Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: http://www.tandfonline.com/loi/ieds20

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To cite this article: Morgane Rousselet, Fanny Feuillet, Marie Gerardin, Pascale Jolliet, Jean-Benoit Hardouin & Caroline Victorri-Vigneau (2017): The French addictovigilance network clinical assessment: Z-drugs, true false twins, Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2017.1346084

To link to this article: http://dx.doi.org/10.1080/14740338.2017.1346084

Accepted author version posted online: 26 Jun 2017.
Published online: 28 Jun 2017.

EXPERT OPINION ON DRUG SAFETY, 2017
https://doi.org/10.1080/14740338.2017.1346084

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ORIGINAL RESEARCH

The French addictovigilance network clinical assessment: Z-drugs, true false twins

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ABSTRACT

Introduction: In France, an addictovigilance network is responsible for evaluating drug dependence, by drawing on pharmacoepidemiological studies, clinical studies and by assessing healthcare professionals' reports on problematic consumption.

Methods: The aim of this study was to determine whether zolpidem and zopiclone have different dependence profiles, based on healthcare professionals' reports, and to identify various consumer dependence profiles among zolpidem users and among zopiclone users. Dependence in reports was assessed using the EGAP scale; a scale developed using the DSM diagnostic dependence criteria.

Results: The comparison of dependence profiles for zolpidem and zopiclone showed differences both in total EGAP score and EGAP item positivity. The descriptive analysis showed that EGAP scores were higher for zolpidem than for zopiclone, suggesting more severe problematic consumption with zolpidem. For zolpidem 2 subpopulations of consumers were identified, with one subpopulation's consumption being more severe than the other, with a significantly higher total EGAP score and more harmful consequences. No subpopulation was highlighted for zopiclone.

Conclusion: These results were in favour of a higher prevalence of physical and compulsive signs of dependence and of harmful consequences of dependence, with zolpidem than with zopiclone.

ARTICLE HISTORY
Received 14 April 2017
Accepted 20 June 2017

KEYWORDS
Dependence profile; epidemiology; safety; zolpidem; zopiclone; Z-drugs

1. Introduction

Zopiclone and zolpidem are two benzodiazepine-like agents also called Z-drugs. They are both indicated in the treatment of occasional or transitory insomnia [1,2]. At the end of phase III clinical trials, no evidence of abuse or dependence potential neither with zolpidem nor zopiclone was reported. Thus, they were considered to be safer than benzodiazepines [3,4]. However, post-marketing data revealed tangible dependence potential for both drugs, and in 2002, zolpidem and zopiclone were added to the list of drugs subject to monitoring by the French Health Products Safety Agency (Agence Nationale de Sécurité du medicament et des produits de santé – ANSM). The French addictovigilance network (FAN) [5], a network of 13 drug dependence evaluation and information centers (Centres d'Evaluation et d'Information sur la Pharmacodependence – Addictovigilance – CEIP-A) throughout France, was asked to manage monitoring under the responsibility of the ANSM. Three investigation periods were requested. As a result of the first investigation period (1993–2003), a reference to the risk of dependence with Z-drugs was added to the French summary of product characteristics for zolpidem and zopiclone in 2004. Following the second (2003–2010) and the third investigation periods (2010–2013), the national committee for narcotics and psychotropic drugs suggested adding zolpidem on the list of drugs subject to special prescription [6]. Recent publication highlighted the necessity of appropriate use of benzodiazepines and Z-drugs in clinical practice [4].

Investigation of the FAN highlighted a difference between zolpidem and zopiclone users and epidemiological studies attempted to understand these differences. An epidemiological study with reimbursement data on zolpidem and zopiclone from the French health insurance database has already shown a potential difference in drug abuse between zolpidem and zopiclone [7]. In fact, results showed the presence of a problematic user class for zolpidem (with more signs of tolerance and more transgressive behavior in order to obtain the drug) but not for zopiclone. Taking those elements into account, zolpidem and zopiclone do not appear to have similar dependence potential. However, case reports lack homogenous assessment of dependence, and the reimbursement database provides a significant epidemiological overview but lacks clinical data [7]. It is all the more important to clarify the distinctions between zolpidem and zopiclone as public health decisions differ from one drug to another. Moreover, recommendations for use could also differ.

One way to clinically assess the potential dependence profile of zolpidem and zopiclone is by analyzing reports by health-care professionals. Indeed, all health-care professionals (regardless of their field of expertise) are required to anonymously report cases of serious drug abuse and

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Article highlights

- Zopiclone and zolpidem are two benzodiazepines-like agents with different dependence potential
- Zolpidem seems to lead to greater dependence than zopiclone
- Physicians should always keep zolpidem dependence effect in mind
- Increased of the initial doses and transgressive behavior with respect to the manner in which the drug is obtained or used should alert the practitioner.

This box summarizes key points contained in the article.

dependence associated with the use of substances or plants with psychoactive effects (articles R5132-97 to R5132-116 of the French code of public health). These spontaneous notification reports (Nots) are reported to the FAN and are essential in determining 'real-life' drug misuse and abuse. In 2006, the FAN created a tool called EGAP (Echelle de GrAvité de la Pharmacodependance – drug dependence severity scale) in order to homogeneously assess drug dependence severity for the drugs cited in the Nots [8–11]. This tool has recently been validated [12] and allows for clinical comparisons between drug dependence profiles.

Thus, the aim of this study was to determine whether zolpidem and zopiclone have different dependence profiles, based on a clinical assessment (NotS), and to identify various consumer dependence profiles among zolpidem users and among zopiclone users.

2. Methods

2.1. Participants

In this article, we shall not use the customary terms 'population' or 'participants'; instead, we shall use the term 'spontaneous notifications' (NotS), which is the term used by the ANSM to refer to reports of drug abuse or dependence spontaneously declared by health-care professionals to the FAN. A notification is composed of three elements: the patient (age, gender, professional and family situation, medical history, history of abuse or dependence), at least one substance (name of the substance or substances, dosage, duration of consumption), and the substance use disorder (description of the patient's clinical situation). All NotS declared by health-care professionals' involved problematic use of at least one substance.

2.2. Measures

2.2.1. Sociodemographic data

The age and gender of the patients were collected.

2.2.2. Evaluation of drug dependence

For all notifications, practitioners from the FAN filled out the EGAP scale [12]. The EGAP scale was developed on the basis of the DSM IV diagnostic criteria [13] especially for FAN evaluation by the Nantes addictovigilance center. The first seven items were derived from the official definition of drug dependence, whereas the last item (item 8) was added by the panel of experts. The EGAP scale is shown in Figure 1.

The scale evaluates two areas. The first area covers the physical and compulsive signs of dependence (items 1–4): tolerance (item 1); withdrawal symptoms when consumption is stopped, or consumption of another product to avoid these symptoms (item 2); higher dose or duration than initially planned (item 3); and desire or failed attempts to stop (item 4). The second area evaluates the adverse consequences identified in the NotS by the health-care professional (items 5–8): substantial amount of time devoted to consumption (item 5); family, professional, social, legal, or financial difficulties associated with consumption (item 6); persistence of consumption, even though the patient is aware of the consequences of consumption on his/her health (item 7); and transgressive behavior with respect to the manner in which the drug is obtained or used (item 8).

The EGAP score is easy to calculate: the numerator corresponds to the number of positive items, and the denominator is the number of items specified. Three scores can be calculated: the total score (i.e. with the eight items of the EGAP scale), the area 1 score (i.e. items 1–4 of the EGAP scale assessing compulsive and physical signs of consumption) and the area 2 score (i.e. items 5–8 of the EGAP scale assessing the harmful consequences of dependence). However, the most commonly used score is the total score. A complete total EGAP score is a score with an eight-point denominator. The EGAP validation study showed that the EGAP score was a reliable and precise measure for evaluating drug dependence (internal consistency: 0.84; concurrent validity: 0.70; and inter-rate reliability: 0.92) [12].

2.3. Procedure

For this study, we selected all NotS covering zolpidem or zopiclone received by the CEIP-A in the Pays de la Loire region (fifth largest French region with five million inhabitants) between 1 January 2008 and 31 September 2016. Only Nots with EGAP total scores without incomplete data were retained.

2.4. Statistical analysis – 'PROMESS' tool [14]

Development of this tool was funded by the French Health Authority [14]. It is a statistical tool which can be used to perform statistical analysis on the FAN database. After quantitative description (number of EGAP positive items) and a qualitative description (which items are positive) of the EGAP scale, this tool enables (i) comparison between different drug dependence profiles based on the EGAP score and (ii) identification of several classes of consumers for the same drug.

2.4.1. Comparison between drug dependence profiles

As described previously, Nots covering problematic zolpidem and zopiclone use were selected. We added Nots covering heroin to the comparison as a positive control as the addiction potential of heroin is well known. For each substance (zolpidem, zopiclone, heroin), the EGAP scores were evaluated using the number of positive items in the

Evaluation of physical and compulsive signs of dependence

1/ Tolerance (effect reduction or dose increase to obtain the same effect as at the beginning)

Yes, no or not specified

2/ Withdrawal symptoms upon termination, or substitution to avoid these symptoms

Yes, no, never stopped or not specified

3/ Higher dose or duration than initially planned

Yes, no or not specified

4/ Desire or unsuccessful attempt to stop consumption

Yes, no or not specified

Evaluation of the adverse consequences of dependence

5/ Time spent obtaining, consuming or recovering from the use of the drug(s) or substance(s)

No, multi-month concern, multi-week concern, weekly or daily concern or not specified

6/ Consumption-related relational or professional problems

No, professional/ family/ social/ medical environment tensions, leaves of absence/ warnings/ family isolation/ notification of the problem, loss of job or housing/ total family breakdown or not specified

7/ Consumption-related health problems, e.g., memory loss, falling caused by taking benzodiazepines, etc.

Yes, no or not specified

8/ Transgressive behaviour

Fraud: exaggeration of symptoms, dose modification, prescription forgery, consumption of illicit substances, etc.

Yes, no or not specified

Misuse

Yes, no or not specified

Figure 1. EGAP (Echelle de GrAvité de la Pharmacodépendance –drug dependence severity scale).

total EGAP score. The positivity of each item was also evaluated. Means and standard deviation (SD) or proportions were calculated. The comparison between zolpidem, zopiclone, and heroin focused on the number of positive items and the positivity of each item. Percentages were compared using Chi-square tests or Fisher's exact test.

2.4.2. Identification of various consumers' dependence profile

Homogeneity analysis was performed to identify relevant subpopulations with different dependence profile in the overall population for zolpidem and zopiclone. The first step of the homogeneity analysis was performed using a 3D graph, with distribution of the NotS according to area 1 score (i.e. compulsive and physical signs of dependence) and the area 2 score (i.e. harmful consequences of dependence). The second step of the homogeneity analysis was performed using hierarchical ascendant classification [15].

3. Results

3.1. Comparison between drug dependence profiles

Fifty six Nots were identified for zolpidem, 32 for zopiclone, and 96 for heroin. For Z-drugs, patients were mostly women (66.1% for zolpidem and 78.1% for zopiclone) and mean age was similar (46.9 (SD 18.6) years for zolpidem and 48.5 (SD 18.1) years for zopiclone). Distribution of the Nots according to the number of positive items on the EGAP score for zolpidem, zopiclone, and heroin is shown in Figure 2.

For zolpidem, more than 20% of the EGAP scores contained eight positive items. The most common EGAP score involved around seven or eight positive items. Item 3 (higher dose or longer duration than initially planned) was positive for all Nots. Items 2 and 4 were positive in more than 70% of the Nots. For zopiclone, 13% of the EGAP scores contained eight positive items. The most common EGAP score involved around three to five positive items. Item 3 was also a common item in

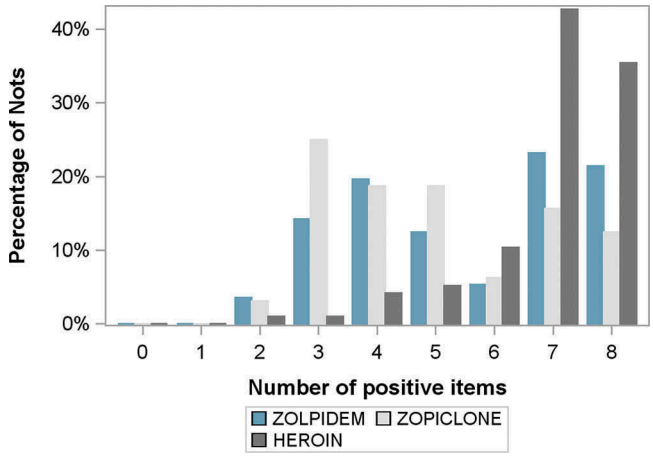

Figure 2. Distribution of Nots according to EGAP total score for heroin, zolpidem and zopiclone.

dependence profiles (84% positivity). It was the most frequent item along with item 4. For heroin, most of the Nots had seven or eight positive items. This was concordant with the high-dependence potential of heroin. The number of positive items tended to be higher for zolpidem than for zopiclone. The percentage of Nots with eight positive items was significantly different between zopiclone and heroin only (p = 0.03). No significant difference was observed either between zolpidem and heroin (p = 0.10) or between zopiclone and zolpidem (p = 0.45). Univariate comparison of item positivity between zolpidem and zopiclone showed a significantly higher rate of positivity with zolpidem for item 1 (tolerance) and item 8 (transgressive behavior).

The cumulative percentage of Nots distribution according to the EGAP total score (Figure 3) also highlighted the higher number of positive items for zolpidem than zopiclone.

Indeed, we observed that heroin had the most severe dependence profile as 78% of the Nots covering heroin had more than six positive items. For zolpidem and zopiclone, the percentages of Nots with more than six positive items were 44.6% and 28.1%, respectively. The curve of the cumulative percentages for zolpidem grew faster than the curve of the cumulative percentages for zopiclone, suggesting a more severe dependence profile for zolpidem than zopiclone.

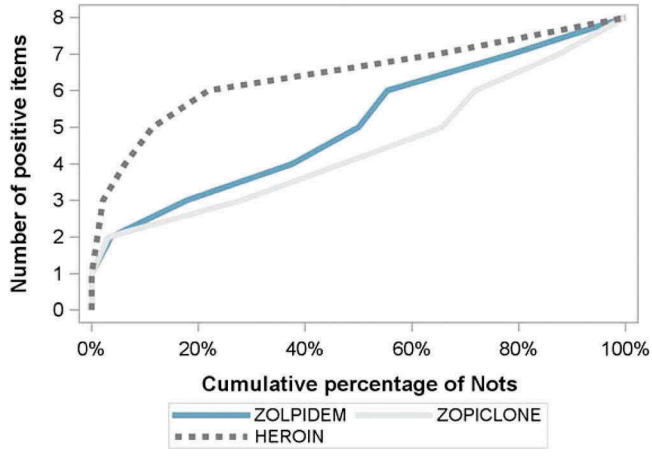

Figure 3. Cumulative percentage of Nots distribution according to EGAP scores for heroin, zolpidem and zopiclone.

3.2. Identification of various consumers' dependence profiles

The 3D graph showing distribution of the Nots according to area 1 of the EGAP score (compulsive and physical signs) and area 2 of the EGAP score (harmful consequences) is provided in Figure 4 for zolpidem and for zopiclone.

For zolpidem, two peaks corresponding to two different populations of zolpidem users were observed in Figure 4: (i) the first (population 1) in the area corresponding to the Nots with three or four positive items in area 1 but no positive item in area 2 (consumption with physical signs of dependence without harmful consequences); (ii) the second (population 2) in the area corresponding to the Nots with four positive items in both area 1 and area 2 (consumption with severe physical signs of dependence and severe harmful consequences). The hierarchical ascendant classification also showed two subpopulations for zolpidem.

For zopiclone, three peaks were observed in Figure 4 but they were lower and wider than for zolpidem, suggesting that Nots are more widely dispersed: (i) the first peak corresponded to Nots with three or four positive items in area 1 but no positive item in area 2 (consumption with physical signs of dependence without harmful consequences); (ii) the second peak corresponded to Nots with two positive items in area 1 and one or two positive items in area 2 (consumption with moderate physical signs of dependence and moderate harmful consequences); and (iii) the third peak corresponded to the Nots with four positive items in both area 1 and area 2 (consumption with severe physical signs of dependence and severe harmful consequences). No subpopulation was highlighted with the hierarchical ascendant classification for zopiclone.

3.3. Comparison of zolpidem subpopulations

The univariate comparison of the two subpopulations is shown in Table 1 and confirmed that population 2 is significantly younger and had more positive items on the EGAP score than population 1. Items from area 2 (harmful consequences) were all significantly more frequent for population 2.

4. Discussion

The first result was that health-care professionals reported more problematic situations with zolpidem than with zopiclone (resulting in more Nots for zolpidem than for zopiclone). These problematic situations correspond to substance use disorders which are the field of the FAN. The issue of complex amnestic behaviors with zolpidem is unaddressed, despite the prime importance of this adverse effect reported to the pharmacovigilance network and mentioned in the approval of the drug [2]. This result was consistent with literature in which we identified more case reports involving problematic use of zolpidem than zopiclone. Problematic situations, both with zolpidem and zopiclone, involved mainly women between

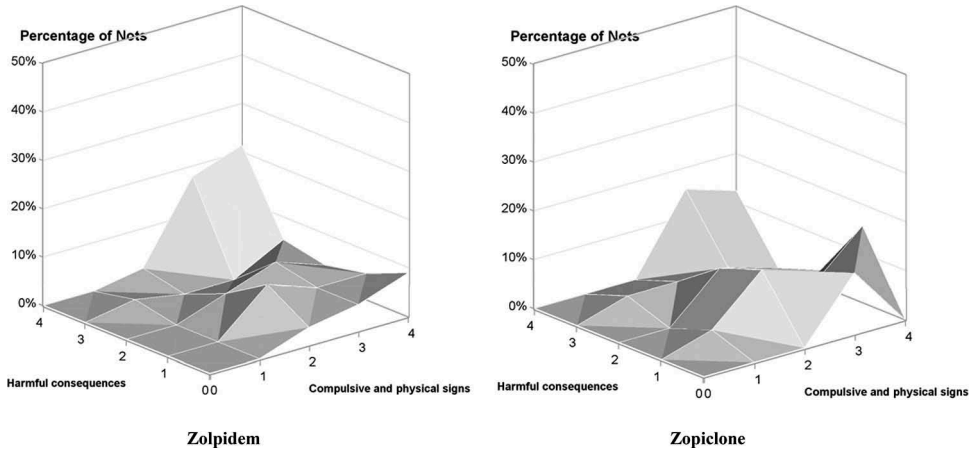

Figure 4. Homogeneity of consumers' dependence profiles for zolpidem and zopiclone.

Table 1. Univariate comparison of the two subpopulations of zolpidem users.

Variables	Population 1 % or m (SD)	Population 2 % or m (SD)	*p*
Number of reports	30 (54%)	26 (46%)	
Age (years)	56.3 (18.8)	35.6 (10.3)	< 0.01
Female	66.7%	65.4%	0.92
Total EGAP score	4.0 (1.0)	7.4 (0.6)	< 0.01
Compulsive and physical signs			
Frequency of item 1	63%	85%	0.14
Frequency of item 2	70%	81%	0.54
Frequency of item 3	100%	100%	
Frequency of item 4	63%	88%	0.06
Harmful consequences			
Frequency of item 5	33%	100%	< 0.01
Frequency of item 6	10%	100%	< 0.01
Frequency of item 7	20%	88%	< 0.01
Frequency of item 8	37%	100%	< 0.01

% = percentage. m = mean. SD = standard deviation. Item 1 = tolerance; item 2 = withdrawal symptoms when consumption is stopped, or consumption of another product to avoid these symptoms; item 3 = higher dose or duration than initially planned; item 4 = desire or failed attempts to stop; item 5 = substantial amount of time devoted to consumption; item 6 = family, professional, social, legal or financial difficulties associated with consumption; item 7 = persistence of consumption, even though the patient is aware of the consequences of consumption on his/her health; item 8 = transgressive behavior with respect to the manner in which the drug is obtained or used.

45 and 50 years. Studies regarding factors associated with zolpidem or zopiclone abuse are scarce and results regarding the influence of gender are mixed. One study on post-marketing surveillance reports about zolpidem failed to show differences according to gender [16]. A Danish register-based study found that problematic long-term use of Z-drugs were associated with female gender [17], and another study with psychiatric outpatient interviews showed that men were more likely to report an unfavorable attitude toward hypnotics than women [18]. It is also possible that reports with Z-drugs were more frequent for women because they are also those who used them the most. Indeed, several studies shown that women were more likely to use hypnotics and benzodiazepines than men [7,18,19] and that this may be associated with the fact that insomnia is more prevalent in women than in men [20]. Nevertheless, pharmacokinetic difference between men and women could also explain the abuse incidence observed. In 2013, the Food and Drug Administration (FDA) mentioned that women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men [21]. Cubala et al. in 2010 highlighted that the pharmacokinetics of zolpidem seems to be related to endocrine factors associated with CYP3A4 metabolism. In women, low free testosterone may contribute to lower CYP3A activity with women achieving up to 50% higher zolpidem plasma levels [22].

Secondly, comparison of the dependence profile for zolpidem and zopiclone showed differences both in total EGAP score and positivity of the EGAP items. Indeed, the descriptive analysis showed that EGAP scores were higher for zolpidem than for zopiclone, suggesting more severe problematic consumption with zolpidem. To our knowledge, this is the first time that the dependence profile of zolpidem and zopiclone has been compared from reports by health-care professionals on problematic use. The advantage of this approach is that it is not limited to published case reports and enables assessment based on all notifications, which corresponds to the FAN's mission. Our approach was also complementary with previous studies that also found higher dependence potential for zolpidem [7,18]. Indeed, unlike the reimbursement database study, results came from actual consumption of zolpidem and zopiclone. Moreover, reports came directly from health-care professionals and could not be biased by the patient's interpretation. This study also added key information about items possibly responsible for differences in dependence between zolpidem and zopiclone. Tolerance (item 1) and transgressive behavior with respect to the manner in which the drug is obtained or used (item 8) were significantly more frequent for zolpidem than for zopiclone.

One hypothesis for tolerance could be that zopiclone receptors are less selective than zolpidem receptor resulting in less sedation. Zolpidem is the only drug exhibiting selectivity for GABA-A receptors containing α_1 subunits which are known to mediate the sedative effect of the benzodiazepines [23], whereas the α_2 subunit mediates the anxiolytic effect. Tolerance to the sedative effects appears faster than tolerance to the anxiolytic effects. Thus, as it is the only effect of zolpidem because of its selectivity we observed more positive tolerance items.

For transgressive behavior, literature also reported problematic routes of administration such as intravenous, intra-arterial, or nasal routes for zolpidem but not for zopiclone [11]. Studies have already shown that some zolpidem users were seeking amphetamine-like effects with very high doses of zolpidem [11]. It is possible that zolpidem consumers, in order to achieve an amphetamine-like effect, resorted to transgressive behavior to obtain a higher dose (doctor shopping, deal, etc.) or to have more effects with the same dose (change in route of administration). This amphetamine-like effect has never been reported for zopiclone. The French health authority is aware of zolpidem's high dependence potential, and the topic was studied by the French Narcotics Commission [24]. The members agreed that zolpidem can be prescribed on secure prescription to prevent prescription counterfeiting and to minimize abuse and dependence caused by excessive zolpidem consumption. This type of measure was not taken for zopiclone, indicating the difference in dependence profile between zolpidem and zopiclone.

Another objective of this study was to identify various consumer dependence profiles among zolpidem users and among zopiclone users. We managed to identify two relevant subpopulations in the Nots for zolpidem consumers but not for zopiclone consumers. For zolpidem, the two subpopulations were problematic as reported by health-care professionals, and both had a high prevalence of compulsive and physical signs of dependence. However, we highlighted one subpopulation (population 2 in Table 1) to be more severe than the other (population 1 in Table 1) with a significantly higher total EGAP score and more harmful consequences. This subpopulation was also younger than the other subpopulation. We can assume that this subpopulation includes consumers that are seeking to obtain zolpidem for its paradoxical stimulant effects and which were identified during the national survey [24]. The second population represented consumers taking zolpidem to treat insomnia and thereafter becoming tolerant, requiring increasingly higher doses. These consumers experience little or no harmful consequences. An epidemiological study exploring the number of subpopulations for zopiclone and zolpidem has already been conducted [7]. This study used latent class analysis [25] of the health insurance database. Four subpopulations were identified for zolpidem and three for zopiclone. The differences with our study could be easily explained by the fact that the latent class analysis was performed on an overall population, while our study focused only on problematic users (those reported by health-care professionals in Nots). The presence of a particular subpopulation consuming zolpidem was also identified in the latent class analysis study [7]. Focus on problematic users allows for greater efficiency in evaluation, by excluding all 'normal users'. This type of analysis is highly instructive and the reports were more severe than in the overall population.

Finally, the 'PROMESS' tool rapidly provides information on dependence or abuse potential for one or several drugs. As we have shown with the example of Z-drugs here, this tool allows for comparison of drug dependence profiles between drugs and identification of different consumers' dependence profiles. One of the limitations of this tool was the small number of reports due to the database only compiling reports received in one French region. The development of this tool was financed by the French health authority [14] and will be developed for use in a national database containing all CEIP-As reports for the entire country. The results in this small sample are already highly promising. Pharmacoepidemiological studies are very important for assessing the safety and use of drugs in the post-marketing phase. Clinical trials are informative but they generally do not focus on dependence concerns, and this can be evaluated only with post-marketing data. The limitations of pharmacoepidemiological studies include the lack or the absence of clinical data. To our knowledge, 'PROMESS' is the only tool available for analyzing clinical data.

5. Conclusion

Zolpidem and zopiclone are two benzodiazepine-like agents with similar indication but with very different dependence profiles. These two drugs were placed under surveillance by the French health authority to monitor data on abuse and/or dependence relating to them. Data available in literature and data produced using the 'PROMESS' tool were concordant as to their different dependence profiles. Reports on zolpidem reveal more severe and preoccupying consumption. A limit was the small number of reported cases of zolpidem and zopiclone abuse or dependence compared with the widespread use of these drugs. This is an intrinsic limitation of the spontaneous reporting system; practitioners do not report all cases of abuse or dependence but only the more severe cases. But, to our knowledge, 'PROMESS' is the only tool for clinically comparing drugs and it could be very useful for evaluating drugs under surveillance and for making public health decisions. Thus, in January 2017, further to the recommendations from the French National Committee for Narcotics and Psychotropic Drugs, zolpidem has now been added to the list of drugs that require special prescription, known as controlled prescription.

Acknowledgments

We wish to extend our thanks the French Health Products Safety Agency (Agence Nationale de Sécurité du medicament et des produits de santé – ANSM) for providing financing. The funding sources had no influence over the study design, or collection, analysis or interpretation of the data, writing of the manuscript or the decision to submit the paper for publication.

Funding

This work was supported by The French Health Products Safety Agency (Agence Nationale de Sécurité du medicament et des produits de santé – ANSM) under Grant 20125057.

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. ANSM Agence Nationale de sécurité du médicament et des produits de santé. Résumé des Caractéristiques du Produit - IMOVANE® (zopiclone). 2016. [Cited 2016 Dec 19]. Available from: http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=61435939&typedoc=R&ref=R0279188.htm
2. ANSM Agence Nationale de sécurité du médicament et des produits de santé. Résumé des Caractéristiques du Produit - STILNOX® (zolpidem). 2016. [Cited 2016 Dec 19]. Available from: http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=63179285&typedoc=R&ref=R0286012.htm
3. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. Drugs. 2000;59:865–889.
4. Dell'Osso B, Albert U, Atti AR, et al. Bridging the gap between education and appropriate use of benzodiazepines in psychiatric clinical practice. Neuropsychiatr Dis Treat. 2015;11:1885–1909.
5. Baumevieille M, Miremont G, Haramburu F, et al. The French system of evaluation of dependence: establishment in a legal system. Therapie. 2001;56:15–22.
6. Victorri-Vigneau C, Gerardin M, Rousselet M, et al. An update on zolpidem abuse and dependence. J Addict Dis. 2014;33:15–23.

•• **First evidence of potential difference in drug abuse between zolpidem and zopiclone.**

7. Victorri-Vigneau C, Feuillet F, Wainstein L, et al. Pharmacoepidemiological characterisation of zolpidem and zopiclone usage. Eur J Clin Pharmacol. 2013;69:1965–1972.
8. Landreat MG, Vigneau CV, Hardouin JB, et al. Can we say that seniors are addicted to benzodiazepines? Subst Use Misuse. 2010;45:1988–1999.
9. Victorri-Vigneau C, Wainstein L, Guillet JY, et al. Diagnostic of pharmacodependence: comparison between patients and doctors approaches. Therapie. 2012;67:167–172.
10. Victorri-Vigneau C, Gerardin-Marais M, Mallaret M, et al. Example of complementarities between evaluation of the Regional Pharmacovigilance Department and Centre of Evaluation and Information on Pharmacodependence. Therapie. 2008;63:468–471.
11. Victorri-Vigneau C, Dailly E, Veyrac G, et al. Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. Br J Clin Pharmacol. 2007;64:198–209.

• **Zolpidem abuse assessment which lead to French approval modification.**

12. Victorri-Vigneau C, Hardouin JB, Rousselet M, et al. Multicentre study for validation of the French addictovigilance network reports assessment tool. Br J Clin Pharmacol. 2016;82:1030–1039.

•• **Validation of the French addictovigilance network EGAP score.**

13. APA. DSM-IV. Manuel diagnostique et statistique des troubles mentaux. 4ème ed. Paris:Trad Paris Masson; 1996.
14. ANSM Agence Nationale de sécurité du médicament et des produits de santé. Appels à projet de recherche - résultats de l'appel à projet 2012. 2016. [Cited2016Dec19]. Available from: http://ansm.sante.fr/L-ANSM2/Appels-a-projets-de-recherche/Resultats-de-l-appel-a-projets-2012/(offset)/6.
15. Lebart L, Morineau A, Piron M. Statistique exploratoire multidimensionnelle. Paris:Dunod; 1995.
16. Hajak G, Muller WE, Wittchen HU, et al. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. Addiction. 2003;98:1371–1378.

•• **Review of cases report for zolpidem and zopiclone abuse.**

17. Andersen AB, Frydenberg M. Long-term use of zopiclone, zolpidem and zaleplon among Danish elderly and the association with sociodemographic factors and use of other drugs. Pharmacoepidemiol Drug Saf. 2011;20:378–385.
18. Yen CF, Yen CN, Ko CH, et al. Correlates of dependence and beliefs about the use of hypnotics among zolpidem and zopiclone users. Subst Use Misuse. 2015;50:350–357.
19. Gerardin M, Victorri-Vigneau C, Guerlais M, et al. Benzodiazepines consumption: does dependence vary with age? Subst Use Misuse. 2014;49:1417–1425.
20. Cubala WJ, Landowski J, Wichowicz HM. Zolpidem abuse, dependence and withdrawal syndrome: sex as susceptibility factor for adverse effects. Br J Clin Pharmacol. 2008;65:444–445.
21. U.S. Food and Drug Administration F. FDA drug safety communication: risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). 2016. [Cited 2017 Jun 14]. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm334033.htm
22. Cubala WJ, Wiglusz M, Burkiewicz A, et al. Zolpidem pharmacokinetics and pharmacodynamics in metabolic interactions involving CYP3A: sex as a differentiating factor. Eur J Clin Pharmacol. 2010;66:955; author reply 7–8.
23. McKernan RM, Rosahl TW, Reynolds DS, et al. Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA(A) receptor alpha1 subtype. Nat Neurosci. 2000;3:587–592.
24. ANSM Agence Nationale de sécurité du médicament et des produits de santé. Compte-rendu de la Commission des Stupéfiants et des Psychotropes du 21 novembre 2013. 2013. ANSM Agence Nationale de sécurité du médicament et des produits de santé. Appels à projet de recherche - résultats de l'appel à projet 2012. 2016. [Cited 2016 Dec 19]. Available from: http://ansm.sante.fr/L-ANSM2/Appels-a-projets-de-recherche/Resultats-de-l-appel-a-projets-2012/(offset)/6.Available from: http//ansm.sante.fr/var/ansm_site/storage/original/application/ab78fffb49da3bf1ef109c45afc4a72a.pdf.
25. Wainstein L, Victorri-Vigneau C, Sebille V, et al. Pharmacoepidemiological characterization of psychotropic drugs consumption using a latent class analysis. Int Clin Psychopharmacol. 2011;26:54–62.