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An Insight into Z-Drug Abuse and Dependence: An Examination of Reports to the European Medicines Agency Database of Suspected Adverse Drug Reactions

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Abstract

Background: Although originally marketed as safe alternatives to the habit-forming benzodiazepines, growing numbers of zaleplon, zolpidem, and zopiclone ("Z-drugs") clinical concerns relating to their potential of abuse, dependence, and withdrawal have been reported over time. We aimed here at assessing these issues analyzing datasets of adverse drug reactions provided by the European Medicines Agency through the EudraVigilance system.
Methods: Analyzing the adverse drug reactions databases of each Z-drug, descriptive analyses have been performed on cases and proportional reporting ratios (PRRs) computed.
Results: An overall number of 33 240 (e.g., 23 420 zolpidem; 9283 zopiclone; and 537 zaleplon) misuse-, abuse-, dependence-, and withdrawal-related adverse drug reactions, corresponding to some 6246 unique patients given Z-drugs, were here identified. Cases were studied and described, including demographic characteristics and clinical data such as concomitant drugs, doses, routes of administration, and outcomes of the reactions (being fatalities recorded). Considering PRR values and in comparison with zopiclone, zolpidem was more frequently involved in both misuse/abuse and withdrawal issues. Zolpidem and zopiclone presented with the same dependence risk, but zopiclone was most involved in overdose adverse drug reactions. Compared with zaleplon, zopiclone presented higher dependence and overdose-related issues but slightly lower misuse/abuse and withdrawal PRR values.
Conclusion: Current data may only represent a gross underestimate of the real prevalence of Z-drug misuse. Caution should be exercised when prescribing those molecules, especially for patients with psychiatric illnesses and/or history of drug abuse. We recommend the need to invest in proactive pharmacovigilance activities to better and promptly detect, understand, and prevent any possible misuse potential of prescribed medications.

Keywords: adverse drug reactions, Z-drugs, zolpidem, zaleplon, zopiclone, EMA

Introduction

Although sharing with benzodiazepines a similar mechanism of action, the non-benzodiazepine hypnotics zaleplon, zolpidem, and zopiclone ("Z-drugs") appeared on the market as safe substitutes for benzodiazepines, purportedly having both a reduced abuse potential and propensity to tolerance and withdrawal due to improved pharmacokinetics (Gunja, 2013). Despite

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Significance Statement

Although originally marketed as safe alternatives to the habit-forming benzodiazepines, growing concerns about zaleplon, zolpidem, and zopiclone ("Z-drugs") abuse, dependence, and withdrawal issues have been reported over the the last decade. The analysis of Z-drug related misuse, abuse, dependence, and withdrawal cases collected by the European Medicines Agency (EMA) EudraVigilance (EV) database here provided provides firm and large-scale evidence that Z-drugs may be abused for recreational purposes. Physicians should prescribe Z-drugs with caution, especially to vulnerable clients.

such expectations, many cases of misuse, abuse, dependence, and death involving Z-drugs have been reported over the last decade or so (Atkin et al., 2018).

Clinical Pharmacological Issues

Z-drugs are GABA-A receptor modulators chemically unrelated to benzodiazepines approved for the short-term management of insomnia disorders (NICE, 2004) due to their hypnotic effects by reducing sleep latency and improving sleep quality (Nutt and Stahl, 2010). Like benzodiazepines, Z-drugs are agonists of the GABA receptor complex and therefore enhance GABA-mediated neuronal inhibition. However, their binding selectivity and pharmacokinetic profiles have been reported to minimize the possibility of side-effects similar to those produced by benzodiazepines, for example, next day sedation, dependence, and withdrawal (NICE, 2004).

Among Z-drugs, zopiclone was the first compound developed, binding with high affinity and functional potency the benzodiazepine receptor complex. With an absorption time of about 2 hours and an elimination half-life of 4 to 5 hours, its clinical use is in the 3.75- to 7.5-mg dosage range (EMC, 2017). Zolpidem is an imidazopyridine with an oral bioavailability of 70% and an elimination half-life of 2.5 hours (NICE, 2004; Nutt and Stahl, 2010). It is normally indicated at 10-mg dosages (Victorri-Vigneau et al., 2007). Zaleplon is a rapidly absorbed pyrazolopyrimidine with an elimination half-life of 1 hour (NICE, 2004). Zaleplon use at a 5- to 20-mg dosage is currently indicated for use only in patients with initial insomnia, and an extended-release formulation is in development (Ebert et al., 2006). Z-drug treatment should usually vary from a few days to 2 weeks with a maximum of 4 weeks, including tapering-off where appropriate.

Misuse, Abuse, Dependence, and Withdrawal Issues

Despite the reported lack of tolerance and dependence (Lader, 1992; Voderholzer et al., 2001; Zammit, 2009), the occurrence of both rebound insomnia (Lader, 1992; Ebert et al., 2006) and withdrawal symptoms after a therapeutic dosage abrupt discontinuation of Z-drugs has been described, and especially so in alcohol-dependent and drug-abusing patients (Ayonrinde and Sampson, 1998; Hajak, 1999; Hajak et al., 2003; Johansson et al., 2003; Ebert et al., 2006; Zammit, 2009; Morinan and Keaney, 2010). Furthermore, a range of case series and postmarketing surveillance studies have given rise to growing clinical concerns among clinicians (Victorri-Vigneau et al., 2014), suggesting that the prevalence of Z-drug misuse issues could have been underestimated compared with benzodiazepines (Zammit, 2009). Z-drug withdrawal symptoms, typically associated with the abrupt cessation of long-term, high-dosage intake, may include insomnia, anxiety, euphoria irritability, tremor, inner restlessness, speech difficulties, abdominal pain, hypertension, tonic-clonic seizures, and confusion/disorientation/delirium (Aranko et al., 1991; Wong et al., 2005; Flynn and Cox, 2006). The use of either idiosyncratic routes of administration (e.g., injecting) or the intake of high dosages may well increase the risk of Z-drug abuse (Victorri-Vigneau et al., 2007). Drug misusers may be attracted by Z-drugs because they are not typically monitored during drug treatment programs (Sikdar and Ruben, 1996; Rooney and O'Conner, 1998; Gunja, 2013; Ott et al., 2017; Schifano et al., 2018).

Z-Drug Current Regulation, Near Misses, and Fatalities

According to the World Health Organization, the occurrence of zolpidem abuse and dependence would be similar to that of benzodiazepines and, different from zopiclone and zaleplon, in 2001 this molecule was placed in the same schedule of benzodiazepines (UNODC, 2001). Conversely, in 2013 the UK's Advisory Council on the Misuse of Drugs concluded that zaleplon and zopiclone should be controlled in the same manner as zolpidem. Overall, zaleplon tends to be reported as the least misused, and zopiclone and zolpidem are both identified as the most misused (ACMD, 2013).

To assess the Z-drug misuse-, abuse-, dependence-, and withdrawal-related issues, our study aimed at analyzing the related European Medicines Agency (EMA) EudraVigilance (EV) databases, collecting the voluntary reports of suspected ADRs for all medicinal products authorized in the European Economic Area (EEA).

Methods

The European pharmacovigilance system and its functions of detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) or any other drug-related problem have been improved in parallel with the 2012 pharmacovigilance legislation (EMA, 2016a; Sessa et al., 2018). The EMA is responsible for the safety monitoring of medicines operating through EV, a system managing and analyzing information on suspected ADRs to medicines that have been authorized in the EEA (EMA, 2016a), although reports are received from non-EEA countries as well (for a better understanding of the EMA organization of data collection, please refer to the supplementary material).

To assess Z-drug misuse issues, a formal request was sent to EMA for all misuse, abuse, dependence, and withdrawal Z-drug-related data. The Individual Case Safety Reports were identified considering the Preferred Terms (PTs) mentioned. The request included the following PTs: "drug abuse," "intentional product misuse," "drug dependence," and "withdrawal syndrome" or all the PTs included in the broad Standardised MedDRA Queries "Drug abuse, dependence and withdrawal" (MedDRA, 2018). The level 2A EV frequency table and line listing of the requested ADRs were here retrieved. Level 2A access meant that cases were provided with general information (e.g., sender, type of report, reporter qualification), some anonymized patient information, reaction (event) information with its outcome, and

drug-related information (e.g., start date, duration, dose, pharmacological form, route of administration) (see also EMA, 2018). In the EV database, each individual patient had a code (EV local number) for unequivocal identification. ADR numbers differed from those referring to single patients, since different reporters/senders could have independently flagged the same ADR to EMA. Conversely, several ADRs (involving various organ classes, hence identified with specific PTs) relating to the searched ADR (e.g., abuse, misuse, dependence, and withdrawal) could have been reported as well for the same patient (HMA EMA, 2017). The zolpidem, zopiclone, and zaleplon data analysis referred to a range of parameters, including sociodemographic characteristics (age and sex), source/reporter country (EEA or non-EEA) and reporter qualification (i.e., pharmacist, physician), ADR outcome (fatal, recovered, resolved), drug dosages, and possible concomitant drug(s). The analysis included cases of abuse/misuse/dependence and withdrawal ADRs, focusing on fatalities as well. Suicides were here reported as "suicide attempt," "suicidal behaviour," and "intentional self-injury"; conversely, "suicidal ideation," and "overdose" (including intentional) were not included (MedDRA, 2018). The ADRs considered here were, per se, voluntary and unsolicited communications reported by both Regulatory Authorities of the EU Member States where the reaction occurred, and/or by the Marketing Authorisation Holders for those ADRs occurring outside the EEA. Within the Standardised MedDRA Queries drug abuse, dependence, and withdrawal section, the following adverse reactions were identified: dependence, drug abuser, drug diversion, drug use disorder, drug withdrawal convulsions, drug withdrawal headache, drug withdrawal syndrome, intentional overdose, intentional product misuse, intentional product use issue, overdose, prescription drug use without prescription, product use in unapproved indication, product use issue, substance use disorder, substance abuser, and withdrawal syndrome. "Misuse" was here meant to be the "intentional use for a therapeutic purpose by a patient or consumer of a product, over-the-counter or prescription, other than as prescribed or not in accordance with the authorised product information." Conversely, "abuse" was defined here as the "intentional, non-therapeutic use by a patient or consumer of a product, over-the-counter or prescription, for a perceived reward or desired non-therapeutic effect including, but not limited to, getting high (euphoria)." The term "addiction," typically replaced by "dependence," is the "overwhelming desire by a patient or consumer to take a drug for non-therapeutic purposes together with inability to control or stop its use despite harmful consequences." Finally, "withdrawal" referred here to "a substance-specific syndrome which follows cessation or reduction in the intake of a psychoactive substance previously regularly used" (MedDRA, 2018). Those ADRs that were listed as "suspect drug," meaning that the reporter suspected this drug and not the concomitant medicine(s) to have caused the index ADR (EMA, 2016a), were here included.

The proportional reporting ratio (PRR) approach, defined as "the ratio between the frequency with which a specific adverse event is reported for the drug of interest (relative to all adverse events reported for the drug) and the frequency with which the same adverse event is reported for the drug(s) in the comparison group (relative to all adverse events for drugs in the comparison group)," was here considered (EMA EV-Ewg, 2006). A PRR >1 suggests that the adverse event is more commonly reported for individuals taking the drug of interest relative to the comparison drug(s), whereas if the PRR value is <1, there is a disproportion of reporting in the sense that the specific event is less frequently reported in association with the suspect drug than with the others. The PRR confidence intervals were here computed as well, indicating with PRR– and PRR+, respectively, the lower and upper bounds of the 95% confidence interval (EMA EV-Ewg, 2006; for a better understanding of the PRR calculation, please refer to the supplementary material).

Ethics

Because of EMA protection of privacy and integrity of individuals, data relating to patients affected were fully and completely deidentified/anonymized; therefore, it was not possible at all to derive from such data the names of the individuals affected by the ADR, not even their country or town. Hence, per definition, the need to obtain their informed consent was here not applicable. Moreover, certain data elements (e.g., names/identifiers of individuals involved; country-specific information, nationally authorized products, etc.) were not disclosed (EMA, 2016b).

The study has been ethically approved by the University of Hertfordshire Ethics Committee, with reference number LMS/PGR/UH/03234 (March 5, 2018).

Results

Zaleplon ADRs

Overall, the number of the EMA 2003 to 2017 zaleplon ADRs collected by was 4270 (Table 1). Of the total number of ADRs, those relating to misuse, abuse, dependence, and withdrawal issues and judged by the reporter as "suspect" were 537 (12.58%), with "intentional overdose" being the most represented (51.9%). Most ADRs were reported by physicians from non-EEA countries (53.2%), while pharmaceutical companies were the most typical (58.6%) reporting agencies. Typically, these ADRs involved adult (18–64 years old) females. A lone Z-drug ingestion was reported in 33/112 (29.4%) of zaleplon, while a concomitant use of prescription drugs mostly involved antidepressants (19.8%), benzodiazepines (17.8%), and ethanol/other Z-drugs (13.9%) has been described. A nasal atypical intake modality was reported in 7 zaleplon cases. No information of dosage was here provided.

Finally, a range of suicide-related ("suicide attempt" and "suicidal ideation") ADRs were reported (13.6% and 5.21%, respectively).

Zolpidem ADRs

Of the total number of zolpidem ADRs (206 315), those relating to misuse-abuse-dependence-withdrawal issues and judged by the reporter as "suspect" were 23 420 (11.35%) (Table 1). Most ADRs were reported by physicians from non-EEA countries (49.7%), pharmaceutical companies having been the most typical (41.3%) reporting agencies. "Drug use disorder" (40.0%), "overdose" (23.7%), and "intentional overdose" (16.7%) were the most represented ADRs. Typically, these ADRs involved adult (18–64 years old) females. A lone Z-drug ingestion was reported in 1856/4374 (42.4%) zolpidem cases, while a concomitant use of prescription drugs was reported, mostly involving antidepressants (26.6%), benzodiazepines (19.0%), and opiates/opioids (14.2%). Moreover, a range of recreational drugs was identified, specifically alcohol (174 cases), cocaine (30 cases), amphetamines (21 cases), and cannabis (13 cases). Atypical intravenous (22 cases), nasal (5 cases), and sublingual (1 case) intake modalities were here reported for zolpidem. Dosages were higher than 20 mg in 7371 ADRs, in 6234 of these cases, the dosage was above 100 mg, and in 20 ADRs (7 cases) it was in excess of 2000 mg. Finally, a range of suicidal

Table 1. Number of EMA Database Z-Drug Misuse-, Abuse-, Dependence-, and Withdrawal-Related ADRs (2003–2017)

	Zaleplon	Zopiclone	Zolpidem
Total no. ADRs	4270	65 140	206 315
Suspect abuse-, misuse-, dependence-, or withdrawal-related ADRs	537 (12.58%) (IC 95%: 11.60–13.61%)	9283 (14.25%) (IC 95%: 13.98–14.52%)	23 420 (11.35%) (IC 95%: 11.21–11.49%)
No. of unique patients	112	1760	4374
Gender most typically represented	F (F/M ratio: 3.9)	F (F/M ratio: 1.09)	F (F/M ratio: 1.6)
Age range (y) most typically represented	18–64 (39%)	18–64 (68%)	18–64 (65.7%)
ADRs most typically represented	Intentional overdose (51.9%), overdose (14.1%), drug use disorder (11.4%)	Intentional overdose (29.9%), overdose (23.1%), drug use disorder (23.1%)	Drug use disorder (40.0%), overdose (23.7%), intentional overdose (16.7%)
Concomitant drugs most typically represented	Antidepressants in 20/101 (19.8%) cases, benzodiazepines in 18/101 (17.8%) cases, ethanol/other Z drugs in 14/101 (13.9%) cases	Benzodiazepines in 891/4374 (20.4%) cases, antidepressants in 658/4374 (15.0%) cases, antipsychotics in 475/4374 (10.9%) cases	Antidepressants in 468/1760 (26.6%) cases, benzodiazepines in 334/1760 (19.0%) cases, opiates/opioids in 250/1760 (14.2%) cases

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; EMA, European Medicines Agency.

behavior-related ADRs was reported for zolpidem, including "intentional self-injury" (102/23 420: 0.5%), "suicidal behavior" (44/23 420: 0.2%), and "suicide attempt" (3101/23 420: 13.2%). The rates of ADRs with a fatal outcome were higher for zolpidem (20.3%) compared with both zopiclone (9.33%) and zaleplon (1.1%).

Zopiclone ADRs

As for zaleplon and zolpidem, most zopiclone-related ADRs were reported by physicians from non-EEA countries (45.8%), with pharmaceutical companies having been the most typical (51.4%) reporting agencies. Of the total number of ADRs (65 140), those relating to misuse-abuse-dependence-withdrawal issues and judged by the reporter as "suspect" were 9283 (14.25%) (Table 1), with the most represented ADRs including: "intentional overdose" (29.9%), "overdose" (23.1%), and "drug use disorder" (23.1%). Typically, these ADRs involved adult (18–64 years old) females. A lone zopiclone ingestion was reported in 416/1760 (23.6%) cases; as for zaleplon and zolpidem, a concomitant use of prescription drugs was reported, mostly involving benzodiazepines in 891/4374 (20.4%) cases, antidepressants in 658/4374 (15.0%) cases, antipsychotics in 475/4374 (10.9%) cases, and opiates/opioids in 131/4374 cases (2.99%). Moreover, a range of recreational drugs was identified (e.g., cannabis in 12 cases, cocaine in 6 cases, methamphetamines in 1 case), and intravenous and subcutaneous intake modalities were reported as well. Finally, as for zolpidem, a range of suicidal behavior-related ADRs was reported, including "intentional self-injury" (111/9283:1.2%), "suicidal behavior" (43/9283: 0.5%), and "suicide attempt" (2526/9283: 27.2%). When dosages were reported, levels in excess of 15 mg were described in 577 (360 individuals) of zopiclone cases, including 205 ADRs (120 cases) where the dosage ingested was in the 450- to 2250-mg range.

Analysis of the PRR Values

Considering the PRR values (Tables 2 and 3), compared with zopiclone, zolpidem was more involved in both misuse/abuse and withdrawal issues, while zopiclone was more involved in overdose ADRs. Conversely, zolpidem and zopiclone presented with the same dependence risk. If compared with zaleplon, zopiclone and zolpidem presented higher dependence and withdrawal, but slightly lower misuse/abuse and withdrawal, PRR values. Lower and upper bounds of the PRR confidence interval are reported in Table 3.

Discussion

To the best of our understanding, this paper is the first to provide uniquely systematic data in terms of identification and analysis of zolpidem, zopiclone, and zaleplon misuse, abuse, dependence, and withdrawal issues. The present data were extracted from a high-quality, large-scale, pharmacovigilance database such as the EMA's EV. Together with the World Health Organization's Drug Monitoring Program, the EV database is considered a worldwide reference standard (Schifano and Chiappini, 2018). Most literature papers, so far, were based on small case series/single case studies (Aranko et al., 1991; Sikdar and Ruben, 1996; Rooney and O'Conner, 1998; Wong et al., 2005; Flynn and Cox, 2006; Chiaro et al., 2018). Conversely, current findings referred to overall much larger (e.g., 33 240 ADRs; corresponding to some 6246 unique cases) numbers of patients presenting with Z-drug misuse issues. Indeed, current data may represent only a gross underestimate of the Z-drug misuse issues' real prevalence. In fact, reports were here submitted spontaneously, and levels of misperception that these drugs are safe, which could prevent professionals from reporting, may still be identified (Medsafe, 1998). The analyses of the EV databases confirmed the diversion potential and the possibility of abuse, misuse, dependence, and withdrawal issues related to all Z-drugs (zaleplon, zopiclone, and zolpidem), albeit some differences have emerged within this group. Compared with zaleplon, the misuse/abuse issues seemed here to be lower for zopiclone and zolpidem. Conversely, compared with zopiclone, zolpidem emerged as being more frequently related to misuse or abuse and withdrawal reports; if

Table 2. Z-Drug Misuse-, Abuse-, Dependence-, Withdrawal-, and Overdose-Related ADRs; PRR Computation

Zaleplon ADRs	No of reactions ADRs	Proportion of zaleplon ADRs
Drug abuser (A1) + drug diversion (A2) + drug use disorder (A3) + intentional product use issue (A4) + intentional product misuse (A5) + prescription drug used without prescription (A6) + product use in unapproved indication (A7) + product use issue (A8) + substance abuser (A9) + substance use disorder (A10)	367	0.089
Dependence (A11)	5	0.001
Withdrawal syndrome (A12) + drug withdrawal syndrome (A13) + drug withdrawal headache (A14) + drug withdrawal (A15)	89	0.023
Intentional overdose (A16) + overdose (A17)	76	0.019
Other adverse events (B)	3733	0.868
Total	4270	1.000
Zopiclone ADRs	No of reactions ADRs	Proportion of zopiclone ADRs
Drug abuser (C1) + drug diversion (C2) + drug use disorder (C3) + intentional product use issue (C4) + intentional product misuse (C5) + prescription drug used without prescription (C6) + product use in unapproved indication (C7) + product use issue (C8) + substance abuser (C9) + substance use disorder (C10)	2507	0.043
Dependence (C11)	138	0.002
Withdrawal syndrome (C12) + drug withdrawal syndrome (C13) + drug withdrawal headache (C14) + drug withdrawal (C15)	718	0.013
Intentional overdose (C16) + overdose (C17)	5920	0.096
Other adverse events (D)	55 857	0.846
Total	65 140	1.000
Zolpidem ADRs	No of reactions ADRs	Proportion of zolpidem ADRs
Drug abuser (E1) + drug diversion (E2) + drug use disorder (E2) + intentional product use issue (E4) + intentional product misuse (E5) + prescription drug used without prescription (E6) + product use in unapproved indication (E7) + product use issue (E8) + substance abuser (E9) + substance use disorder (E10)	9744	0.050
Dependence (E11)	423	0.002
Withdrawal syndrome (E12) + drug withdrawal syndrome (E13) + drug withdrawal headache (E14) + drug withdrawal (E15)	2433	0.018
Intentional overdose (E16) + overdose (E17)	10 820	0.056
Other adverse events (F)	182 895	0.874
Total	206 315	1.000

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

Table 3. Z-Drug PRR Values

	PRR Zolpidem vs Zaleplon (PRR– and PRR+)	PRR Zopiclone vs Zaleplon (PRR– and PRR+)	PRR Zolpidem vs Zopiclone (PRR– and PRR+)
Misuse/abuse ADRs	0.57 (0.55–0.59)	0.48 (0.43–0.53)	1.16 (1.11–1.21)
Dependence ADRs	2.00 (0.82–4.8)	2.00 (0.81–4.80)	1.00
Withdrawal ADRs	0.79 (0.76–0.81)	0.56 (0.29–1.06)	1.38 (1.27–1.49)
Overdose ADRs	2.90 (2.31–3.60)	5.00 (4.00–6.2)	0.58 (0.56–0.60)

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

compared with zaleplon, zolpidem was more frequently related to dependence and overdose reports. Among Z-drugs, zolpidem was the most frequently reported in the EV dataset, being associated with intravenous administration, very high dosage consumption, and concomitant use of recreational drugs. These data are consistent with previous suggestions (Griffiths and Johnson, 2005; Rousselet et al., 2017) and recent reports based on both zolpidem-related falsified prescription rates in France (Jouanjus et al., 2018) and clinical dependence issue data from an Indian tertiary care center (Shukla et al., 2017). Overall, zaleplon ADRs were numerically lower than zopiclone- and zolpidem-related ADRs and less frequently associated with both idiosyncratic/atypical ways of administration and concomitant recreational drug intake. Hence, one could tentatively identify in zaleplon the relatively (Desousa, 2009; Paparrigopulos et al., 2008) "most safe" Z-drug. A full comparison among Z-drugs should, however, consider as well the precise worldwide prescription figures, which could serve as a proper denominator. Indeed, within the Z-drug group, one could argue that zaleplon may present with the lowest availability levels due to its higher purchase costs (NICE, 2004). Regarding zopiclone use, Jaffe et al. (2004) assessed its use among 297 drug addicts who had been consecutively admitted to addiction treatment centers in the United Kingdom. It emerged that more than half had used zopiclone, which ranked fourth after diazepam, temazepam, and nitrazepam. About 80% of zopiclone users had obtained the drug through a prescription, but 42% reported having purchased it on the streets (Jaffe et al., 2004). Analyzing the misuse patterns of benzodiazepine

and Z-drug users, Kapil et al. reported that 29.6% had ever misused them, with 40.5% of individuals misusing at least 2 of these medications. Diazepam (53.4%) and zopiclone (24.1%) were the most frequently reported medications, with decreasing numbers of individuals misusing lorazepam (22.4%), alprazolam (17.2%), zaleplon (11.2%), nitrazepam (10.3%), phenazepam (7.8%), and zolpidem (5.2%). Moreover, iUsing data from a health insurance reimbursement database, which collects information from 77% of the French population, Ponté et al. (2018) assessed the extent and risk of opioid analgesic abuse related to benzodiazepines and hypnotics; they considered both the molecules' Doctor Shopping Quantity (intended to assess the extent of abuse) and the Doctor Shopping Index (DSI; intended to identify a signal of abuse). Interestingly, they found that the Doctor Shopping Quantity of anxiolytics and hypnotics (influenced by their large availability levels) was 10 times higher than that of opioids. Conversely, the DSI of opioids (2.79%) was higher than that of both hypnotics (2.06%) and anxiolytics (1.81%). Among benzodiazepines, flunitrazepam and zolpidem presented with the highest DSI values (13.2% and 2.2%, respectively) (Ponté et al., 2018). Overall, higher levels of physical and compulsive signs of dependence with zolpidem, rather than with zopiclone (Griffiths and Johnson, 2005; Rousselet et al., 2017; Ponté et al., 2018), have been described.

Current Z-drug data are consistent with the new trends in prescription drug misuse (Throckmorton et al., 2018), which is at times occurring within the context of the rising levels of novel psychoactive substances misuse (Schifano et al., 2018). It is, however, concerning that a range of other prescription and recreational psychotropics were here identified in combination with Z-drugs, including antidepressants, benzodiazepines, antipsychotics, other Z-drugs, opiates/opioids, alcohol, cannabis, cocaine, methamphetamine, and ketamine. The present data may support previous hypotheses, for example, that there may be 2 subsets of individuals misusing Z-drugs; the first group may include patients with psychiatric comorbidities (Zammit, 2009; Lin et al., 2017), who were originally started with these molecules for insomnia but who developed tolerance and withdrawal phenomena, therefore requiring increasing dosages overtime (Griffiths and Johnson, 2005); and the second population may include young people, who are ingesting large Z-drug dosages in combination with other recreational compounds and through idiosyncratic intake modalities (Sikdar and Ruben, 1996; Ayonrinde and Sampson, 1998; Rooney and O'Conner, 1998; Hajak, 1999; Johansson et al., 2003), which can increase the drug bioavailability levels (Victorri-Vigneau et al., 2007) and hence facilitate achieving better euphoria.

Fatalities were here reported for all Z-drugs, although this typically occurred mostly with zolpidem and zopiclone, both typically ingested in a poly-drug misuse scenario, thus confirming previous reports (Garnier et al., 1994; Casula et al., 2013; Gunja, 2013). The comparatively low levels of zaleplon toxicity/fatalities here identified could, however, be associated with the molecule's ultra-short half-life and rapid antemortem metabolism, which can affect its detection (Gunja, 2013). Mortality from Z-drugs may be similar to that of benzodiazepines (Garnier et al., 1994; Reith et al., 2003). A UK study on zopiclone-related deaths (Buckley and McManus, 2004) found that the zopiclone fatal toxicity index was similar to that of zolpidem but lower compared with flurazepam, flunitrazepam, temazepam, triazolam, and nitrazepam. It is of interest to note that a number of suicidal behavior-related ADRs (e.g., suicide attempts, suicidal ideation) were here identified, and especially so for both zolpidem and zopiclone. This confirms previous findings, suggesting increasing levels of suicidal ideation, suicide attempts, and suicide risk in patients administered with Z-drugs (Brower et al., 2011; MCCall et al., 2017).

Limitations

The number of any given compound-related ADRs may not reflect the full extent of the molecule's potential of misuse. In fact, levels of reporting, which is voluntary in nature, depend on the index molecule clinician's awareness of safety concerns, its market availability levels, and extent of use. Furthermore, a Z-drug illicit market exists (Kapil et al., 2014), further complicating the computation of a reliable, Z-drug availability level denominator. The ADRs reports presented with missing data, such as the dosages ingested and the background diagnosis. Based on the current reporting rules in the EEA, report duplications were possible as well, that is, the same ADR could be reported by different healthcare professionals. To mitigate this issue, however, the number of individual cases was unequivocally identified through a code number. Finally, suspected ADRs do not conclusively prove causality between a specific drug and a given ADR; the ADR may be a symptom of another illness, or it could be associated with another medical product taken by the patient at the same time or caused by their interaction.

Conclusions

In being perceived as more effective and tolerable hypnotics, the level of Z-drug availability has increased over time in parallel with a decrease in benzodiazepine prescriptions (Siriwardena et al., 2006; ACMD, 2013). However, both previous number of anecdotal reports and current data may well suggest that the misuse, abuse, dependence, and withdrawal issues may be associated with the use of all Z-drugs, although zaleplon may present comparatively lower levels of risk. Present data may further support the need to encourage careful prescribing, in line with the UK government's initiative to review the evidence for dependence on, and withdrawal from, prescribed medicines (Pollmann et al., 2015; Kuntz et al., 2017; Gov.uk, 2018). Special caution is here suggested in prescribing Z-drugs to vulnerable clients, for example, inmates, those with psychiatric comorbidities, and recreational drug misusers. To manage clinical Z-drug dependence cases, the use of benzodiazepines (e.g., diazepam or clonazepam), gabapentinoids, trazodone, and quetiapine has been suggested (Mariani and Levin, 2007; Pottie et al., 2018).

Voluntary reporting systems should be improved, with new tools/approaches hopefully to be made available. To assess the abuse potential of centrally active drugs, a range of both premarketing evaluation and proactive postmarketing surveillance activities should be strongly encouraged. A proactive pharmacovigilance may help monitor and anticipate changes in drug abuse, using elements of clinical, epidemiological, basic science, and social science expertise to increase clinicians' awareness of drug safety issues (Throckmorton et al., 2018).

Supplementary Data

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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