sorted by SPS. The value of SPS is between 0 and 100. The most popular term (in our case the main drug name, e.g., "Lyrica") has a normalized score of 100, which is the maximum score. All other queries have a score under this value. This indicator represents the total number of searches divided by the total number of related searches on the specific country or region at the given time range. This is the default method used by Google in a tool called "Google Trends," to compare relative popularity between topics. For example, an SPS of 50 is assigned to a query that has been searched half as often as the top query. Queries with a search rate $<1\%$ are not reported and are signed with a 0 SPS which is neither a percentage value nor an absolute value of searches. Combining more than one term or queries, the value can be above 100. Considering the large number of queries, we can safely assume that all referred statistics come from big data volumes.

We obtained the monthly SPS for all abuse-related terms for each drug. We developed timelines representing the cumulative search interest over time for the abuse-related terms beginning at 2007Q1 and ending at 2020Q2.

Disproportionality Analysis

Disproportionality analysis was conducted to investigate the association between abuse-related events and the tested drugs in comparison to all other drugs and all other events in the FAERS database. The reporting odds ratio (ROR) was used to quantify this association, and a larger ROR demonstrates a more frequent co-reporting of the tested drug and the selected term as well as a stronger safety signal. We detected safety signals when the number of reports with the combination of the tested drug and selected event was >3 and the lower boundary of the 95% confidence interval of ROR was >1 (16). The disproportionality analysis and RORs were calculated using the OpenVigil2.1-MedDRA (18).

Correlation Between FAERS and Search Analytics Domains

A correlation coefficient is a statistical metric that measures the probability of two variables to change together. It describes both the strength and the direction of the relationship. The Pearson correlation coefficient is the most well-known metric, which evaluates the linear relationship between two variables. The Spearman correlation coefficient evaluates the monotonic relationship between two continuous or ordinal variables. The difference is that, in a monotonic relationship, the variables tend to change in the same direction, increasing or decreasing their values, but not necessarily at a constant rate, as in a linear relationship. Unlike Pearson's correlation, Spearman's method does not require normality of the variables and, thus, it is a non-parametric statistic.

RESULTS

Google Search Analytics

According to the analysis for the cumulative period, the overall abuse-related terms had an average SPS of 8 for Levetiracetam, 11.25 for pregabalin, 22.5 for gabapentin, and 45.5 for Clonazepam (**Figure 1**). Considering that Google is receiving billion queries per day, even low values of SPS in the given time

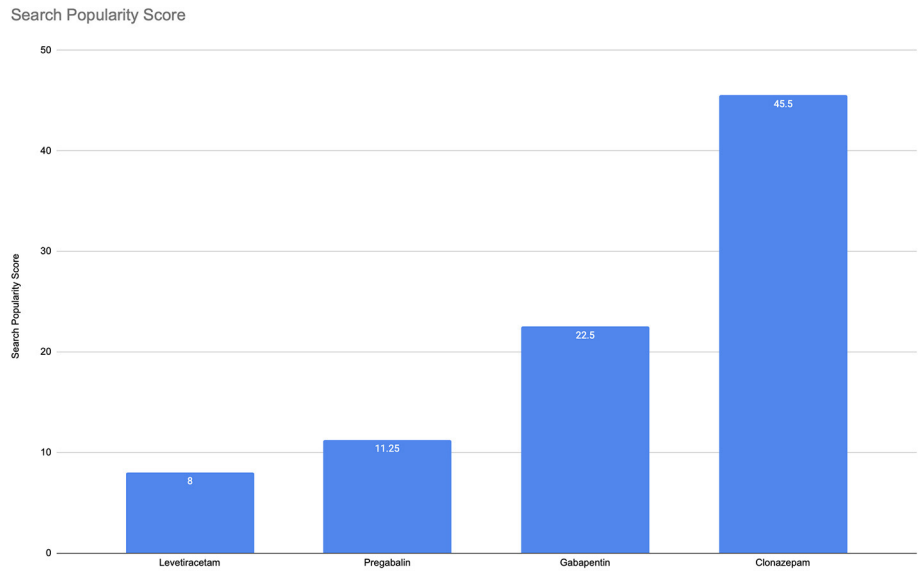

FIGURE 1 | Search Popularity Score (SPS) in the Google analytics domain for the four drugs.

range represent millions of queries about a topic (22). A non-formal interpretation of these numbers could be as follows: e.g., for pregabalin, for every 100 search queries related to pregabalin, there are 11.25 more queries (on top of the 100) related to pregabalin and abuse related terms.

Figure 2 shows the search interest over time for pregabalin, gabapentin, and clonazepam. The search volume for levetiracetam was significantly low, and thus, there were not enough data to be reported by the Google engine. While this may sound as a serious limiting condition, instead it ensures that the reported data are accurate and cannot be affected or modified by a small number of people who perform search queries producing "fake" trends.

The median values of search analytics over time were 82.5, IQR [53.25, 128] for pregabalin, 37, IQR [16.25, 47] for gabapentin, and 203.5, IQR [145.25, 258] for clonazepam.

Disproportionality Analysis

During the period of 2007–2020Q2, there were in total 7430750 reports submitted in FAERS. The total number of reports (N) was larger for pregabalin (N = 107,905) and gabapentin (N = 102,386), and about half for each of the controls, clonazepam (N = 55,856), and levetiracetam (N = 43,842). For the primary term "drug abuse and dependence" (N = 118,980), safety signals were identified for both gabapentinoids (pregabalin: ROR 2.78 95% CI [2.70–2.86]; gabapentin ROR 1.83 95% CI [1.76–1.90]), while the positive control clonazepam had the largest signal (ROR 4.47 95% CI [4.32–4.62]), and the negative control levetiracetam had a very weak signal (ROR 1.10 95% CI [1.02–1.18]). The secondary terms followed the same pattern of signals (clonazepam > pregabalin ≥ gabapentin > levetiracetam), except for euphoria-related terms, for which pregabalin had the largest ROR and overdose-related terms, for which the gabapentinoids and levetiracetam demonstrated similar signals (**Table 2**). **Figure 3** shows the number of reported adverse events related to abuse terms in the FAERS database.

Correlation Between FAERS and Search Analytics Domains

A monotonic correlation was found between FAERS and Google searches for clonazepam (r = 0.295; p = 0.030, **Figure 4A**), gabapentin (r = 0.558; $p < 0.001$, **Figure 4B**), and pregabalin (r = 0.587; $p < 0.001$, **Figure 4C**). Since Google reports only volumes with a significant number of searches, which can be considered as big data volumes, we were not able to collect the amount of data required for analysis for levetiracetam.

DISCUSSION

Based on extensive literature search, this is the first study investigating the abuse potential of pregabalin and gabapentin using two different pharmacovigilance methods: disproportionality analysis in the FAERS and Google search analytics. A positive control and a negative control were used, the benzodiazepine clonazepam, with a well-known abuse profile and the antiepileptic levetiracetam, with a previously unreported abuse potential, respectively.

Signals in the FAERS Database

Our disproportionality analysis of the FAERS revealed the following pattern of signals: clonazepam > pregabalin ≥ gabapentin > levetiracetam, both for the primary term "drug abuse and dependence" and the secondary terms (withdrawal, tolerance, overdose). Our results confirm previous findings from the pharmacovigilance domain that highlight the abuse potential of pregabalin. According to the review of the

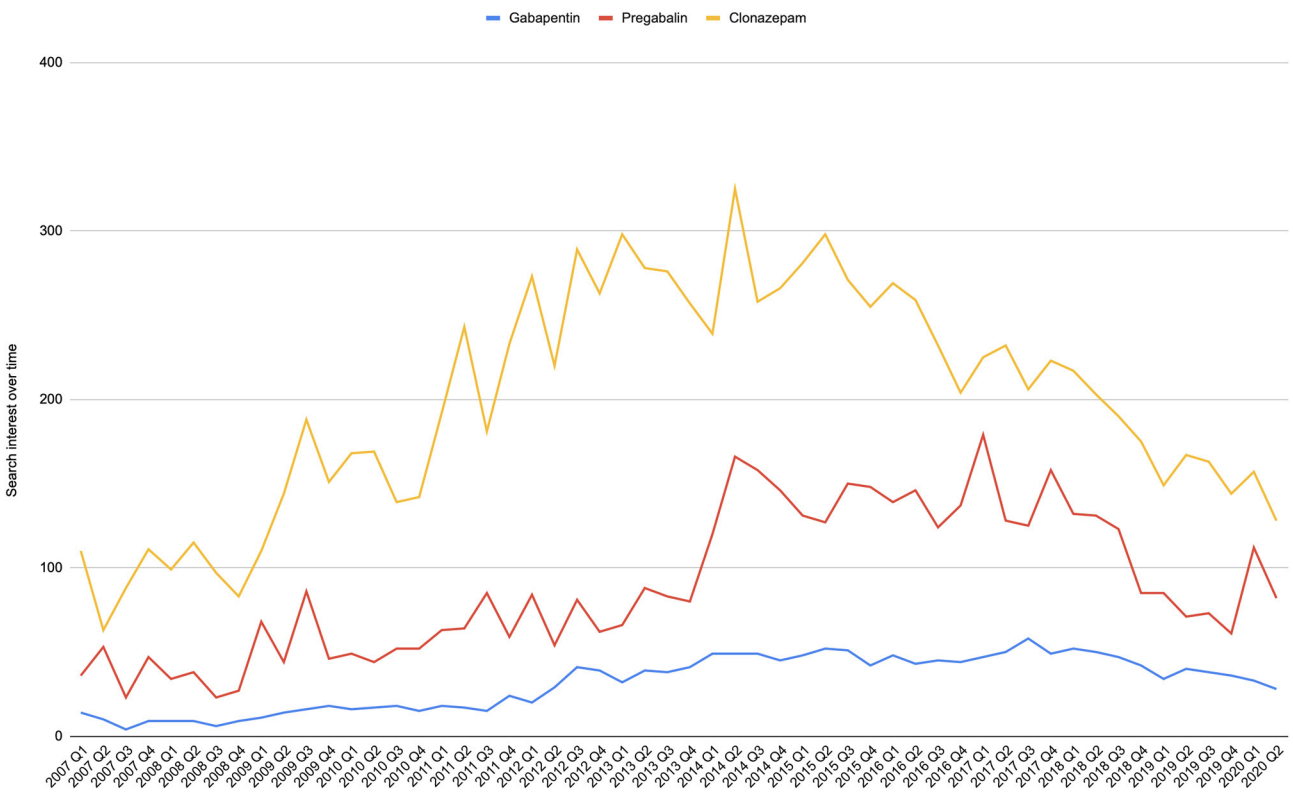

FIGURE 2 | Search interest over time for abuse-related terms in the search analytics domain. For the period 2007Q1 to 2020Q2, the search interest over time for abuse-related terms is represented in timelines for each drug and is expressed as quarterly relative search volume for overall abused-linked terms.

TABLE 2 | Number of reports and ROR & 95% CI related to drug abuse per drug.

	Pregabalin (*N* = 107,905)	**Gabapentin (*N* = 102,386)**	**Levetiracetam (*N* = 43,842)**	**Clonazepam (*N* = 55,856)**
Drug abuse and dependence (*N* = 118,980)	ROR 2.78 95% CI [2.70–2.86]; *N* = 4,558	ROR 1.83 95% CI [1.76–1.90]; *N* = 2,924	ROR 1.10 95 %CI [1.02–1.18]; *N* = 767	ROR 4.47 95% CI [4.32–4.62]; *N* = 3,700
Drug withdrawal (*N* = 28,149)	ROR 3.76 95% CI [3.56–3.96]; *N* = 1,463	ROR 2.09 95% CI [1.95–2.25]; *N* = 796	ROR 1.54 95 % CI [1.36–1.74]; *N* = 254	ROR 4.81 95% CI [4.51–5.13]; *N* = 976
Overdose (*N* = 85,274)	ROR 1.69 95% CI [1.61–1.76]; *N* = 2,053	ROR 1.65 95% CI [1.57–1.72]; *N* = 1,904	ROR 1.98 95% CI [1.86–2.11]; *N* = 979	ROR 4.29 95% CI [4.12–4.46]; *N* = 2,588
Drug tolerance (*N* = 1,965)	ROR 4.73 95% CI [3.96–5.66]; *N* = 128	ROR 3.76 95% CI [3.07–4.61]; *N* = 98	ROR 0.78 95% CI [0.40–1.49]; *N* = 9	ROR 6.94 95% CI [5.66–8.51]; *N* = 98
Euphoria-related events (*N* = 280,097)	ROR 2.87 95% CI [2.81–2.93]; *N* = 10,664	ROR 2.09 95% CI [2.04–2.14]; *N* = 7,644	ROR 1.27 95% CI [1.22–1.33]; *N* = 2,077	ROR 2.41 95% CI [2.33–2.48]; *N* = 4,765

Each drug has been compared with all other drugs in the FAERS database. The study population consisted of 6993352 reports.

EudraVigilance database, adverse drug reactions were more frequently reported for pregabalin use compared to gabapentin (23). Pharmacovigilance data from FAERS have also shown adverse drug events from pregabalin use and in general gabapentinoid abuse with a prevalence in young and male individuals (10). In contrast, from the EudraVigilance database review, there were adverse drug reaction reports related to abuse/dependence and misuse of pregabalin and gabapentin with a prevalence in female adults (9). The last decade, apart from gabapentinoid abuse there has also been reported extended misuse, with a greater potential of misuse for pregabalin (9). The misuse of pregabalin has been strongly linked to its

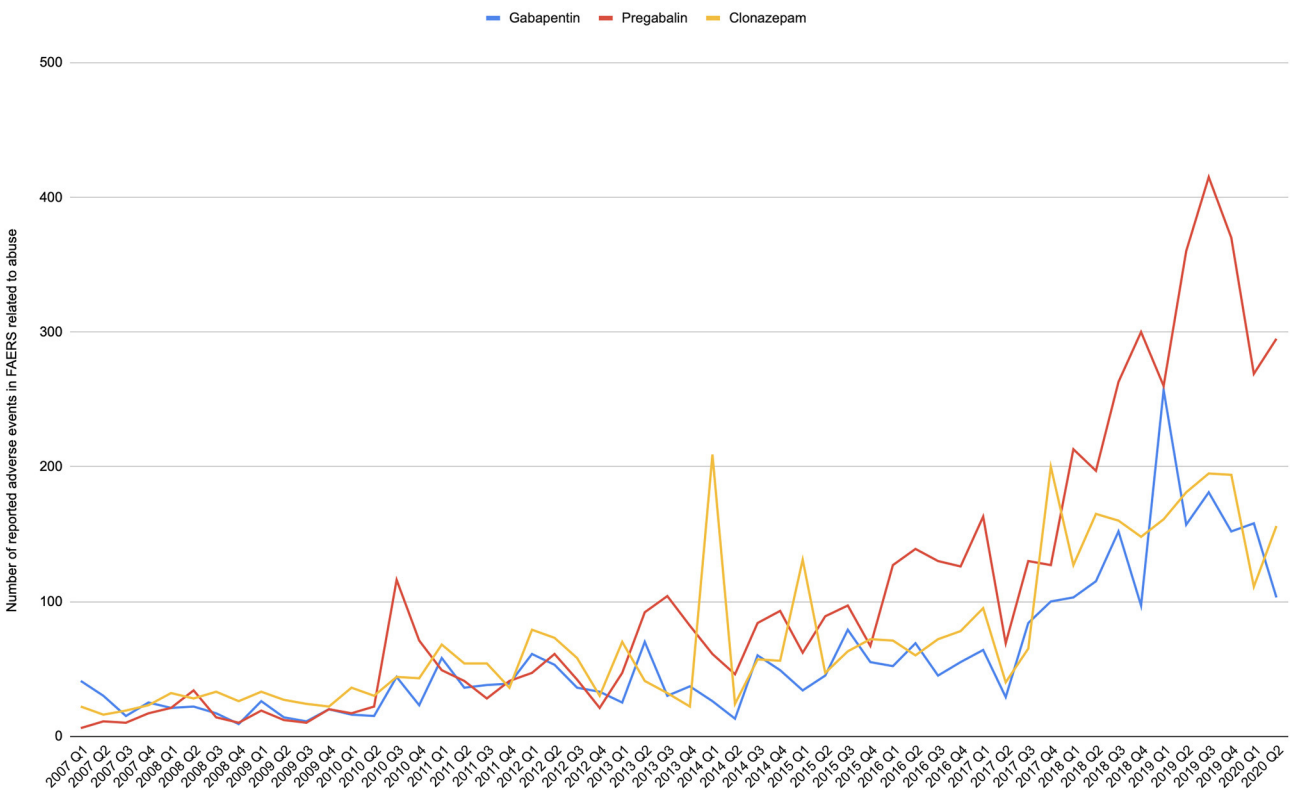

FIGURE 3 | Number of reported adverse events in the FAERS database related to abuse.

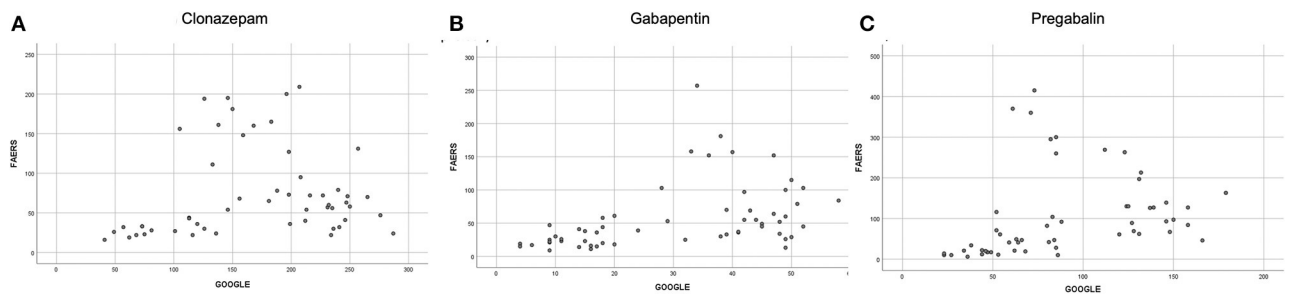

FIGURE 4 | Correlation between FAERS and Google searches for **(A)** clonazepam ($r = 0.295$; $p = 0.030$); **(B)** gabapentin ($r = 0.558$; $p < 0.001$); **(C)** pregabalin ($r = 0.587$; $p < 0.001$).

strong sedative and psychedelic effects. It has been stated that pregabalin misuse is more likely to occur in new users (24). Besides being considered as less powerful than pregabalin, gabapentin misuse was also associated with similar psychedelic effects. A few substances have been reported for misuse in combination with gabapentin, such as cannabis, alcohol, selective serotonin reuptake inhibitors (SSRIs), LSD, amphetamine, and gamma-hydroxybutyrate (GHB) (8, 25). There is agreement from other studies that the majority of individuals that have been reported for pregabalin abuse have a history of other substance and medication abuse as well (11, 26). The differences in the pharmacokinetic and pharmacodynamic profile of the gabapentinoids should be carefully examined in order to understand pregabalin's higher abuse potential compared to gabapentin (11, 25).

Signals in the Google Analytics Domain

The Google search analytics data are big data. Their volume, velocity, and variety are far beyond any other dataset of collected data, such as the adverse event reports. While they

cannot be considered as a safe source for safety signals, their recognition of the potential is rising (27), and their use in pharmacovigilance is emerging. A recently published study of the French Addictovigilance Network combined Google Trends with the analysis of the global database of individual case safety reports (VigiBase) (28). Our team has recently published this method of combining different data sources of drug safety surveillance, Google search analytics, and disproportionality analysis of the US FAERS database (12) to detect safety signals. Data from this timeline series from 2004Q1 to 2017Q2 revealed a consistent association of abuse-related searches in the Google search engine with the antidepressant mirtazapine, and a similar pattern of association between abuse-related events and the drug was found in FAERS. The results of this previous study already suggested that search analytics and disproportionality analysis of FAERS may be used combined as a supplementary pharmacovigilance tool. Signals of gabapentinoid abuse found agreed with the signals for the positive and negative control drugs (clonazepam and levetiracetam). The generic pattern for FAERS was clonazepam $\geq$ pregabalin $\geq$ gabapentin $\geq$ levetiracetam. The Google domain pattern was slightly different: clonazepam $\geq$ gabapentin $\geq$ pregabalin $\geq$ levetiracetam. This difference can be explained by the fact that gabapentin was first approved for use in 1993 and in 2018 it was the eleventh most commonly prescribed medication in the United States, with more than 46 million prescriptions in 2018 and an increasing number of prescription over time (5). On the other hand, pregabalin (FDA approved in 2004) had an estimated number of 11.5 million prescriptions in 2018 in the United States being in ranking 70th among the most commonly prescribed medication (4). It should also be noted that disproportionality analysis cannot quantify the true risk, which should also be the case for the Google domain (29).

Correlation Between the Domains

A significant monotonic correlation was found between FAERS and Google searches for gabapentin ($r = 0.558$; $p < 0.001$), pregabalin ($r = 0.587$; $p < 0.001$), and clonazepam ($r = 0.295$; $p = 0.030$). This relationship between two totally different domains indicates that when one of the values changes in one domain, there is a significant probability to change in the same way in the other domain. Thus, changes of abuse-related searches on Google for pregabalin, gabapentin, or clonazepam are accompanied by analogous changes of abuse-related events in FAERS and vice versa. There is no causality on this fact but, rather, a similar behavior of two data domains. Interestingly, there were not enough big data volumes for levetiracetam to develop the timelines and, thus, no comparison could be made.

Study Limitations

Our study has some methodological considerations and limitations. Disproportionality analysis cannot differentiate between recreational, self-treatment, or mixed type of abuse; however, it is a suitable tool to quantitate signals of abuse of known and novel psychoactive substances. Further, the causal relationship between drugs and the adverse event (abuse) cannot be verified without a clinically performed causality assessment, while confounders as comorbidity and concomitant drugs cannot also be assessed properly. Regarding search analytics, since Google only reports large datasets, terms such as dependence, tolerance, and misuse have not provided substantial numbers and were not included in the analysis. In addition, the algorithms and their updates utilized by Google to analyze data are not publicly available. Finally, there were not enough data volumes before 2007.

CONCLUSION

Concluding, the present study revealed a safety signal for the abuse potential of pregabalin and gabapentin using two different methods of surveillance, the FAERS database analysis and big data search analytics. We suggest that these methods can be used in combination as a supplementary pharmacovigilance tool to detect drug safety signals.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: http://openvigil.sourceforge.net/.

AUTHOR CONTRIBUTIONS

GP: project development and manuscript writing and editing. DS and SS: data collection, data analysis, and manuscript drafting. NP and IT: data analysis and manuscript editing. AG: review of the final manuscript. All authors contributed to the article and approved the submitted version.

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