

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

ZORRO study Protocol – French healthcare reimbursement database analysis and field study focusing the impact's evaluation of secure prescription pads on zolpidem consumption and sedative drug misuse.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027443
Article Type:	Protocol
Date Submitted by the Author:	23-Oct-2018
Complete List of Authors:	<p>Gerardin, Marie; University hospital of Nantes, Department of Clinical Pharmacology</p> <p>Rousselet, Morgane; University hospital of Nantes, Department of Clinical Pharmacology; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch"</p> <p>Caillet, Pascal; University hospital of Nantes, Department of Clinical Pharmacology</p> <p>Grall-Bronnec, Marie; University Hospital of Nantes, Clinical Investigation Unit BALANCED "BehaviorAL AddictioNs and ComplEx mood Disorders"; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch"</p> <p>Loue, Pierre; University Hospital of Rouen, Departement of General medical</p> <p>Jolliet, Pascale; University hospital of Nantes, Department of Clinical Pharmacology; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch"</p> <p>Victorri-Vigneau, C; University Hospital of Nantes, Department of Clinical Pharmacology; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch"</p>
Keywords:	zolpidem, secured prescription, change in law, impact, addictovigilance, Substance misuse < PSYCHIATRY

SCHOLARONE™
Manuscripts

1
2
3 1 **Title:** ZORRO study Protocol – French healthcare reimbursement database analysis and field study
4
5 2 focusing the impact’s evaluation of secure prescription pads on zolpidem consumption and sedative drug
6
7 3 misuse.
8
9

10 4
11
12 5 **Authors:**
13

14 6 Marie GERARDIN, Clinical Pharmacology Department, Nantes University Hospital, Nantes, France,
15
16 7 9 quai Moncousu, 44 093 Nantes cedex 1, France. marie.gerardin@chu-nantes.fr
17
18

19 8 Morgane ROUSSELET, Clinical Pharmacology Department, Nantes University Hospital, Nantes,
20
21 9 France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. Addictology and Psychiatry Department,
22
23 10 Nantes University Hospital, 85 rue de Saint-Jacques, 44093 Nantes cedex 1, France. INSERM U1246
24
25 11 SPHERE “methodS in Patient-centered outcomes and HHealth ResEarch”, Nantes and Tours University, 22
26
27 12 boulevard Benoni Goullin, 44 000 Nantes, France. morgane.rousselet@chu-nantes.fr
28
29

30 13 Pascal CAILLET, Clinical Pharmacology Department, Nantes University Hospital, Nantes, France, 9
31
32 14 quai Moncousu, 44 093 Nantes cedex 1, France. pascal.caillet@chu-nantes.fr
33
34

35 15 Marie GRALL-BRONNEC, Addictology and Psychiatry Department, Nantes University Hospital, 85
36
37 16 rue de Saint-Jacques, 44093 Nantes cedex 1, France. INSERM U1246 SPHERE “methodS in Patient-
38
39 17 centered outcomes and HHealth ResEarch”, Nantes and Tours University, 22 boulevard Benoni Goullin, 44
40
41 18 000 Nantes, France. marie.bronnec@chu-nantes.fr
42
43

44 19 Pierre LOUE, General medical Departement, Rouen faculty of medicine, Rouen University
45
46 20 Hospital. peterloue@me.com
47

48 21 Pascale JOLLIET, Clinical Pharmacology Department, Nantes University Hospital, Nantes, France,
49
50 22 9 quai Moncousu, 44 093 Nantes cedex 1, France. INSERM U1246 SPHERE “methodS in Patient-centered
51
52
53
54
55
56
57
58
59
60

1
2
3 23 outcomes and HHealth ResEarch”, Nantes and Tours University, 22 boulevard Benoni Goullin, 44 000
4
5
6 24 Nantes, France. pascale.jolliet@univ-nantes.fr

7
8 25 Caroline VICTORRI-VIGNEAU, Clinical Pharmacology Department, Nantes University Hospital,
9
10 26 Nantes, France, 9 quai Moncouso, 44 093 Nantes cedex 1, France. INSERM U1246 SPHERE “methodS in
11
12 27 Patient-centered outcomes and HHealth ResEarch”, Nantes and Tours University, 22 boulevard Benoni
13
14 28 Goullin, 44 000 Nantes, France. caroline.vigneau@chu-nantes.fr

15
16
17 29 **Corresponding author:**

18
19 30 Caroline VICTORRI-VIGNEAU

20
21 31 Adress: Clinical Pharmacology Department, Nantes University Hospital, Nantes, France,

22
23 32 9 quai Moncouso, 44 093 Nantes cedex 1, France

24
25 33 Phone : +33240084073

26
27 34 E-Mail : caroline.vigneau@chu-nantes.fr

35 **ABSTRACT**

36 **Introduction**

37 In recent years, data collected by the French Addictovigilance Network (FAN) has shown the potential for
38 abuse and addiction associated with zolpidem (the most sold hypnotic drug in France). Since the 10th of
39 April 2017, new regulations have come into force that require zolpidem to be prescribed on special
40 secure prescription pads, in order to reduce the risk of abuse or misuse. This measure has far reaching
41 repercussions that are not only limited to the consumption of zolpidem but also extend to the usage of
42 sedative medication on a whole.

43 The objective of the ZORRO study (ZOlpidem and the Reinforcement of the Regulation of prescription
44 Orders) is to evaluate the overall impact of the new regulatory framework requiring that zolpidem be
45 prescribed on special secure prescription pads. The overall impact will be evaluated according to three
46 axes: the impact on the number of consumers, on the type of consumption (chronic use versus
47 occasional use, problematic consumption versus non-problematic use), and on the consumption of other
48 sedative molecules.

49 **Methods and analysis**

50 The ZORRO study is an epidemiological, observational, national multi-center, non-controlled, prospective
51 research project supported by the French National Agency for Medicines and Health Products Safety
52 (ANSM). The evaluation of the impact of the regulatory framework change relative to zolpidem will be
53 done on the one hand via an epidemiological study of the French National Health Insurance data base
54 and on the other hand by the implementation of field studies of prescribers and consumers of zolpidem.

55 **Ethics and dissemination**

56 The local Research Ethics Committee (GNEDS) approved this study on 3 March 2018. Results will be
57 presented in national and international conferences and submitted to peer-reviewed journals.

58 **Trial registration number** NCT03584542

1
2
3
4 59
5 60 **Keywords**
6
7 61 Zolpidem, secured prescription, change in law, impact, addictovigilance, misuse.
8
9 62

10
11 63 **ARTICLE SUMMARY**

12
13 64 **Strengths and limitations of the study**

14
15 65 This study will contribute to setting up an innovative impact measure in order to evaluate the efficacy of
16
17 66 institutions' response to the issue of zolpidem misuse and dependence.

18
19
20
21 67 The study will be representative of the French population by use of the French healthcare database
22
23 68 SNDS, with a focus on how physicians and problematic consumers have coped with the change in law by
24
25 69 use of complementary field studies.

26
27
28 70 Owing to technical constraints inherent to medico-administrative database use, use of drug not
29
30 71 reimbursed will not be observable in the SNDS database, as well as many clinical data that are not
31
32 72 routinely gathered.

33
34
35
36 73 A lack of representativity may occur during participants' recruitment regarding the part of the project
37
38 74 involving field sampling.

39
40
41 75
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

76 INTRODUCTION

77 Zolpidem is a medicinal substance that has been the target of a number of regulatory framework
78 changes in both French national and international spheres. Worldwide, a number of cases of misuse of
79 zolpidem have been described (Europe and the United-States [1, 2]). The World Health Organisation
80 (WHO) believes that the frequency of cases of abuse or addiction to zolpidem is similar to that associated
81 with hypnotic benzodiazepines [3] and in a ruling of July 15th 2002, zolpidem was placed by the United
82 Nations in the table IV of the Vienna convention which aims to control the abuse and trafficking of
83 psychotropic substances.

84 In France, the French Addictovigilance network (FAN), piloted by the French National Agency for
85 Medicines and Health Products Safety (ANSM) is in charge of the surveillance of cases of abuse and
86 addiction associated with any drug or substance with a psychoactive effect. The surveillance is based on
87 a network of 13 Centre for evaluation of and information on drug dependence and addiction monitoring
88 (CEIP-A), who evaluate the addictive potential of a given drug via notifications provided by health
89 professionals [4], and via specifically developed pharmaco-epidemiology tools [5, 6].

90 Some controlled medicines and psychotropic substances are under reinforced surveillance by the ANSM
91 as they are associated with a risk of misuse and addiction. As is the case for zolpidem. In France,
92 zolpidem is enlisted on the list I of harmful substances, that is to say it is considered as a substance
93 associated with a health risk. An initial national survey of the addictovigilance network in 2002 found
94 serious and worrying cases of abuse and addiction to zolpidem. The 2002 survey revealed the existence
95 of two consumer groups: a population of chronic high dosage consumers with a therapeutic usage of
96 zolpidem, and a population of "misusers" in search of an effect other than hypnotic (euphoria, wellbeing
97 or stimulant effect). The same survey also found, via the analysis of the FAN pharmaco-epidemiology
98 tools, that zolpidem is a substance prone to abuse [7]. Following to this conclusion the Summary of
99 Product Characteristics (SPC) of zolpidem was modified, with notably the addition of a warning with

1
2
3 100 respect to addiction. In June 2011, an update of data relative to the addictive potential of zolpidem,
4
5 101 presented before the National Commission of Narcotics and Psychotropic Substances (CNSP), found the
6
7 102 same two consumer groups as in the 2002 survey, with cases of seemingly increasing gravity associated
8
9 103 with the consumption of particularly high dosages [8]. In light of these results, the prescription of
10
11 104 zolpidem on special secure prescription pads was put forward by the CNSP. In 2012, the FAN tools all,
12
13 105 once again, proclaim zolpidem as a problematic substance.
14
15

16
17 106 The analytical and surveillance tools of the FAN allow for the identification of the problem of addiction,
18
19 107 they also provide transversal data relative to specific population groups, however they do not provide a
20
21 108 general population risk profile, nor a comparison to other molecules. A research program based on the
22
23 109 French National Health Insurance data base, allowed for the collection of quantitative data in the general
24
25 110 population via an analysis of the usage of zolpidem and zopiclone [9]. The results of this research
26
27 111 program provided the identification of a number of different clinical profiles of zolpidem consumers: (i)
28
29 112 « non-problematic » consumers, the largest group; (ii) individuals who could have developed a tolerance
30
31 113 to the hypnotic effects of zolpidem, for whom the prescription of alternative hypnotic/anxiolytic
32
33 114 medication is justified; (iii) potential problematic consumers of zolpidem (1%) (high rate of fraudulent
34
35 115 behavior, excessive usage, non-respect of guidelines and medical-pharmaceutical nomadism). In 2017,
36
37 116 another research program gave insight into the characteristics of the two aforementioned consumer
38
39 117 groups via the analysis of reports from health professionals [10].
40
41
42

43
44 118 Following to these results, on the 11th of January 2017, the ANSM decreed that as from April the 10th
45
46 119 2017, the prescription of zolpidem was to be done on secure prescription pads [11]. The ANSM stated
47
48 120 that « this measure is taken in order to limit the risk of abuse and misuse » and « to encourage correct
49
50 121 usage ». In a country where the consumption of psychotropic drugs is high, a ruling that impacts the
51
52 122 most sold hypnotic drug [12, 13] will disrupt not only its' usage but also on a larger scale the overall
53
54
55

1
2
3 123 prescription of sedative substances. The current project aims to develop a means to measure the impact
4
5 124 of this new ruling, in the scope of works of the ANSM, that is to say, in terms of the reduction of the risk
6
7
8 125 of abuse, the improvement of correct use of zolpidem and the change in prescriptions of sedative
9
10 126 molecules. This project forms part of the evaluation of zolpidem done by the Nantes CEIP-A, the
11
12 127 organization in charge of its follow up. In addition to the tools used by the FAN [5], this project will allow
13
14 128 for a longitudinal evaluation of the trajectories of different patients, as well as providing insight into the
15
16
17 129 general population.
18
19 130

21 131 **METHODS AND ANALYSIS**

23 132 **Aim**

25 133 The objective of the ZORRO study (Zolpidem and the Reinforcement of the Regulation of prescription
26
27 134 Orders) is to evaluate the overall impact of the obligation to use secure prescription pads for zolpidem.
28
29
30 135 We propose a multimodal approach that will provide valuable insight into three key questions: 1) what is
31
32 136 the impact of this measure on the number of consumers? 2) What is the impact of this measure on the
33
34 137 type of consumption? 3) What is the impact of this measure on the consumption of other sedative
35
36
37 138 molecules?
38

39 139 **Study design**

41 140 This scientific project is based on a multimodal epidemiological approach, which combines a
42
43 141 retrospective cohort study involving the use of the French National Health Information data base (SNDS,
44
45 142 formerly known as the French National Inter-schemes Health Insurance data base (SNIIRAM)) [14] and a
46
47
48 143 transversal study involving the gathering in-field of clinical data of different populations: general
49
50 144 practitioners that prescribe zolpidem as well as consumers (both patients having consulted a general
51
52 145 practitioner and those having recourse to specialized care centers dedicated to drug dependence). To
53
54 146 our knowledge, a study of this amplitude does not exist in France.
55

1
2
3 147 These two approaches will provide insight into three key areas:
4

- 5 148 - To evaluate the impact of the measure on the number of consumers, we will estimate via the
6
7 149 SNDS data base the prevalence and the incidence of zolpidem consumers in the general
8
9 population before and after the regulatory framework change.
10 150
11
12 151 - To evaluate the impact of the measure on the type of consumption, we will explore the changes
13
14 152 in the modes of consumption: occasional use *versus* chronic use and problematic use *versus* non-
15
16 153 problematic use. Problematic use is defined as a consumption outside of the SPC guidelines for at
17
18 154 least one of the following parameters: the duration of consumption, the dosage, the means of
19
20 155 procurement, the routes of administration or the search for an effect other than hypnotic. This
21
22 156 evaluation will be done both from SNDS data base for the evaluation of the general population
23
24 157 and from the field studies for the evaluation of problematic consumers of zolpidem (patients of
25
26 158 general practitioners and users of specialized care centers dedicated to drug dependence).
27
28 159 - To evaluate the impact of the measure on the consumption of other sedative molecules, we will
29
30 160 analyze the reporting of prescriptions and the changes observed both in the general population
31
32 161 in the SNDS data base as well as among prescribers and problematic consumers of zolpidem
33
34 162 (patients of general practitioners and users of specialized care centers for users of specialized
35
36 163 care centers dedicated to drug dependence).
37
38
39
40

41 164 **Setting of the study**

42
43 165 The Nantes CEIP-A, is the national investigating center in charge of the management, surveillance and
44
45 166 coordination of the entire project. General practitioners, their patients and users of zolpidem will be
46
47 167 recruited across France. The gathering and the analysis of data (SNDS data base and field studies) will be
48
49 168 centralized by the Nantes CEIP-A.
50

51
52 169 A multi-disciplinary pilot committee, comprised of pharmacologists, general practitioners, a
53
54 170 methodologist bio-statistician, a clinical study technician and of an addictologist psychiatrist, has been
55

56 8
57
58
59
60

1
2
3 171 constituted in order to define the research protocol and in order to insure the scientific and
4
5 172 methodological validity of the study.
6
7

8 173

9
10 174 **Patient and public involvement**
11

12 175

13
14 176 Patients were not involved in the design of the study.
15
16

17 177

18 178 **Populations**
19

20 179

21
22 180 *Analysis of the SNDS database*
23
24

25 181

26
27 182 The study sample will include all patients in the database during the period from the 1st of January 2016
28
29 183 to the 31st of December 2018. The target population of our research will be constituted of consumers of
30
31 184 zolpidem present in the SNDS database between the 1st of January 2016 and the 31st of December 2018.
32
33

34 185

35
36 186 *Field study among General practitioners*
37
38

39 187

40
41
42 188 Practitioners, situated within the national borders, will be randomly selected from the list of the National
43
44 189 Health Insurance for Wage laborers (CNAMTS). Practitioners specialized in the care of addictions and
45
46 190 used to working with the FAN, will also be solicited [15]. All practitioners with an independent practice at
47
48 191 the time of change in regulatory framework and who agree to participate, via oral consent, will be
49
50 192 included.
51
52

53 193
54
55
56
57
58
59
60

1
2
3 194 *Field study among problematic consumers of zolpidem (patients of general practitioners and users of*
4
5 195 *specialized care centers dedicated to drug dependence)*
6
7
8
9 196

10
11 197 Patients of general practitioners will be selected by participating practitioners. Users can also be selected
12
13 198 by participating specialized care centers dedicated to drug dependence (addiction care and prevention
14
15 199 centers (CSAPA) and drug-user risk reduction centers (CAARUD). All subjects (patients and users) with a
16
17 200 problematic usage of zolpidem before the coming into force of the new regulatory framework and who
18
19 201 provide their oral consent to participate, will be included in the study. A problematic consumption of
20
21 202 zolpidem will be defined according to the DSM 5 criteria of substance use disorder. Under aged or
22
23 203 protected individuals as well as subjects with French language difficulties (understanding, reading or
24
25 204 writing) incompatible with the filling out of a questionnaire, will not be included in the study.
26
27
28
29 205

30 206 **Materials**

31
32 207

33 34 208 *Analysis of the SNDS database*

35
36 209

37
38
39 210 The SNDS data base is described in detail in the publication by Martin-Latry *et al* [14] as well as on related
40
41 211 internet sites [16, 17]. The data analyzed will be sociodemographic data of the patients and the
42
43 212 medication delivered to them (denomination, quantity, medical specialty of the prescribing practitioner).
44
45 213 The access to the data will be done in accordance with current rulings and practice.
46
47

48 214

49 215 *Field study among general practitioners*

50
51 216
52
53
54
55
56
57
58
59
60

1
2
3 217 Participating general practitioners will reply to short telephone questionnaire, which will gather
4
5 218 information on their perceptions and their prescription strategy following to the new regulatory
6
7 219 framework (continuation of zolpidem on a secure prescription pad, prescription of a different sedative
8
9 220 drug, cease in hypnotic prescriptions). The criteria for their choices will also be explored.
10
11

12 221

13
14 222 *Field study among problematic consumers of zolpidem (patients and users)*
15

16 223

17
18 224 Patients and users will fill out a two-part auto-questionnaire. The first part will evaluate the consumption
19
20 225 of zolpidem before the coming into force of the new regulatory framework (dosages used, duration,
21
22 226 pursued effects and effects felt) and their change or not after the coming into force of the new
23
24 227 regulatory framework (cease, change in dosage, relay to another drug or sedative substance). The
25
26 228 second part of the questionnaire will be filled out only by patients or users for whom a change is
27
28 229 observed and it will gather information pertaining to the favored replacement substance (dosages used,
29
30 230 duration, pursued effects and effects felt).
31
32

33 231

34
35 232 **Study size**
36

37 233

38
39 234 *Analysis of the SNDS database:*
40

41
42 235 In light of the retrospective nature of the study and of the data bases used, the calculation of a power is
43
44 236 not necessary, in accordance with the good practice guidelines of the European Network of Centers for
45
46 237 Pharmaco-epidemiology and Pharmacovigilance [18].
47
48

49 238

50
51 239 *Field studies among prescribing general practitioners and problematic consumers of zolpidem:*
52
53
54
55

1
2
3 240 Three hundred practitioners will be selected in order to insure that at least one hundred practitioners
4
5 241 participate in the recruitment of problematic consumers of zolpidem. For feasibility reasons, the number
6
7 242 of general practitioner patients to be included depends upon the construction of a convenience sample.
8
9
10 243 This sample is estimated to be about 200 patients. Furthermore, 200 users will be recruited via the
11
12 244 specialized care centers dedicated to drug dependence.
13
14
15 245

16 17 246 **Statistical methods**

18
19 247 All variables will undergo a descriptive analysis. Quantitative variables will be described using usual
20
21 248 position (mean or median) and dispersion (standard deviation, interquartile range) parameters. The
22
23 249 normality of their distribution will be assessed numerically (normality test) and graphically. For normally
24
25 250 distributed quantitative variables, mean and standard deviation will be used. For non-normally
26
27 251 distributed variables, median and interquartile ranges will be used. Qualitative variables will be
28
29 252 described using number and frequency tables for each parameter. All analysis will be conducted with SAS
30
31 253 software. Specific statistical methods will be implemented in order to answer each question adequately.
32
33
34
35 254

36
37 255 *Impact of the measure on the number of consumers: estimation of prevalence and incidence of zolpidem*
38
39 256 *users within the SNDS database before and after the regulatory framework change.*
40
41

42 257
43
44 258 A number of periods will be studied (figure 1). The proportion of patients having received at least one
45
46 259 delivery of zolpidem during the period 2 and during the period 4 will be compared using a Mc Nemar test
47
48 260 for paired proportion. Patients missing from one of the two periods will be recorded as non-users. The
49
50 261 significance threshold will be fixed at 5%. An incident user will be defined as a patient receiving a first
51
52 262 delivery of zolpidem without any prior delivery over the preceding 6 months. The number of incident
53
54
55

263 users within each period will be compared using a Poisson model. The significance threshold for each
264 coefficient will be fixed at 5%.

265

266 *Impact on the type of consumption regarding changes in treatment duration*

267

268 *Within the SNDS database:* The length of the first treatment episode will be evaluated by
269 calculating the number of days covered by the initial delivery (theoretical length of treatment). The
270 predicted variable will be the duration of treatment over a threshold (yes/no). The period will be entered
271 as a covariate in the model, enabling the study of the effect of the period on the probability of the
272 treatment being chronic while taking into account the correlation of treatment characteristics for a given
273 patient.

274 *Within the field study among problematic consumers of zolpidem:* A descriptive analysis will be
275 performed, with the characterization of the duration of treatment with zolpidem before the regulatory
276 framework change and of the duration of treatment with zolpidem or of the replacement
277 drug/substance after the regulatory framework change.

278

279 *Impact on the type of consumption addressing changes in the type of consumption, problematic or non-*
280 *problematic:*

281

282 *Within the SNDS database:* A latent class analysis (LCA) will be conducted within each period,
283 including the following variables: age, sex, presence of a chronic disease, poor economic status,
284 prescribing practitioners specialty (only whether or not a general practitioner), number of different
285 prescribing practitioners (doctor shopping), number of dispensing pharmacies (pharmacy shopping),
286 excess use (mean monthly medication possession ratio [19] (MPR) > 1 during the period), adherence to

13

1
2
3 287 French good practice guidelines regarding hypnotics, presence of an associated psychiatric disorder. The
4
5 288 analysis will be repeated during periods 2 and 4. In order to study the transitions between clusters over
6
7 289 time, a latent transition analysis (LTA) will be performed. The choice of the best model will be made
8
9 290 considering Bayesian Information Criterion (BIC). The choice of the best model will also be made with
10
11 291 consideration to the stability of the model (proportion of convergences among the 5000 iterations), the
12
13 292 BIC (lower is better) and the interpretability of the model.
14
15
16
17 293

18
19 294 *Within the field observational study among problematic consumers of zolpidem: A descriptive*
20
21 295 *analysis will be performed. We will compare the number and the distribution of the positives criteria of*
22
23 296 *problematic consumers (patients et users) before (for zolpidem treatment) and after the coming into*
24
25 297 *force of the new regulatory framework (for zolpidem treatment or replacement substances): duration of*
26
27 298 *consumption, dosage, manner in which zolpidem or other substance is obtained, route of administration*
28
29 299 *or pursued effects different from the expected effect of the treatment or substance. Parametric or non-*
30
31 300 *parametric paired-tests will be used for comparisons, according to the distributions of each variable. For*
32
33 301 *each hypothesis test, an alpha risk of 5% will be used. In case of multiple testing, a correction of the*
34
35 302 *significance threshold will be applied to avoid alpha risk inflation (Hochberg's method).*
36
37
38
39 303

40
41 304 *Impact on the consumption of other sedative molecules: analysis of prescription deferrals and switches*
42
43
44 305

45
46 306 *Within the SNDS database, regarding characterization of consumption trajectories:*
47

48 307 First of all, a time series analysis will be performed on aggregated monthly data (proportion of users per
49
50 308 month) to compare the changes in the consumption of zolpidem and other sedatives across all the study
51
52 309 periods. Cross-correlation between the different time series will be studied in order to identify if
53
54
55

1
2
3 310 zolpidem users have shifted their consumption to other drugs since the change in regulatory framework.
4
5
6 311 Secondly, a sequence analysis will be performed using dedicated tools (TramineR, SeqHMM and
7
8 312 arulesSequences packages in R software). This will include a cluster analysis of the sequences, in order to
9
10 313 identify typical trajectories in consumption and their modification following to the change in the
11
12 314 regulatory framework.

14 315 *Within the field study among physicians:* A descriptive analysis of changes in prescription
15
16 316 behavior and motives for change will be performed.

18 317 *Within the field study among problematic consumers of zolpidem:* A descriptive analysis of the
19
20 318 number of molecules tried as a replacement and the molecules that best replaced zolpidem, if
21
22 319 applicable, after the change in regulatory framework, will be performed. In patients stopping zolpidem,
23
24 320 but switching to another molecule, a univariate analysis of the same variables will be conducted in order
25
26 321 to describe the use of zolpidem before the coming into force of the new regulatory framework and the
27
28 322 use of other sedative drugs used in place of zolpidem after the coming into force of the new regulatory
29
30 323 framework. For each hypothesis test, an alpha risk of 5% will be used. In case of multiple testing, a
31
32 324 correction of the significance threshold will be applied to avoid alpha risk inflation (Hochberg's method).
33
34
35
36
37
38

39 326 **DISCUSSION**

40
41 327
42
43 328 The evaluation of the addictive power of zolpidem by the addictovigilance network, required over the
44
45 329 past, above and beyond the tools of the CEIP-A, the implementation of specific research programs. The
46
47 330 evaluation of the impact of the change in the regulatory framework will similarly require the
48
49 331 implementation of specific research programs. This project offers a design and a methodology which are
50
51 332 complementary to the tools of the CEIP-A [4], indispensable to the measurement of the impact, that we
52
53 333 believe to be major, of a change in the prescription requirements of the most sold hypnotic in France.
54
55

1
2
3 334 The ZORRO project aims to develop a method to measure the impact of the change in regulatory
4
5 335 framework on practitioners' prescriptions of sedative molecules. This evaluation is complex, as in order
6
7 336 to be thorough it must precisely measure the different aspects of the consequences of the regulatory
8
9 337 framework change, both from a quantitative and qualitative point of view. Rather than doing a single
10
11 338 study, we prefer to employ a strategy based on a number of different, and complementary,
12
13 339 methodological approaches. We have anticipated some possible bias: for the analysis of information
14
15 340 from a data base, we chose the data from the SNDS base as it contains information close to that of the
16
17 341 real consumption (more so than the sales figures of pharmaceutical laboratories for example).
18
19 342 Concerning the periods of reference BEFORE and AFTER, we have voluntarily chosen periods distant from
20
21 343 the times of announcement and the coming into force of the change in regulatory framework in order to
22
23 344 minimize bias linked to the transition period. Although, the regulatory framework change came into
24
25 345 force in April 2017, the ANSM had published information on the measure as from January 2017. A part of
26
27 346 the practitioners that prescribe zolpidem therefore anticipated the change in the regulatory framework
28
29 347 and started to change their prescription strategy as from January 2017. One of the limits of the SNDS
30
31 348 data base, that justifies our multimodal approach, is the complete absence of clinical information
32
33 349 concerning the effects pursued or felt by patients, as well as the modification in routes of administration.
34
35 350 Concerning the in-field clinical study, the principal bias is a memory bias of the questioned subjects. The
36
37 351 time between the change in the regulatory framework and the implementation of the study is however
38
39 352 incompressible as it is necessary to give patients and users sufficient hindsight in order to evaluate the
40
41 353 changes in their consumption of zolpidem. In fact, the questions have been formulated in a simplified
42
43 354 manner, and our project targets the most problematic consumers, who should remember with little
44
45 355 difficulty the changes, having an impact on their daily lives, following to the new regulatory framework.
46
47 356 A possible declarative bias does exist among patients and users, although this bias was taken into
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 357 account, in order to minimize it, in the conception of the questionnaire. On the one hand the
4
5
6 358 questionnaire is completely anonymous. On the other hand, for patients, the questionnaire is filled-in
7
8 359 away from any medical presence and handed back in a sealed envelope that is opened only by the
9
10 360 Nantes CEIP-A for data analysis. The subjects recruited via specialized care centers dedicated to drug
11
12 361 dependence are used to being questioned on their substance consumption by the CEIP-A personnel, in
13
14 362 the framework of their mission of surveillance of cases of addition to and abuse of psychoactive
15
16 363 substances. Our personnel have therefore developed an expertise in the realization of projects of this
17
18 364 type among the users of specialized care centers dedicated to drug dependence. The strengths of this
19
20 365 project lie within its' multimodal approach that allows, on the one hand, to document numerous
21
22 366 possible consequences of the regulatory framework change, and on the other hand, to insure the overall
23
24 367 coherence of the different studies via the management by an expert team in the field, coordinated by
25
26 368 the French national reference center on the addictive potential of zolpidem. This project may very well
27
28 369 have a double impact: On the one hand, it will provide additional data essential to the ANSMs' mission of
29
30 370 surveillance of the risk relative to overdose, abuse, addiction and misuse of sedative substances ; On the
31
32 371 other hand, this project could be the defining point of a series of steps (communication and information
33
34 372 campaigns , ...) designed to manage the public health issues surrounding zolpidem and to measure their
35
36 373 overall impact.
37
38
39
40
41
42

43 375 **ETHICS AND DISSEMINATION:**
44
45 376 **Ethics approval**
46
47 377 The protocol was approved on the 11/06/2018 by the Committee for the Protection of the Population
48
49 378 (CPP) and on the 12/04/2018 by the Committee of Expertise in Research, Studies and Evaluations in the
50
51 379 Field of Health (CEREES). It was also submitted to the National Commission of Information Technology
52
53 380 and Liberties (CNIL).
54
55
56
57
58
59
60

1
2
3 381 **Information to participants**
4

5 382 For the epidemiological analysis of the SNDS database: Not applicable
6

7 383 Practitioners: all practitioners will receive clear information regarding the study orally during the
8
9
10 384 telephone interview. Practitioners that participate in the recruitment of patients will also receive written
11
12 385 information.
13

14 386 Patients and users: general practitioners and the study agents in the specialized care centers dedicated
15
16 387 to drug dependence agree to inform all patients and users, in a clear and impartial manner, about the
17
18 388 protocol. They will also provide written information.
19

20
21 389 **Consent to participate**
22

23 390 For the epidemiological analysis of the SNDS database: Not applicable
24

25 391 Practitioners: oral non-refusal to participate will be sought before delivery of the telephone
26
27 392 questionnaire. Practitioners that accept to reply to the telephone questionnaire will be considered as not
28
29 393 in opposition of the study. For the recruitment of patients, practitioners that fill in the documents
30
31 394 relative to the inclusion of a patient will be considered as agreeing to participate in the study.
32
33

34 395 Patients and users: oral non-refusal from patients and users will be sought. Subjects (patients or users)
35
36 396 that fill out an auto questionnaire will be considered as agreeing to participate in the study.
37
38

39 397 **Consent for publication**
40

41 398 The written information documents provided to practitioners, patients and users, state that the
42
43 399 anonymous information gathered during the study is likely to be used in scientific publications and public
44
45 400 communications.
46

47 401 **Availability of data and material**
48

49 402 Not applicable
50
51

52 403
53
54
55
56

404 **REFERENCES**

- 405 1. Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-
406 benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data.
407 *Addict Abingdon Engl.* 2003;98:1371–8.
- 408 2. Yen C-F, Yen C-N, Ko C-H, Hwang T-J, Chen C-S, Chen T-T, et al. Correlates of dependence and beliefs
409 about the use of hypnotics among zolpidem and zopiclone users. *Subst Use Misuse.* 2015;50:350–7.
- 410 3. Comité OMS d'experts de la pharmacodépendance (1998 : Genève S, Organization WH. Comité OMS
411 d'experts de la pharmacodépendance : trente et unième rapport. WHO Expert Committee on Drug
412 Dependence : thirty-first report. 1999. <http://apps.who.int/iris/handle/10665/42285>. Accessed 17 Aug
413 2018.
- 414 4. Jouanjus E, Gibaja V, Kahn J-P, Haramburu F, Daveluy A. Signal identification in addictovigilance: the
415 functioning of the French system. *Therapie.* 2015;70:113–31.
- 416 5. Micaleff J, Jolliet P, Victorri-Vigneau C, Mallaret M, Richard N, Haramburu F, et al. [First meeting of the
417 French CEIP (centres d'évaluation et d'information sur la pharmacodépendance). Assessment of the
418 abuse and pharmacodependence potential during drug development]. *Therapie.* 2008;63:55–65.
- 419 6. Jouanjus E, Guernec G, Lapeyre-Mestre M, French Addictovigilance Network. Medical prescriptions
420 falsified by the patients: a 12-year national monitoring to assess prescription drug diversion. *Fundam Clin*
421 *Pharmacol.* 2018.
- 422 7. Victorri-Vigneau C, Dailly E, Veyrac G, Jolliet P. Evidence of zolpidem abuse and dependence: results of
423 the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J*
424 *Clin Pharmacol.* 2007;64:198–209.

- 1
2
3 425 8. Victorri-Vigneau C, Gérardin M, Rousselet M, Guerlais M, Grall-Bronnec M, Jolliet P. An update on
4
5 426 zolpidem abuse and dependence. *J Addict Dis.* 2014;33:15–23.
6
7
8
9 427 9. Victorri-Vigneau C, Feuillet F, Wainstein L, Grall-Bronnec M, Pivette J, Chaslerie A, et al.
10
11 428 Pharmacoepidemiological characterisation of zolpidem and zopiclone usage. *Eur J Clin Pharmacol.*
12
13 429 2013;69:1965–72.
14
15
16 430 10. Rousselet M, Feuillet F, Gerardin M, Jolliet P, Hardouin J-B, Victorri-Vigneau C. The French
17
18 431 addictovigilance network clinical assessment: Z-drugs, true false twins. *Expert Opin Drug Saf.*
19
20 432 2017;16:1063–9.
21
22
23
24 433 11. ANSM : Agence nationale de sécurité du médicament et des produits de santé. Prescription
25
26 434 obligatoire du zolpidem sur ordonnance sécurisée - Point d'Information. 2017.
27
28 435 [http://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-](http://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information)
29
30 436 [obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information](http://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information). Accessed 17 Apr 2018.
31
32
33
34 437 12. ANSM : Agence nationale de sécurité du médicament et des produits de santé. Etat des lieux en 2013
35
36 438 de la consommation des benzodiazépines en France - Point d'Information. 2014. [http://ansm.sante.fr/S-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-de-la-consommation-des-benzodiazepines-en-France-Point-d-Information)
37
38 439 [informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-de-la-consommation-des-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-de-la-consommation-des-benzodiazepines-en-France-Point-d-Information)
39
40 440 [benzodiazepines-en-France-Point-d-Information](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-de-la-consommation-des-benzodiazepines-en-France-Point-d-Information). Accessed 17 Apr 2018.
41
42
43
44 441 13. ANSM : Agence nationale de sécurité du médicament et des produits de santé. Etat des lieux de la
45
46 442 consommation des benzodiazépines - Point d'Information. 2017. [http://ansm.sante.fr/S-informer/Points-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-Information)
47
48 443 [d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-Information)
49
50 444 [Information](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-Information). Accessed 17 Apr 2018.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 445 14. Martin-Latry K, Bégaud B. Pharmacoepidemiological research using French reimbursement
4
5 446 databases: yes we can! *Pharmacoepidemiol Drug Saf.* 2010;19:256–65.
6
7
8
9 447 15. Moracchini C, Orleans V, Miloudi S, Frauger E, Micallef J, Thirion X, et al. [General Practitioners'
10
11 448 Contribution to Dependence Assessment: the OPEMA Programme]. *Thérapie.* 2012;67:397–404.
12
13
14 449 16. Accueil | SNDS. <https://www.snds.gouv.fr/SNDS/Accueil>. Accessed 28 Jun 2018.
15
16
17 450 17. ameli.fr - Sniiram. <https://www.ameli.fr/l-assurance-maladie/statistiques-et->
18
19 451 [publications/sniiram/finalites-du-sniiram.php](https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/sniiram/finalites-du-sniiram.php). Accessed 28 Jun 2018.
20
21
22
23 452 18. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).
24
25 453 Guide on Methodological Standards in Pharmacoepidemiology (Revision 5) EMA/95098. 2010.
26
27 454 http://www.encepp.eu/standards_and_guidances/. Accessed 17 Apr 2018.
28
29
30
31 455 19. Sattler ELP, Lee JS, Perri M. Medication (re)fill adherence measures derived from pharmacy claims
32
33 456 data in older Americans: a review of the literature. *Drugs Aging.* 2013;30:383–99.
34
35
36 457 **AUTHOR STATEMENT**
37
38 458 MG contributed to the questionnaires development and wrote the first draft of the manuscript.
39
40
41 459 MR wrote the first draft of the protocol, contributed to the questionnaires development and to the
42
43 460 manuscript redaction.
44
45
46
47 461 PC designed statistical analysis of the SNDS database and contributed to the manuscript redaction.
48
49
50 462 MGB provided her expertise in the area of addictology. She contributed to the preparation of the
51
52 463 zolpidem problematic consumers' questionnaire and validated their relevance to evaluate problematic
53
54 464 use.
55
56
57
58
59
60

1
2
3 465 PL contributed to the questionnaires development.
4
5

6 466 PJ validated the final draft of the protocol and the manuscript.
7

8 467 CVV is responsible for the project management. She designed the study and finalized the protocol.
9

10 468 All authors read and approved the final manuscript.
11
12
13

14 469

15
16 470 **FUNDING STATEMENT**
17

18 471 This work was supported by ANSM grant number AAP-2017-027
19

20 472 **COMPETING INTERESTS**
21

22 473 The authors declare that they have no competing interests. For this project, the University Hospital of
23

24 474 Nantes has received funding only from the ANSM.
25
26
27

28 475 **ACKNOWLEDGEMENTS**
29

30 476 We would like to thank, in addition to the authors, all who have worked on this project in order to make
31

32 477 it possible : Marie-Lyne Pinot for her help in the elaboration of the call to tender, Léa Ferrand for her
33

34 478 work with the regulatory bodies, all the CEIP-A for their valuable participation in the recruitment of
35

36 479 practitioners as well as the specialized care centers dedicated to drug dependence of their respective
37

38 480 regions. We would also like to thank the ANSM for the financial support they provided so that this
39

40 481 research project may be completed, and the Nantes University Hospital for the payment of publication
41

42 482 charges of this manuscript.
43
44

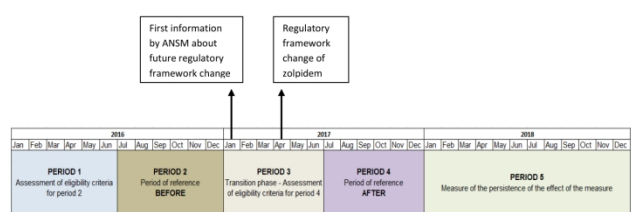
45 483 **WORD COUNT**
46

47 484 4258
48
49

50 485
51
52
53
54
55
56

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: Periods of study of the SNDS data base



ANSM: French National Agency for Medicines and Health Products Safety.

Periods of study of the SNDS database

825x583mm (72 x 72 DPI)

BMJ Open

ZORRO study Protocol – French national health insurance database analysis and field study focusing on the impact of secure prescription pads on zolpidem consumption and sedative drug misuse.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027443.R1
Article Type:	Protocol
Date Submitted by the Author:	19-Mar-2019
Complete List of Authors:	Gerardin, Marie; University hospital of Nantes, Department of Clinical Pharmacology Rousselet, Morgane; University hospital of Nantes, Department of Clinical Pharmacology; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch" Caillet, Pascal; University hospital of Nantes, Department of Clinical Pharmacology Grall-Bronnec, Marie; University Hospital of Nantes, Clinical Investigation Unit BALANCED "BehaviorAL AddictioNs and ComplEx mood Disorders"; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch" Loue, Pierre; University Hospital of Rouen, Departement of General medicine Jolliet, Pascale; University hospital of Nantes, Department of Clinical Pharmacology; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch" Victorri-Vigneau, C; University Hospital of Nantes, Department of Clinical Pharmacology; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch"
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Addiction
Keywords:	zolpidem, secured prescription, change in law, impact, addictovigilance, Substance misuse < PSYCHIATRY

SCHOLARONE™
Manuscripts

1
2
3 **Title:** ZORRO study Protocol – French national health insurance database analysis and field study
4
5 focusing on the impact of secure prescription pads on zolpidem consumption and sedative drug
6
7 misuse.
8
9

10
11
12 **Authors:**
13

14 Marie GERARDIN, Clinical Pharmacology Department, Nantes University Hospital, Nantes,
15 France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. marie.gerardin@chu-nantes.fr
16
17

18 Morgane ROUSSELET, Clinical Pharmacology Department, Nantes University Hospital, Nantes,
19 France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. Addictology and Psychiatry Department,
20 Nantes University Hospital, 85 rue de Saint-Jacques, 44093 Nantes cedex 1, France. INSERM U1246
21 SPHERE “methodS in Patient-centered outcomes and HHealth ResEarch”, Nantes and Tours University,
22 22 boulevard Benoni Goullin, 44 000 Nantes, France. morgane.rousselet@chu-nantes.fr
23
24
25

26 Pascal CAILLET, Clinical Pharmacology Department, Nantes University Hospital, Nantes,
27 France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. pascal.caillet@chu-nantes.fr
28
29

30 Marie GRALL-BRONNEC, Addictology and Psychiatry Department, Nantes University Hospital,
31 85 rue de Saint-Jacques, 44093 Nantes cedex 1, France. INSERM U1246 SPHERE “methodS in Patient-
32 centered outcomes and HHealth ResEarch”, Nantes and Tours University, 22 boulevard Benoni Goullin,
33 44 000 Nantes, France. marie.bronnec@chu-nantes.fr
34
35
36

37 Pierre LOUE, General medical Department, Rouen faculty of medicine, Rouen University
38 Hospital. peterloue@me.com
39
40

41 Pascale JOLLIET, Clinical Pharmacology Department, Nantes University Hospital, Nantes,
42 France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. INSERM U1246 SPHERE “methodS in
43 Patient-centered outcomes and HHealth ResEarch”, Nantes and Tours University, 22 boulevard Benoni
44 Goullin, 44 000 Nantes, France. pascale.jolliet@univ-nantes.fr
45
46
47

48 Caroline VICTORRI-VIGNEAU, Clinical Pharmacology Department, Nantes University Hospital,
49 Nantes, France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. INSERM U1246 SPHERE “methodS
50
51
52

1
2
3 in Patient-centered outcomes and HHealth ResEarch”, Nantes and Tours University, 22 boulevard
4
5 Benoni Goullin, 44 000 Nantes, France. caroline.vigneau@chu-nantes.fr
6
7

8 **Corresponding author:**

9
10 Caroline VICTORRI-VIGNEAU

11
12 Adress: Clinical Pharmacology Department, Nantes University Hospital, Nantes, France,

13
14 9 quai Moncouso, 44 093 Nantes cedex 1, France

15
16 Phone : +33240084073

17
18 E-Mail : caroline.vigneau@chu-nantes.fr
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Introduction

In recent years, data collected by the French Addictovigilance Network (FAN) has shown the potential for abuse and addiction associated with zolpidem (the most sold hypnotic drug in France). Since the 10th of April 2017, new regulations have come into force that require zolpidem to be prescribed on special secure prescription pads, in order to reduce the risk of abuse or misuse. This measure has far-reaching repercussions that are not only limited to the consumption of zolpidem but also extend to the usage of sedative medication on a whole.

The objective of the ZORRO study (ZOlpidem and the Reinforcement of the Regulation of prescription Orders) is to evaluate the overall impact of the new regulatory framework requiring zolpidem to be prescribed on special secure prescription pads. Three axes will be evaluated: the number of consumers, the type of consumption (chronic use versus occasional use, problematic consumption versus non-problematic use), and the consumption of other sedative molecules.

Methods and analysis

The ZORRO study is an epidemiological, observational, national multi-center, non-controlled, prospective research project supported by the French National Agency for Medicines and Health Products Safety (ANSM). The evaluation of the impact of the regulatory framework change relative to zolpidem will be done according to two axes: via an epidemiological study of the French National Health Insurance database and by the implementation of field studies of prescribers and consumers of zolpidem.

Ethics and dissemination

The local Research Ethics Committee (GNEDS) approved this study on 3 March 2018. Results will be presented in national and international conferences and submitted to peer-reviewed journals.

Trial registration number NCT03584542

Keywords

Zolpidem, secured prescription, change in law, impact, addictovigilance, misuse.

ARTICLE SUMMARY

Strengths and limitations of the study

This study will contribute to setting up an innovative impact measure in order to evaluate the efficacy of institutions' response to the issue of zolpidem misuse and dependence.

The study will be representative of the French population by use of the French healthcare database SNDS, with a focus on how physicians and problematic consumers have coped with the change in law by use of complementary field studies.

Owing to technical constraints inherent to medico-administrative database use, the use of drugs that are not reimbursed is not be observable in the SNDS database, as well as clinical data that is not routinely gathered.

A lack of representativity may occur during participants' recruitment regarding the part of the project involving field sampling.

INTRODUCTION

In recent years, zolpidem has been the best-selling hypnotic drug in France. Worldwide, a number of cases of misuse of zolpidem have been described (in Europe and in the United-States [1, 2]). The World Health Organisation (WHO) believes that the frequency of cases of abuse or addiction to zolpidem is similar to that associated with hypnotic benzodiazepines [3]. As a result, Zolpidem has been the target of a number of regulatory framework changes in both French national and international spheres. In particular, the United Nations has placed zolpidem in table IV of the Vienna convention which aims to control the abuse and trafficking of psychotropic substances (ruling of July 15th 2002)

In France, the French Addictovigilance network (FAN), piloted by the French National Agency for Medicines and Health Products Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé; ANSM) is in charge of the surveillance of cases of abuse and addiction associated with any drug or substance with a psychoactive effect. The surveillance is based on a network of 13 Centres for evaluation of and information on drug dependence and addiction monitoring (Centres d'Evaluation et d'Information sur la Pharmacodépendance-Addictovigilance; CEIP-A), who evaluate the addictive potential of a given drug via notifications provided by health professionals [4], and via specifically-developed pharmaco-epidemiology tools [5, 6].

Some controlled medicines and psychotropic substances (including zolpidem) are under reinforced surveillance by the ANSM as they are associated with a risk of misuse and addiction. In France, zolpidem is enlisted on the list I of harmful substances, that is to say, it is considered as a substance associated with a health risk. An initial national survey of the addictovigilance network in 2002 found serious and worrying cases of abuse and addiction to zolpidem. The 2002 survey revealed the existence of two consumer groups: a population of chronic high dosage consumers with a therapeutic usage of zolpidem, and a population of "misusers" in search of an effect other than hypnotic (euphoria, wellbeing or stimulant effect). The same survey also found, via the analysis of the FAN pharmaco-epidemiology tools, that zolpidem is a substance prone to abuse [7]. Following to

1
2
3 this conclusion, the Summary of Product Characteristics (SPC) of zolpidem was modified, with
4 notably the addition of a warning with respect to addiction. In June 2011, an update of data relative
5 to the addictive potential of zolpidem found the same two consumer groups as in the 2002 survey
6 with cases of increasing severity associated with the consumption of particularly high dosages [8]. In
7 light of these results, the prescription of zolpidem on special secure prescription pads was put
8 forward by the National Commission of Narcotics and Psychotropic Substances (Commission
9 Nationale des Stupéfiants et Psychotropes; CNSP). In 2012, the FAN tools all, once again, proclaim
10 zolpidem as a problematic substance.

11
12 The surveillance tools of the FAN allow for the identification of the problem of addiction in specific
13 population groups, but they do not provide a general population risk profile. However, the analysis of
14 quantitative data, in the French National Health Insurance database, relative to the usage of
15 zolpidem and zopiclone in the general population [9], provided the identification of a number of
16 different clinical profiles of zolpidem consumers: (i) « non-problematic » consumers, the largest
17 group; (ii) individuals who could have developed a tolerance to the hypnotic effects of zolpidem, for
18 whom the prescription of alternative hypnotic/anxiolytic medication is justified; (iii) potential
19 problematic consumers of zolpidem (1%) (high rate of fraudulent behavior, excessive usage, non-
20 respect of guidelines and medical-pharmaceutical nomadism). In 2017, another research program
21 gave insight into the characteristics of the two aforementioned consumer groups via the analysis of
22 reports from health professionals [10].

23
24 Following to these results, on the 11th of January 2017, the ANSM decreed that as from April the 10th
25 2017, the prescription of zolpidem was to be done on secure prescription pads [11]. The ANSM
26 stated that « this measure is taken in order to limit the risk of abuse and misuse » and « to
27 encourage correct usage ». In a country where the consumption of psychotropic drugs is high, a
28 ruling that impacts the most sold hypnotic drug [12, 13] will disrupt not only its' usage but also on a
29 larger scale the overall prescription of sedative substances (hypnotics and anxiolytics). The current
30 project aims to develop a means to measure the impact of this new ruling, in the scope of works of
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 the ANSM, that is to say, in terms of the reduction of the risk of abuse, the improvement of correct
4 use of zolpidem and the change in prescriptions of sedative molecules. This project forms part of the
5 evaluation of zolpidem done by the Nantes CEIP-A, the organization in charge of its follow up. In
6 addition to the tools used by the FAN [5], this project will allow for a longitudinal evaluation of the
7 trajectories of different patients, as well as providing insight into the general population.
8
9
10
11
12
13
14
15

16 **METHODS AND ANALYSIS**

17 **Aim**

18
19 The objective of the ZORRO study (ZOlpidem and the Reinforcement of the Regulation of prescription
20 Orders) is to evaluate the overall impact of the obligation to use secure prescription pads for
21 zolpidem. We propose a multimodal approach that will provide valuable insight into three key
22 questions: 1) what is the impact of this measure on the number of consumers? 2) What is the impact
23 of this measure on the type of consumption? 3) What is the impact of this measure on the
24 consumption of other sedative molecules?
25
26
27
28
29
30
31
32
33

34 **Study design**

35
36 This scientific project is based on a multimodal epidemiological approach, which combines a
37 retrospective cohort study and a transversal field study. The cohort study draws from the French
38 National Health Information database (Système National des Données de Santé; SNDS, formerly
39 known as the French National Inter-schemes Health Insurance database (Système National
40 d'Information Inter-Régimes de l'Assurance Maladie; SNIIRAM)) [14]. The transversal field study
41 involves the gathering in-field of clinical data of different populations: general practitioners that
42 prescribe zolpidem as well as consumers (both patients having consulted a general practitioner and
43 those having recourse to specialized care centers dedicated to drug dependence). To our knowledge,
44 a study of this amplitude does not exist in France.
45
46
47
48
49
50
51
52
53
54

55
56 These two approaches will provide insight into three key areas:
57
58
59
60

- 1
2
3 - To evaluate the impact of the measure on the number of consumers, we will estimate via the
4 SNDS database the prevalence and the incidence of zolpidem consumers in the general
5 population before and after the regulatory framework change.
6
7
8
9
10 - To evaluate the impact of the measure on the type of consumption, we will explore the
11 changes in the modes of consumption: occasional use *versus* chronic use and problematic
12 use *versus* non-problematic use. Problematic use is defined as consumption outside of the
13 SPC guidelines for at least one of the following parameters: the duration of consumption, the
14 dosage, the means of procurement, the routes of administration or the search for an effect
15 other than hypnotic. This evaluation will be done both from SNDS database for the
16 evaluation of the general population and from the field studies for the evaluation of
17 problematic consumers of zolpidem (patients of general practitioners and users of
18 specialized care centers dedicated to drug dependence).
19
20
21
22
23
24
25
26
27
28
29
30 - To evaluate the impact of the measure on the consumption of other sedative molecules, we
31 will analyze the reporting of prescriptions and the changes observed both in the general
32 population in the SNDS database as well as among prescribers and problematic consumers of
33 zolpidem (patients of general practitioners and users of drug-user risk reduction centers or
34 specialized care centers dedicated to drug dependence).
35
36
37
38
39
40

41 **Setting of the study**

42
43 The Nantes CEIP-A, is the national investigating center in charge of the management, surveillance
44 and coordination of the entire project. General practitioners, their patients and users of zolpidem
45 will be recruited across France. Recruitment as well as the gathering and the analysis of data (SNDS
46 database and field studies) will be done by the Nantes CEIP-A.
47
48
49

50
51
52 A multi-disciplinary pilot committee, comprised of pharmacologists, general practitioners, a
53 methodologist bio-statistician, a clinical study technician and of an addictologist psychiatrist, has
54 been constituted in order to define the research protocol and in order to insure the scientific and
55 methodological validity of the study.
56
57
58
59
60

Patient and public involvement

Patients were not involved in the design of the study.

Populations

Analysis of the SNDS database

The study sample will include all patients in the database during the period from the 1st of January 2016 to the 31st of December 2018. The target population of our research will be constituted of consumers of zolpidem included in the SNDS database between the 1st of January 2016 and the 31st of December 2018.

Field study among General practitioners

Practitioners, situated within the national borders, will be randomly selected from the list of the National Health Insurance for Wage laborers (Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés; CNAMTS). Practitioners specialized in the care of addictions and used to working with the FAN, will also be solicited [15]. Practitioners with an independent practice at the time of change in regulatory framework and who agree to participate, via oral consent, will be included.

Field study among problematic consumers of zolpidem (patients of general practitioners and users of specialized care centers dedicated to drug dependence)

Participating practitioners will select patients who presented a problematic use of zolpidem before the coming into force of the new regulatory framework. Patients will be included in the study if they provide their oral consent to participate. Participating practitioners will give them a questionnaire to complete in the waiting room and return in a sealed envelope. Participating specialized care centers

1
2
3 dedicated to drug dependence (Centre de Soins, d'Accompagnement et de Prévention en
4 Addictologie; CSAPA) and drug-user risk reduction centers (Centre d'Accueil et d'Accompagnement à
5 la Réduction des risques pour Usagers de Drogues; CAARUD) will select users who presented a
6
7 problematic use of zolpidem before the coming into force of the new regulatory framework. Users
8
9 will be included in the study if they provide their oral consent to participate. The facility staff will
10
11 provide them with a questionnaire to complete. A problematic consumption of zolpidem is defined
12
13 according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria of
14
15 Substance Use Disorder. Under aged or protected individuals as well as subjects with French
16
17 language difficulties (understanding, reading or writing) incompatible with the filling out of a
18
19 questionnaire, will not be included in the study.
20
21
22
23
24
25
26

27 **Materials**

28 *Analysis of the SNDS database*

29
30
31 The SNDS database is described in detail in the publication by Bezin *et al* [14] as well as on related
32
33 internet sites [16, 17]. The SNDS links several existing databases: the SNIIRAM, the nationwide claims
34
35 database of the French National Healthcare system; the national hospital database (Programme de
36
37 Médicalisation des Systèmes d'Information; PMSI) and the national death registry (Centre
38
39 d'épidémiologie sur les causes médicales de Décès; CepiDC). The SNDS covers more than 98% of the
40
41 French population (66 million people) from birth (or immigration) to death (or emigration), even in
42
43 case of change in occupation or retirement. Data is individual and anonymous. The SNDS contains a
44
45 longitudinal record of health encounters, hospital diagnoses and drugs deliveries relative to
46
47 outpatient medical care claims, including all reimbursed drugs, information from hospital discharge
48
49 summaries, and date of death.
50
51
52
53
54
55
56
57

58 *Field study among general practitioners*

1
2
3 Participating general practitioners will reply to short telephone questionnaire, which will gather
4
5 information on their perceptions and their prescription strategy following to the new regulatory
6
7 framework (continuation of zolpidem on a secure prescription pad, prescription of a different
8
9 sedative drug, cease in hypnotic prescriptions). The criteria for their choices will also be explored.
10
11
12

13 14 *Field study among problematic consumers of zolpidem (patients and users)*

15
16 Patients and users will fill out a two-part auto-questionnaire. The first part will evaluate the
17
18 consumption of zolpidem before the coming into force of the new regulatory framework (dosages
19
20 used, duration, pursued effects and effects felt) and their change or not after the coming into force
21
22 of the new regulatory framework (cease, change in dosage, relay to another drug or sedative
23
24 substance). The second part of the questionnaire will be filled out only by patients or users for whom
25
26 a change is observed and it will gather information pertaining to the favored replacement substance
27
28 (dosages used, duration, pursued effects and effects felt). General practitioners and staff of the
29
30 CSAPA and CCARUD will return the completed questionnaires to the CEIP-A in Nantes for analysis.
31
32
33
34
35

36 **Study size**

37 38 39 40 *Analysis of the SNDS database:*

41
42 In light of the retrospective nature of the study and of the databases used, the calculation of a power
43
44 is not necessary, in accordance with the good practice guidelines of the European Network of
45
46 Centers for Pharmaco-epidemiology and Pharmacovigilance [18].
47
48
49
50

51 52 *Field studies among prescribing general practitioners and problematic consumers of zolpidem:*

53
54 Three hundred practitioners will be selected in order to insure that at least one hundred
55
56 practitioners participate in the recruitment of problematic consumers of zolpidem. For feasibility
57
58 reasons, the number of general practitioner patients to be included depends upon the construction
59
60

1
2
3 of a convenience sample. This sample is estimated to be about 200 patients. Furthermore, 200 users
4
5 will be recruited via the specialized care centers dedicated to drug dependence.
6
7
8
9

10 **Statistical methods**

11 All variables will undergo a descriptive analysis. Quantitative variables will be described using usual
12 position (mean or median) and dispersion (standard deviation, interquartile range) parameters. The
13 normality of their distribution will be assessed numerically (normality test) and graphically. For
14 normally distributed quantitative variables, mean and standard deviation will be used. For non-
15 normally distributed variables, median and interquartile ranges will be used. Qualitative variables will
16 be described using number and frequency tables for each parameter. All analysis will be conducted
17 with SAS software. Specific statistical methods will be implemented in order to answer each question
18 adequately.
19
20
21
22
23
24
25
26
27
28
29
30
31

32 *Impact of the measure on the number of consumers: estimation of prevalence and incidence of*
33 *zolpidem users within the SNDS database before and after the regulatory framework change*
34
35
36

37 A number of periods will be studied (figure 1). The proportion of patients having received at least
38 one delivery of zolpidem during the period 2 and during the period 4 will be compared using a Mc
39 Nemar test for paired proportion. Patients missing from one of the two periods will be recorded as
40 non-users. The significance threshold will be fixed at 5%. An incident user will be defined as a patient
41 receiving a first delivery of zolpidem without any prior delivery over the preceding 6 months. The
42 number of incident users within each period will be compared using a Poisson model. The
43 significance threshold for each coefficient will be fixed at 5%.
44
45
46
47
48
49
50
51
52
53
54

55 *Impact on the type of consumption regarding changes in treatment duration*
56

57 *Within the SNDS database:* The length of the first treatment episode will be evaluated by
58 calculating the number of days covered by the initial delivery (theoretical length of treatment). The
59
60

1
2
3 predicted variable will be the duration of treatment over a threshold (yes/no). The period will be
4 entered as a covariate in the model, enabling the study of the effect of the period on the probability
5 of the treatment being chronic while taking into account the correlation of treatment characteristics
6 for a given patient.
7
8
9
10

11 *Within the field study among problematic consumers of zolpidem:* A descriptive analysis will
12 be performed, with the characterization of the duration of treatment with zolpidem before the
13 regulatory framework change and of the duration of treatment with zolpidem or of the replacement
14 drug/substance after the regulatory framework change.
15
16
17
18
19

20
21
22
23 *Impact on the type of consumption addressing changes in the type of consumption, problematic or*
24 *non-problematic*
25
26

27 *Within the SNDS database:* A latent class analysis (LCA) will be conducted within each period,
28 including the following variables: age, sex, presence of a chronic disease, poor economic status,
29 prescribing practitioners specialty (only whether or not a general practitioner), number of different
30 prescribing practitioners (doctor shopping), number of dispensing pharmacies (pharmacy shopping),
31 excess use (mean monthly medication possession ratio [19] (MPR) > 1 during the period), adherence
32 to French good practice guidelines regarding hypnotics (encompassing the absence of association
33 with others benzodiazepines), presence of an associated psychiatric disorder (identified by
34 concomitant drug use, i.e opioids substitution treatments, psycholeptic and psychoanaleptic drugs).
35 The analysis will be repeated during periods 2 and 4. In order to study the transitions between
36 clusters over time, a latent transition analysis (LTA) will be performed. The choice of the best model
37 will be made considering Bayesian Information Criterion (BIC). The choice of the best model will also
38 be made with consideration to the stability of the model (proportion of convergences among the
39 5000 iterations), the BIC (lower is better) and the interpretability of the model.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 *Within the field observational study among problematic consumers of zolpidem: A descriptive*
4 analysis will be performed. We will compare the number and the distribution of the positive criteria
5 of problematic consumers (patients et users) before (for zolpidem treatment) and after the coming
6 into force of the new regulatory framework (for zolpidem treatment or replacement substances):
7 duration of consumption, dosage, manner in which zolpidem or other substance is obtained, route of
8 administration or pursued effects different from the expected effect of the treatment or substance.
9 Parametric or non-parametric paired-tests will be used for comparisons, according to the
10 distributions of each variable. For each hypothesis test, an alpha risk of 5% will be used. In case of
11 multiple testing, a correction of the significance threshold will be applied to avoid alpha risk inflation
12 (Hochberg's method).
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27

28 *Impact on the consumption of other sedative molecules: analysis of prescription deferrals and*
29 switches
30
31

32 *Within the SNDS database, regarding characterization of consumption trajectories:*

33 Firstly, a time series analysis will be performed on aggregated monthly data (proportion of users per
34 month) to compare the changes in the consumption of zolpidem and other sedatives across all the
35 study periods. Cross-correlation between the different time series will be studied in order to identify
36 if zolpidem users have shifted their consumption to other drugs since the change in regulatory
37 framework. Secondly, a sequence analysis will be performed using dedicated tools (TramineR,
38 SeqHMM and arulesSequences packages in R software). This will include a cluster analysis of the
39 sequences, in order to identify typical trajectories in consumption and their modification following to
40 the change in the regulatory framework.
41
42
43
44
45
46
47
48
49
50
51

52 *Within the field study among physicians: A descriptive analysis of changes in prescription*
53 behaviour and motives for change will be performed.
54
55

56 *Within the field study among problematic consumers of zolpidem: A descriptive analysis of*
57 the number of molecules tried as a replacement and the molecules that best replaced zolpidem, if
58
59
60

1
2
3 applicable, after the change in regulatory framework, will be performed. In patients stopping
4 zolpidem, but switching to another molecule, a univariate analysis of the same variables will be
5 conducted in order to describe the use of zolpidem before the coming into force of the new
6 regulatory framework and the use of other sedative drugs used in place of zolpidem after the coming
7 into force of the new regulatory framework. For each hypothesis test, an alpha risk of 5% will be
8 used. In case of multiple testing, a correction of the significance threshold will be applied to avoid
9 alpha risk inflation (Hochberg's method).
10
11
12
13
14
15
16
17
18
19
20

21 **DISCUSSION**

22
23
24
25 The evaluation of the addictive power of zolpidem by the addictovigilance network, required over
26 the past, above and beyond the tools of the CEIP-A, the implementation of specific research
27 programs. The evaluation of the impact of the change in the regulatory framework will similarly
28 require the implementation of specific research programs. This project offers a design and a
29 methodology which are complementary to the tools of the CEIP-A [4], indispensable to the
30 measurement of the impact, that we believe to be major, of a change in the prescription
31 requirements of the most sold hypnotic in France. The ZORRO project aims to develop a method to
32 measure the impact of the change in regulatory framework on practitioners' prescriptions of
33 sedative molecules. This evaluation is complex, as in order to be thorough it must precisely measure
34 the different aspects of the consequences of the regulatory framework change, both from a
35 quantitative and qualitative point of view. Rather than doing a single study, we prefer to employ a
36 strategy based on a number of different, and complementary, methodological approaches. We have
37 anticipated some possible bias: for the analysis of information from a database, we chose the data
38 from the SNDS database as it contains information close to that of the real consumption. In the
39 absence of available data on the drugs actually taken by patients, this database provides information
40 on the drugs that patients obtain from pharmacies, which is more accurate than sales data for
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 example. Concerning the periods of reference before and after, we have voluntarily chosen periods
4
5 distant from the times of announcement and the coming into force of the change in regulatory
6
7 framework in order to minimize bias linked to the transition period. Although the regulatory
8
9 framework change came into force in April 2017, the ANSM had published information on the
10
11 measure as from January 2017. A part of the practitioners prescribing zolpidem therefore anticipated
12
13 the change in the regulatory framework and started to change their prescription strategy as from
14
15 January 2017. One of the limits of the SNDS database, that justifies our multimodal approach, is the
16
17 complete absence of clinical information concerning the effects pursued or felt by patients, as well as
18
19 the modification in routes of administration. Concerning the in-field clinical study, the principal bias
20
21 is a memory bias of the questioned subjects. The time between the change in the regulatory
22
23 framework and the implementation of the study is however incompressible as it is necessary to give
24
25 patients and users sufficient hindsight in order to evaluate the changes in their consumption of
26
27 zolpidem. In fact, the questions have been formulated in a simplified manner, and our project targets
28
29 the most problematic consumers, who should remember with little difficulty the changes, having an
30
31 impact on their daily lives, following to the new regulatory framework. A possible declarative bias
32
33 does exist among patients and users, although this bias was taken into account, in order to minimize
34
35 it, in the conception of the questionnaire. On the one hand the questionnaire is completely
36
37 anonymous. On the other hand, for patients, the questionnaire is filled-in away from any medical
38
39 presence and handed back in a sealed envelope that is opened only by the Nantes CEIP-A for data
40
41 analysis. The CEIP-A personnel are accustomed to interviewing subjects recruited via specialized care
42
43 centers dedicated to drug dependence on their substance consumption, in the framework of their
44
45 mission of surveillance of addition and abuse of psychoactive substances. Our personnel have
46
47 therefore developed an expertise in the realization of projects of this type among the users of
48
49 specialized care centers dedicated to drug dependence. The strengths of this project lie within its'
50
51 multimodal approach. It allows, on the one hand, to document numerous possible consequences of
52
53 the regulatory framework change, and on the other hand, to insure the overall coherence of the
54
55
56
57
58
59
60

1
2
3 different studies via the management by an expert team in the field, coordinated by the French
4 national reference center on the addictive potential of zolpidem. This project may very well have a
5 double impact: on the one hand, it will provide additional data essential to the ANSMs' mission of
6 surveillance of the risk relative to overdose, abuse, addiction and misuse of sedative substances; on
7 the other hand, this project could be the defining point of a series of steps (for example
8 communication and information campaigns) designed to manage the public health issues
9 surrounding zolpidem and to measure their overall impact.
10
11
12
13
14
15
16
17
18
19
20

21 **ETHICS AND DISSEMINATION:**

22 **Ethics approval**

23
24 The Committee for the Protection of the Population (CPP) approved the protocol on the 11/06/2018
25 and the Committee of Expertise in Research, Studies and Evaluations in the Field of Health (CEREES)
26 on the 12/04/2018. The National Commission of Information Technology and Liberties (CNIL) gave a
27 favorable opinion.
28
29
30
31
32

33 **Information to participants**

34 For the epidemiological analysis of the SNDS database: not applicable

35
36 Practitioners: all practitioners will receive clear information regarding the study orally during the
37 telephone interview. Practitioners that participate in the recruitment of patients will also receive
38 written information.
39
40
41
42
43

44 Patients and users: general practitioners and the study agents in the specialized care centers
45 dedicated to drug dependence agree to inform all patients and users, in a clear and impartial
46 manner, about the protocol. They will also provide written information.
47
48
49
50

51 **Consent to participate**

52 For the epidemiological analysis of the SNDS database: not applicable

53
54 Practitioners: oral non-refusal to participate will be sought before delivery of the telephone
55 questionnaire. Practitioners that accept to reply to the telephone questionnaire will be considered as
56
57
58
59
60

1
2
3 not in opposition of the study. For the recruitment of patients, practitioners that fill in the
4 documents relative to the inclusion of a patient will be considered as agreeing to participate in the
5 study.
6
7
8

9 Patients and users: oral non-refusal from patients and users will be sought. Subjects (patients or
10 users) that fill out an auto questionnaire will be considered as agreeing to participate in the study.
11
12

13 **Consent for publication**

14
15 The written information documents provided to practitioners, patients and users, state that the
16 anonymous information gathered during the study is likely to be used in scientific publications and
17 public communications.
18
19
20
21
22

23 **Availability of data and material**

24
25 Not applicable
26

27 **Figure legends**

28
29 Figure 1: Periods of study of the SNDS database
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1. Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addict Abingdon Engl*. 2003;98:1371–8.
2. Yen C-F, Yen C-N, Ko C-H, Hwang T-J, Chen C-S, Chen T-T, et al. Correlates of dependence and beliefs about the use of hypnotics among zolpidem and zopiclone users. *Subst Use Misuse*. 2015;50:350–7.
3. WHO Expert Committee on Drug Dependence : thirty-first report. 1999. <http://apps.who.int/iris/handle/10665/42285>. Accessed 17 Aug 2018.
4. Jouanjus E, Gibaja V, Kahn J-P, Haramburu F, Daveluy A. Signal identification in addictovigilance: the functioning of the French system. *Therapie*. 2015;70:113–31.
5. Micallef J, Jolliet P, Victorri-Vigneau C, Mallaret M, Richard N, Haramburu F, et al. [First meeting of the French CEIP (centres d'évaluation et d'information sur la pharmacodépendance). Assessment of the abuse and pharmacodependence potential during drug development]. *Therapie*. 2008;63:55–65.
6. Jouanjus E, Guernec G, Lapeyre-Mestre M, French Addictovigilance Network. Medical prescriptions falsified by the patients: a 12-year national monitoring to assess prescription drug diversion. *Fundam Clin Pharmacol*. 2018;32(3):306-322.
7. Victorri-Vigneau C, Dailly E, Veyrac G, Jolliet P. 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.
8. Victorri-Vigneau C, Gérardin M, Rousselet M, Guerlais M, Grall-Bronnec M, Jolliet P. An update on zolpidem abuse and dependence. *J Addict Dis*. 2014;33:15–23.

- 1
2
3 9. Victorri-Vigneau C, Feuillet F, Wainstein L, Grall-Bronnec M, Pivette J, Chaslerie A, et al.
4
5 Pharmacoepidemiological characterisation of zolpidem and zopiclone usage. *Eur J Clin Pharmacol*.
6
7 2013;69:1965–72.
8
9
10
11 10. Rousselet M, Feuillet F, Gerardin M, Jolliet P, Hardouin J-B, Victorri-Vigneau C. The French
12
13 addictovigilance network clinical assessment: Z-drugs, true false twins. *Expert Opin Drug Saf*.
14
15 2017;16:1063–9.
16
17
18 11. ANSM : Agence nationale de sécurité du médicament et des produits de santé. Prescription
19
20 obligatoire du zolpidem sur ordonnance sécurisée - Point d'Information. 2017.
21
22 [http://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-](http://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information)
23
24 [obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information](http://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information). Accessed 17 Apr 2018.
25
26
27
28 12. ANSM : Agence nationale de sécurité du médicament et des produits de santé. Etat des lieux en
29
30 2013 de la consommation des benzodiazépines en France - Point d'Information. 2014.
31
32 [http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-de-la-consommation-des-benzodiazepines-en-France-Point-d-Information)
33
34 [de-la-consommation-des-benzodiazepines-en-France-Point-d-Information](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-de-la-consommation-des-benzodiazepines-en-France-Point-d-Information). Accessed 17 Apr 2018.
35
36
37
38 13. ANSM : Agence nationale de sécurité du médicament et des produits de santé. Etat des lieux de
39
40 la consommation des benzodiazépines - Point d'Information. 2017. [http://ansm.sante.fr/S-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-Information)
41
42 [informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-Information)
43
44 [benzodiazepines-Point-d-Information](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-Information). Accessed 17 Apr 2018.
45
46
47
48 14. J. Bezin, M. Duong, R. Lassalle, C. Droz, A. Pariente, P. Blin, et al. The national healthcare system
49
50 claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology.
51
52 *Pharmacoepidemiol. Drug Saf.*, 26 (8) (2017), pp. 954-962
53
54
55
56 15. Moracchini C, Orleans V, Miloudi S, Frauger E, Micallef J, Thirion X, et al. [General Practitioners'
57
58 Contribution to Dependence Assessment: the OPEMA Programme]. *Therapie*. 2012;67:397–404.
59
60

1
2
3 16. Accueil | SNDS. <https://www.snds.gouv.fr/SNDS/Accueil>. Accessed 28 Jun 2018.
4
5

6 17. ameli.fr - Sniiram. [https://www.ameli.fr/l-assurance-maladie/statistiques-et-](https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/sniiram/finalites-du-sniiram.php)
7
8 publications/sniiram/finalites-du-sniiram.php. Accessed 28 Jun 2018.
9

10
11 18. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP).
12 Guide on Methodological Standards in Pharmacoepidemiology (Revision 5) EMA/95098. 2010.
13
14 http://www.encepp.eu/standards_and_guidances/. Accessed 17 Apr 2018.
15
16
17

18
19 19. Sattler ELP, Lee JS, Perri M. Medication (re)fill adherence measures derived from pharmacy
20 claims data in older Americans: a review of the literature. *Drugs Aging*. 2013;30:383–99.
21
22
23

24 25 **AUTHOR STATEMENT**

26 MG contributed to the questionnaires development and wrote the first draft of the manuscript.
27
28

29
30 MR wrote the first draft of the protocol, contributed to the questionnaires development and to the
31 manuscript redaction.
32
33

34
35 PC designed statistical analysis of the SNDS database and contributed to the manuscript redaction.
36
37

38 MGB provided her expertise in the area of addictology. She contributed to the preparation of the
39 zolpidem problematic consumers' questionnaire and validated their relevance to evaluate
40 problematic use.
41
42
43
44

45
46 PL contributed to the questionnaires development.
47
48

49 PJ validated the final draft of the protocol and the manuscript.
50

51 CVV is responsible for the project management. She designed the study and finalized the protocol.
52

53 All authors read and approved the final manuscript.
54
55

56 57 58 **FUNDING STATEMENT** 59 60

1
2
3 This work was supported by ANSM grant number AAP-2017-027
4

5 **COMPETING INTERESTS**
6

7 The authors declare that they have no competing interests. For this project, the University Hospital
8
9 of Nantes has received funding only from the ANSM.
10
11

12 **ACKNOWLEDGEMENTS**
13

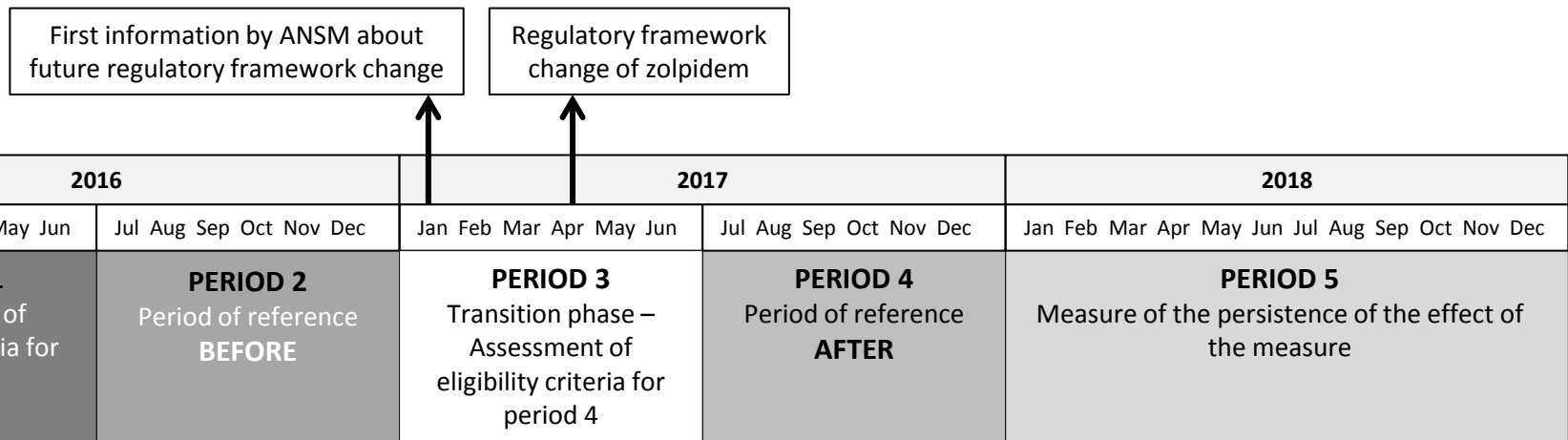
14 We would like to thank, in addition to the authors, all who have worked on this project in order to
15
16 make it possible : Marie-Lyne Pinot for her help in the elaboration of the call to tender, Léa Ferrand
17
18 for her work with the regulatory bodies, all the CEIP-A for their valuable participation in the
19
20 recruitment of practitioners as well as the specialized care centers dedicated to drug dependence of
21
22 their respective regions. We would also like to thank the ANSM for the financial support they
23
24 provided so that this research project may be completed, and the Nantes University Hospital for the
25
26 payment of publication charges of this manuscript.
27
28
29

30 **WORD COUNT**
31

32 4209
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: Periods of study of the SNDS database

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15



ANSM: French National Agency for Medicines and Health Products Safety

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

BMJ Open

ZORRO study Protocol – French national health insurance database analysis and field study focusing on the impact of secure prescription pads on zolpidem consumption and sedative drug misuse.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027443.R2
Article Type:	Protocol
Date Submitted by the Author:	13-May-2019
Complete List of Authors:	Gerardin, Marie; University hospital of Nantes, Department of Clinical Pharmacology Rousselet, Morgane; University hospital of Nantes, Department of Clinical Pharmacology; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch" Caillet, Pascal; University hospital of Nantes, Department of Clinical Pharmacology Grall-Bronnec, Marie; University Hospital of Nantes, Clinical Investigation Unit BALANCED "BehaviorAL AddictioNs and ComplEx mood Disorders"; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch" Loue, Pierre; University Hospital of Rouen, Departement of General medicine Jolliet, Pascale; University hospital of Nantes, Department of Clinical Pharmacology; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch" Victorri-Vigneau, C; University Hospital of Nantes, Department of Clinical Pharmacology; INSERM , U1246 SPHERE "methodS in Patient-centered outcomes and HEalth ResEarch"
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Addiction
Keywords:	zolpidem, secured prescription, change in law, impact, addictovigilance, Substance misuse < PSYCHIATRY

SCHOLARONE™
Manuscripts

1
2
3 **Title:** ZORRO study Protocol – French national health insurance database analysis and field study
4
5 focusing on the impact of secure prescription pads on zolpidem consumption and sedative drug
6
7 misuse.
8
9

10
11
12 **Authors:**
13

14 Marie GERARDIN, Clinical Pharmacology Department, Nantes University Hospital, Nantes,
15 France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. marie.gerardin@chu-nantes.fr
16
17

18 Morgane ROUSSELET, Clinical Pharmacology Department, Nantes University Hospital, Nantes,
19 France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. Addictology and Psychiatry Department,
20 Nantes University Hospital, 85 rue de Saint-Jacques, 44093 Nantes cedex 1, France. INSERM U1246
21 SPHERE “methodS in Patient-centered outcomes and HHealth ResEarch”, Nantes and Tours University,
22 22 boulevard Benoni Goullin, 44 000 Nantes, France. morgane.rousselet@chu-nantes.fr
23
24
25
26
27

28 Pascal CAILLET, Clinical Pharmacology Department, Nantes University Hospital, Nantes,
29 France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. pascal.caillet@chu-nantes.fr
30
31
32

33 Marie GRALL-BRONNEC, Addictology and Psychiatry Department, Nantes University Hospital,
34 85 rue de Saint-Jacques, 44093 Nantes cedex 1, France. INSERM U1246 SPHERE “methodS in Patient-
35 centered outcomes and HHealth ResEarch”, Nantes and Tours University, 22 boulevard Benoni Goullin,
36 44 000 Nantes, France. marie.bronnec@chu-nantes.fr
37
38
39
40
41
42

43 Pierre LOUE, General medical Department, Rouen faculty of medicine, Rouen University
44 Hospital. peterloue@me.com
45
46
47

48 Pascale JOLLIET, Clinical Pharmacology Department, Nantes University Hospital, Nantes,
49 France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. INSERM U1246 SPHERE “methodS in
50 Patient-centered outcomes and HHealth ResEarch”, Nantes and Tours University, 22 boulevard Benoni
51 Goullin, 44 000 Nantes, France. pascale.jolliet@univ-nantes.fr
52
53
54
55

56 Caroline VICTORRI-VIGNEAU, Clinical Pharmacology Department, Nantes University Hospital,
57 Nantes, France, 9 quai Moncousu, 44 093 Nantes cedex 1, France. INSERM U1246 SPHERE “methodS
58
59
60

1
2
3 in Patient-centered outcomes and HHealth ResEarch", Nantes and Tours University, 22 boulevard
4
5 Benoni Goullin, 44 000 Nantes, France. caroline.vigneau@chu-nantes.fr
6
7

8 **Corresponding author:**

9
10 Caroline VICTORRI-VIGNEAU

11
12 Adress: Clinical Pharmacology Department, Nantes University Hospital, Nantes, France,

13
14 9 quai Moncouso, 44 093 Nantes cedex 1, France

15
16 Phone : +33240084073

17
18 E-Mail : caroline.vigneau@chu-nantes.fr
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Introduction

In recent years, data collected by the French Addictovigilance Network (FAN) has shown the potential for abuse and addiction associated with zolpidem (the most sold hypnotic drug in France). Since the 10th of April 2017, new regulations have come into force that require zolpidem to be prescribed on special secure prescription pads, in order to reduce the risk of abuse or misuse. This measure has far-reaching repercussions that are not only limited to the consumption of zolpidem but also extend to the usage of sedative medication on a whole.

The objective of the ZORRO study (ZOlpidem and the Reinforcement of the Regulation of prescription Orders) is to evaluate the overall impact of the new regulatory framework requiring zolpidem to be prescribed on special secure prescription pads. Three axes will be evaluated: the number of consumers, the type of consumption (chronic use versus occasional use, problematic consumption versus non-problematic use), and the consumption of other sedative molecules.

Methods and analysis

The ZORRO study is an epidemiological, observational, national multi-center, non-controlled, prospective research project supported by the French National Agency for Medicines and Health Products Safety (ANSM). The evaluation of the impact of the regulatory framework change relative to zolpidem will be done according to two axes: via an epidemiological study of the French National Health Insurance database and by the implementation of field studies of prescribers and consumers of zolpidem.

Ethics and dissemination

The Nantes Research Ethics Committee (Groupe Nantais d'Ethique dans le Domaine de la Santé; GNEDS), the Committee for the Protection of the Population (CPP), and the Committee of Expertise in Research, Studies and Evaluations in the Field of Health (CEREES) approved this study. Results will be presented in national and international conferences and submitted to peer-reviewed journals.

Trial registration number NCT03584542

Keywords

Zolpidem, secured prescription, change in law, impact, addictovigilance, misuse.

ARTICLE SUMMARY

Strengths and limitations of the study

This study will contribute to setting up an innovative impact measure in order to evaluate the efficacy of institutions' response to the issue of zolpidem misuse and dependence.

The study will be representative of the French population by use of the French healthcare database SNDS, with a focus on how physicians and problematic consumers have coped with the change in law by use of complementary field studies.

Owing to technical constraints inherent to medico-administrative database use, the use of drugs that are not reimbursed is not be observable in the SNDS database, as well as clinical data that are not routinely gathered.

A lack of representativity may occur during participants' recruitment regarding the part of the project involving field sampling.

INTRODUCTION

In recent years, zolpidem has been the best-selling hypnotic drug in France. Worldwide, a number of cases of misuse of zolpidem have been described (in Europe and in the United-States [1, 2]). The World Health Organisation (WHO) believes that the frequency of cases of abuse or addiction to zolpidem is similar to that associated with hypnotic benzodiazepines [3]. As a result, Zolpidem has been the target of a number of regulatory framework changes in both French national and international spheres. In particular, the United Nations has placed zolpidem in table IV of the Vienna convention which aims to control the abuse and trafficking of psychotropic substances (ruling of July 15th 2002)

In France, the French Addictovigilance network (FAN), piloted by the French National Agency for Medicines and Health Products Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé; ANSM) is in charge of the surveillance of cases of abuse and addiction associated with any drug or substance with a psychoactive effect. The surveillance is based on a network of 13 Centres for evaluation of and information on drug dependence and addiction monitoring (Centres d'Evaluation et d'Information sur la Pharmacodépendance-Addictovigilance; CEIP-A), who evaluate the addictive potential of a given drug via notifications provided by health professionals [4], and via specifically-developed pharmaco-epidemiology tools [5, 6].

Some controlled medicines and psychotropic substances (including zolpidem) are under reinforced surveillance by the ANSM as they are associated with a risk of misuse and addiction. In France, zolpidem is enlisted on the list I of harmful substances, that is to say, it is considered as a substance associated with a health risk. An initial national survey of the addictovigilance network in 2002 found serious and worrying cases of abuse and addiction to zolpidem. The 2002 survey revealed the existence of two consumer groups: a population of chronic high dosage consumers with a therapeutic usage of zolpidem, and a population of "misusers" in search of an effect other than hypnotic (euphoria, wellbeing or stimulant effect). The same survey also found, via the analysis of the FAN pharmaco-epidemiology tools, that zolpidem is a substance prone to abuse [7]. Following to

1
2
3 this conclusion, the Summary of Product Characteristics (SPC) of zolpidem was modified, with
4 notably the addition of a warning with respect to addiction. In June 2011, an update of data relative
5 to the addictive potential of zolpidem found the same two consumer groups as in the 2002 survey
6 with cases of increasing severity associated with the consumption of particularly high dosages [8]. In
7 light of these results, the prescription of zolpidem on special secure prescription pads was put
8 forward by the National Commission of Narcotics and Psychotropic Substances (Commission
9 Nationale des Stupéfiants et Psychotropes; CNSP). In 2012, the FAN tools all, once again, proclaim
10 zolpidem as a problematic substance.

11
12 The surveillance tools of the FAN allow for the identification of the problem of addiction in specific
13 population groups, but they do not provide a general population risk profile. However, the analysis of
14 quantitative data, in the French National Health Insurance database, relative to the usage of
15 zolpidem and zopiclone in the general population [9], provided the identification of a number of
16 different clinical profiles of zolpidem consumers: (i) « non-problematic » consumers, the largest
17 group; (ii) individuals who could have developed a tolerance to the hypnotic effects of zolpidem, for
18 whom the prescription of alternative hypnotic/anxiolytic medication is justified; (iii) potential
19 problematic consumers of zolpidem (1%) (high rate of fraudulent behaviour, excessive usage, non-
20 respect of guidelines and medical-pharmaceutical nomadism). In 2017, another research program
21 gave insight into the characteristics of the two aforementioned consumer groups via the analysis of
22 reports from health professionals [10].

23
24 Following to these results, on the 11th of January 2017, the ANSM decreed that as from April the 10th
25 2017, the prescription of zolpidem was to be done on secure prescription pads [11]. The ANSM
26 stated that « this measure is taken in order to limit the risk of abuse and misuse » and « to
27 encourage correct usage ». In a country where the consumption of psychotropic drugs is high, a
28 ruling that impacts the most sold hypnotic drug [12, 13] will disrupt not only its' usage but also on a
29 larger scale the overall prescription of sedative substances (hypnotics and anxiolytics). The current
30 project aims to develop a means to measure the impact of this new ruling, in the scope of works of
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 the ANSM, that is to say, in terms of the reduction of the risk of abuse, the improvement of correct
4 use of zolpidem and the change in prescriptions of sedative molecules. This project forms part of the
5 evaluation of zolpidem done by the Nantes CEIP-A, the organization in charge of its follow up. In
6 addition to the tools used by the FAN [5], this project will allow for a longitudinal evaluation of the
7 trajectories of different patients, as well as providing insight into the general population.
8
9
10
11
12
13
14
15

16 **METHODS AND ANALYSIS**

17 **Aim**

18
19 The objective of the ZORRO study (ZOlpidem and the Reinforcement of the Regulation of prescription
20 Orders) is to evaluate the overall impact of the obligation to use secure prescription pads for
21 zolpidem. We propose a multimodal approach that will provide valuable insight into three key
22 questions: 1) what is the impact of this measure on the number of consumers? 2) What is the impact
23 of this measure on the type of consumption? 3) What is the impact of this measure on the
24 consumption of other sedative molecules?
25
26
27
28
29
30
31
32
33

34 **Study design**

35
36 This scientific project is based on a multimodal epidemiological approach, which combines a
37 retrospective cohort study and a transversal field study. The cohort study draws from the French
38 National Health Information database (Système National des Données de Santé; SNDS, formerly
39 known as the French National Inter-schemes Health Insurance database (Système National
40 d'Information Inter-Régimes de l'Assurance Maladie; SNIIRAM)) [14]. The transversal field study
41 involves the gathering in-field of clinical data of different populations: general practitioners, that
42 prescribe zolpidem, as well as consumers (both patients having consulted a general practitioner and
43 those having recourse to specialized care centers dedicated to drug dependence). To our knowledge,
44 a study of this amplitude does not exist in France.
45
46
47
48
49
50
51
52
53
54

55
56 These two approaches will provide insight into three key areas:
57
58
59
60

- 1
2
3 - To evaluate the impact of the measure on the number of consumers, we will estimate via the
4 SNDS database the prevalence and the incidence of zolpidem consumers in the general
5 population before and after the regulatory framework change.
6
7
8
9
10 - To evaluate the impact of the measure on the type of consumption, we will explore the
11 changes in the modes of consumption: occasional use *versus* chronic use and problematic
12 use *versus* non-problematic use. Problematic use is defined as consumption outside of the
13 SPC guidelines for at least one of the following parameters: the duration of consumption, the
14 dosage, the means of procurement, the routes of administration or the search for an effect
15 other than hypnotic. This evaluation will be done both from SNDS database for the
16 evaluation of the general population and from the field studies for the evaluation of
17 problematic consumers of zolpidem (patients of general practitioners and users of
18 specialized care centers dedicated to drug dependence).
19
20
21
22
23
24
25
26
27
28
29
30 - To evaluate the impact of the measure on the consumption of other sedative molecules, we
31 will analyze the reporting of prescriptions and the changes observed both in the general
32 population in the SNDS database as well as among prescribers and problematic consumers of
33 zolpidem (patients of general practitioners and users of drug-user risk reduction centers or
34 specialized care centers dedicated to drug dependence).
35
36
37
38
39
40

41 **Setting of the study**

42
43 The Nantes CEIP-A, is the national investigating center in charge of the management, surveillance
44 and coordination of the entire project. General practitioners, their patients and users of zolpidem
45 will be recruited across France. Recruitment as well as the gathering and the analysis of data (SNDS
46 database and field studies) will be done by the Nantes CEIP-A.
47
48
49

50
51
52 A multi-disciplinary pilot committee, comprised of pharmacologists, general practitioners, a
53 methodologist bio-statistician, a clinical study technician and of an addictologist psychiatrist, has
54 been constituted in order to define the research protocol and in order to insure the scientific and
55 methodological validity of the study.
56
57
58
59
60

Patient and public involvement

Patients were not involved in the design of the study.

Populations

Analysis of the SNDS database

The study sample will include all patients in the database during the period from the 1st of January 2016 to the 31st of December 2018. The target population of our research will be constituted of consumers of zolpidem included in the SNDS database between the 1st of January 2016 and the 31st of December 2018.

Field study among General practitioners

Practitioners, situated within the national borders, will be randomly selected from the list of the National Health Insurance for Wage laborers (Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés; CNAMTS). Practitioners specialized in the care of addictions and used to working with the FAN, will also be solicited [15]. Practitioners with an independent practice at the time of change in regulatory framework and who agree to participate, via oral consent, will be included. The inclusion period will run from the second quarter of 2018 to the end of 2019.

Field study among problematic consumers of zolpidem (patients of general practitioners and users of specialized care centers dedicated to drug dependence)

Participating practitioners will select patients who presented a problematic use of zolpidem before the coming into force of the new regulatory framework. Patients will be included in the study if they provide their oral consent to participate. Participating practitioners will give them a questionnaire to complete in the waiting room and return in a sealed envelope. Participating specialized care centers

1
2
3 dedicated to drug dependence (Centre de Soins, d'Accompagnement et de Prévention en
4 Addictologie; CSAPA) and drug-user risk reduction centers (Centre d'Accueil et d'Accompagnement à
5 la Réduction des risques pour Usagers de Drogues; CAARUD) will select users who presented a
6
7 problematic use of zolpidem before the coming into force of the new regulatory framework. The
8
9 inclusion period for patients and users will be the same as for general practitioners (second quarter
10
11 of 2018 to the end of 2019). Users will be included in the study if they provide their oral consent to
12
13 participate. The facility staff will provide them with a questionnaire to complete. A problematic
14
15 consumption of zolpidem is defined according to the Diagnostic and Statistical Manual of Mental
16
17 Disorders 5th edition (DSM-5) criteria of Substance Use Disorder. Under aged or protected individuals
18
19 as well as subjects with French language difficulties (understanding, reading or writing) incompatible
20
21 with the filling out of a questionnaire, will not be included in the study.
22
23
24
25
26
27
28
29

30 **Materials**

31 *Analysis of the SNDS database*

32
33 The SNDS database is described in detail in the publication by Bezin *et al* [14] as well as on related
34
35 internet sites [16, 17]. The SNDS links several existing databases: the SNIIRAM, the nationwide claims
36
37 database of the French National Healthcare system; the national hospital database (Programme de
38
39 Médicalisation des Systèmes d'Information; PMSI) and the national death registry (Centre
40
41 d'épidémiologie sur les causes médicales de Décès; CeperDC). The SNDS covers more than 98% of the
42
43 French population (66 million people) from birth (or immigration) to death (or emigration), even in
44
45 case of change in occupation or retirement. Data are individual and anonymous. The SNDS contains a
46
47 longitudinal record of health encounters, hospital diagnoses and drugs deliveries relative to
48
49 outpatient medical care claims, including all reimbursed drugs, information from hospital discharge
50
51 summaries, and date of death.
52
53
54
55
56
57
58
59
60

Field study among general practitioners

1
2
3 Participating general practitioners will reply to short telephone questionnaire, which will gather
4
5 information on their perceptions and their prescription strategy following to the new regulatory
6
7 framework (continuation of zolpidem on a secure prescription pad, prescription of a different
8
9 sedative drug, or cease in hypnotic prescriptions). The criteria for their choices will also be explored.
10
11
12

13 14 *Field study among problematic consumers of zolpidem (patients and users)*

15
16 Patients and users will fill out a two-part auto-questionnaire. The first part will evaluate the
17
18 consumption of zolpidem before the coming into force of the new regulatory framework (dosages
19
20 used, duration, pursued effects and effects felt) and their change or not after the coming into force
21
22 of the new regulatory framework (cease, change in dosage, relay to another drug or sedative
23
24 substance). The second part of the questionnaire will be filled out only by patients or users for whom
25
26 a change is observed and it will gather information pertaining to the favored replacement substance
27
28 (dosages used, duration, pursued effects and effects felt). General practitioners and staff of the
29
30 CSAPA and CCARUD will return the completed questionnaires to the CEIP-A in Nantes for analysis.
31
32
33
34
35

36 **Study size**

37 38 39 40 *Analysis of the SNDS database:*

41
42 In light of the retrospective nature of the study and of the databases used, the calculation of a power
43
44 is not necessary, in accordance with the good practice guidelines of the European Network of
45
46 Centers for Pharmaco-epidemiology and Pharmacovigilance [18].
47
48
49
50

51 52 *Field studies among prescribing general practitioners and problematic consumers of zolpidem:*

53
54 Three hundred practitioners will be selected in order to insure that at least one hundred
55
56 practitioners participate in the recruitment of problematic consumers of zolpidem. For feasibility
57
58 reasons, the number of general practitioner patients to be included depends upon the construction
59
60

1
2
3 of a convenience sample. This sample is estimated to be about 200 patients. Furthermore, 200 users
4
5 will be recruited via the specialized care centers dedicated to drug dependence.
6
7
8
9

10 **Statistical methods**

11 All variables will undergo a descriptive analysis. Quantitative variables will be described using usual
12 position (mean or median) and dispersion (standard deviation, interquartile range) parameters. The
13 normality of their distribution will be assessed numerically (normality test) and graphically. For
14 normally distributed quantitative variables, mean and standard deviation will be used. For non-
15 normally distributed variables, median and interquartile ranges will be used. Qualitative variables will
16 be described using number and frequency tables for each parameter. All analysis will be conducted
17 with SAS software. Specific statistical methods will be implemented in order to answer each question
18 adequately.
19
20
21
22
23
24
25
26
27
28
29
30
31

32 *Impact of the measure on the number of consumers: estimation of prevalence and incidence of*
33 *zolpidem users within the SNDS database before and after the regulatory framework change*
34
35
36

37 A number of periods will be studied (figure 1). The proportion of patients having received at least
38 one delivery of zolpidem during the period 2 and during the period 4 will be compared using a Mc
39 Nemar test for paired proportion. Patients missing from one of the two periods will be recorded as
40 non-users. The significance threshold will be fixed at 5%. An incident user will be defined as a patient
41 receiving a first delivery of zolpidem without any prior delivery over the preceding 6 months. The
42 number of incident users within each period will be compared using a Poisson model. The
43 significance threshold for each coefficient will be fixed at 5%.
44
45
46
47
48
49
50
51
52
53
54

55 *Impact on the type of consumption regarding changes in treatment duration*
56

57 *Within the SNDS database:* The length of the first treatment episode will be evaluated by
58 calculating the number of days covered by the initial delivery (theoretical length of treatment). The
59
60

1
2
3 predicted variable will be the duration of treatment over a threshold (yes/no). The period will be
4 entered as a covariate in the model, enabling the study of the effect of the period on the probability
5 of the treatment being chronic while taking into account the correlation of treatment characteristics
6 for a given patient.
7
8
9
10

11 *Within the field study among problematic consumers of zolpidem:* A descriptive analysis will
12 be performed, with the characterization of the duration of treatment with zolpidem before the
13 regulatory framework change and of the duration of treatment with zolpidem or of the replacement
14 drug/substance after the regulatory framework change.
15
16
17
18
19

20
21
22
23 *Impact on the type of consumption addressing changes in the type of consumption, problematic or*
24 *non-problematic*
25
26

27 *Within the SNDS database:* A latent class analysis (LCA) will be conducted within each period,
28 including the following variables: age, sex, presence of a chronic disease, poor economic status,
29 prescribing practitioners specialty (only whether or not a general practitioner), number of different
30 prescribing practitioners (doctor shopping), number of dispensing pharmacies (pharmacy shopping),
31 excess use (mean monthly medication possession ratio [19] (MPR) > 1 during the period), adherence
32 to French good practice guidelines regarding hypnotics (encompassing the absence of association
33 with others benzodiazepines), presence of an associated psychiatric disorder (identified by
34 concomitant drug use, i.e opioids substitution treatments, psycholeptic and psychoanaleptic drugs).
35 The analysis will be repeated during periods 2 and 4. In order to study the transitions between
36 clusters over time, a latent transition analysis (LTA) will be performed. The choice of the best model
37 will be made considering Bayesian Information Criterion (BIC). The choice of the best model will also
38 be made with consideration to the stability of the model (proportion of convergences among the
39 5000 iterations), the BIC (lower is better) and the interpretability of the model.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 *Within the field observational study among problematic consumers of zolpidem:* A descriptive
4 analysis will be performed. We will compare the number and the distribution of the positive criteria
5 of problematic consumers (patients et users) before (for zolpidem treatment) and after the coming
6 into force of the new regulatory framework (for zolpidem treatment or replacement substances):
7 duration of consumption, dosage, manner in which zolpidem or other substance is obtained, route of
8 administration or pursued effects different from the expected effect of the treatment or substance.
9 Parametric or non-parametric paired-tests will be used for comparisons, according to the
10 distributions of each variable. For each hypothesis test, an alpha risk of 5% will be used. In case of
11 multiple testing, a correction of the significance threshold will be applied to avoid alpha risk inflation
12 (Hochberg's method).
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27

28 *Impact on the consumption of other sedative molecules: analysis of prescription deferrals and*
29 *switches*
30
31

32 *Within the SNDS database, regarding characterization of consumption trajectories:*

33 Firstly, a time series analysis will be performed on aggregated monthly data (proportion of users per
34 month) to compare the changes in the consumption of zolpidem and other sedatives across all the
35 study periods. Cross-correlation between the different time series will be studied in order to identify
36 if zolpidem users have shifted their consumption to other drugs since the change in regulatory
37 framework. Secondly, a sequence analysis will be performed using dedicated tools (TramineR,
38 SeqHMM and arulesSequences packages in R software). This will include a cluster analysis of the
39 sequences, in order to identify typical trajectories in consumption and their modification following to
40 the change in the regulatory framework.
41
42
43
44
45
46
47
48
49
50
51

52 *Within the field study among physicians:* A descriptive analysis of changes in prescription
53 behaviour and motives for change will be performed.
54
55

56 *Within the field study among problematic consumers of zolpidem:* A descriptive analysis of
57 the number of molecules tried as a replacement and the molecules that best replaced zolpidem, if
58
59
60

1
2
3 applicable, after the change in regulatory framework, will be performed. In patients stopping
4 zolpidem, but switching to another molecule, a univariate analysis of the same variables will be
5
6 conducted in order to describe the use of zolpidem before the coming into force of the new
7
8 regulatory framework and the use of other sedative drugs used in place of zolpidem after the coming
9
10 into force of the new regulatory framework. For each hypothesis test, an alpha risk of 5% will be
11
12 used. In case of multiple testing, a correction of the significance threshold will be applied to avoid
13
14 alpha risk inflation (Hochberg's method).
15
16
17
18
19
20

21 **DISCUSSION**

22
23
24
25 The evaluation of the addictive power of zolpidem by the addictovigilance network required over the
26
27 past, above and beyond the tools of the CEIP-A, the implementation of specific research programs.
28
29 The evaluation of the impact of the change in the regulatory framework will similarly require the
30
31 implementation of specific research programs. This project offers a design and a methodology which
32
33 are complementary to the tools of the CEIP-A [4], indispensable to the measurement of the impact,
34
35 which we believe to be major, of a change in the prescription requirements of the most sold hypnotic
36
37 in France. The ZORRO project aims to develop a method to measure the impact of the change in
38
39 regulatory framework on practitioners' prescriptions of sedative molecules. This evaluation is
40
41 complex, as in order to be thorough it must precisely measure the different aspects of the
42
43 consequences of the regulatory framework change, both from a quantitative and qualitative point of
44
45 view. Rather than doing a single study, we prefer to employ a strategy based on a number of
46
47 different, and complementary, methodological approaches. We have anticipated some possible bias:
48
49 for the analysis of information from a database, we chose the data from the SNDS database as it
50
51 contains information close to that of the real consumption. In the absence of available data on the
52
53 drugs actually taken by patients, this database provides information on the drugs that patients
54
55 obtain from pharmacies, which is more accurate than sales data for example. Concerning the periods
56
57
58
59
60

1
2
3 of reference before and after, we have voluntarily chosen periods distant from the times of
4 announcement and the coming into force of the change in regulatory framework in order to
5 minimize bias linked to the transition period. Although the regulatory framework change came into
6 force in April 2017, the ANSM had published information on the measure as from January 2017. A
7 part of the practitioners prescribing zolpidem therefore anticipated the change in the regulatory
8 framework and started to change their prescription strategy as from January 2017. One of the limits
9 of the SNDS database, that justifies our multimodal approach, is the complete absence of clinical
10 information concerning the effects pursued or felt by patients, as well as the modification in routes
11 of administration. Concerning the in-field clinical study, the principal bias is a memory bias of the
12 questioned subjects. The time between the change in the regulatory framework and the
13 implementation of the study is however incompressible as it is necessary to give patients and users
14 sufficient hindsight in order to evaluate the changes in their consumption of zolpidem. In fact, the
15 questions have been formulated in a simplified manner, and our project targets the most
16 problematic consumers, who should remember with little difficulty the changes, having an impact on
17 their daily lives, following to the new regulatory framework. A possible declarative bias does exist
18 among patients and users, although this bias was taken into account, in order to minimize it, in the
19 conception of the questionnaire. On the one hand the questionnaire is completely anonymous. On
20 the other hand, for patients, the questionnaire is filled-in away from any medical presence and
21 handed back in a sealed envelope that is opened only by the Nantes CEIP-A for data analysis. The
22 CEIP-A personnel are accustomed to interviewing subjects recruited via specialized care centers
23 dedicated to drug dependence on their substance consumption, in the framework of their mission of
24 surveillance of addition and abuse of psychoactive substances. Our personnel have therefore
25 developed an expertise in the realization of projects of this type among the users of specialized care
26 centers dedicated to drug dependence. The strengths of this project lie within its' multimodal
27 approach. It allows, on the one hand, to document numerous possible consequences of the
28 regulatory framework change, and on the other hand, to insure the overall coherence of the
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 different studies via the management by an expert team in the field, coordinated by the French
4 national reference center on the addictive potential of zolpidem. This project may very well have a
5 double impact: on the one hand, it will provide additional data essential to the ANSMs' mission of
6 surveillance of the risk relative to overdose, abuse, addiction and misuse of sedative substances; on
7 the other hand, this project could be the defining point of a series of steps (for example
8 communication and information campaigns) designed to manage the public health issues
9 surrounding zolpidem and to measure their overall impact.
10
11
12
13
14
15
16
17
18
19
20

21 **ETHICS AND DISSEMINATION:**

22 **Ethics approval**

23
24 The Committee for the Protection of the Population (CPP) approved the protocol on the 11/06/2018,
25 the local Research Ethics Committee (Groupe Nantais d'Ethique dans le Domaine de la Santé; GNEDS)
26 on the 05/03/2018 and the Committee of Expertise in Research, Studies and Evaluations in the Field
27 of Health (CEREES) on the 12/04/2018. The National Commission of Information Technology and
28 Liberties (CNIL) gave a favorable opinion.
29
30
31
32
33
34
35

36 **Information to participants**

37 For the epidemiological analysis of the SNDS database: not applicable

38
39 Practitioners: all practitioners will receive clear information regarding the study orally during the
40 telephone interview. Practitioners that participate in the recruitment of patients will also receive
41 written information.
42
43
44
45
46

47 Patients and users: general practitioners and the study agents in the specialized care centers
48 dedicated to drug dependence agree to inform all patients and users, in a clear and impartial
49 manner, about the protocol. They will also provide written information.
50
51
52
53

54 **Consent to participate**

55 For the epidemiological analysis of the SNDS database: not applicable
56
57
58
59
60

1
2
3 Practitioners: oral non-refusal to participate will be sought before delivery of the telephone
4 questionnaire. Practitioners that accept to reply to the telephone questionnaire will be considered as
5
6 not in opposition of the study. For the recruitment of patients, practitioners that fill in the
7
8 documents relative to the inclusion of a patient will be considered as agreeing to participate in the
9
10 study.
11
12

13
14 Patients and users: oral non-refusal from patients and users will be sought. Subjects (patients or
15
16 users) that fill out an auto questionnaire will be considered as agreeing to participate in the study.
17

18 **Consent for publication**

19
20 The written information documents provided to practitioners, patients and users, state that the
21
22 anonymous information gathered during the study is likely to be used in scientific publications and
23
24 public communications.
25
26

27 **Availability of data and material**

28
29 Not applicable
30

31 **Figure legends**

32
33
34 Figure 1: Periods of study of the SNDS database
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1. Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addict Abingdon Engl*. 2003;98:1371–8.
2. Yen C-F, Yen C-N, Ko C-H, Hwang T-J, Chen C-S, Chen T-T, et al. Correlates of dependence and beliefs about the use of hypnotics among zolpidem and zopiclone users. *Subst Use Misuse*. 2015;50:350–7.
3. WHO Expert Committee on Drug Dependence : thirty-first report. 1999. <http://apps.who.int/iris/handle/10665/42285>. Accessed 17 Aug 2018.
4. Jouanjus E, Gibaja V, Kahn J-P, Haramburu F, Daveluy A. Signal identification in addictovigilance: the functioning of the French system. *Therapie*. 2015;70:113–31.
5. Micallef J, Jolliet P, Victorri-Vigneau C, Mallaret M, Richard N, Haramburu F, et al. [First meeting of the French CEIP (centres d'évaluation et d'information sur la pharmacodépendance). Assessment of the abuse and pharmacodependence potential during drug development]. *Therapie*. 2008;63:55–65.
6. Jouanjus E, Guernec G, Lapeyre-Mestre M, French Addictovigilance Network. Medical prescriptions falsified by the patients: a 12-year national monitoring to assess prescription drug diversion. *Fundam Clin Pharmacol*. 2018;32(3):306-322.
7. Victorri-Vigneau C, Dailly E, Veyrac G, Jolliet P. 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.
8. Victorri-Vigneau C, Gérardin M, Rousselet M, Guerlais M, Grall-Bronnec M, Jolliet P. An update on zolpidem abuse and dependence. *J Addict Dis*. 2014;33:15–23.

- 1
2
3 9. Victorri-Vigneau C, Feuillet F, Wainstein L, Grall-Bronnec M, Pivette J, Chaslerie A, et al.
4
5 Pharmacoepidemiological characterisation of zolpidem and zopiclone usage. *Eur J Clin Pharmacol*.
6
7 2013;69:1965–72.
8
9
10
11 10. Rousselet M, Feuillet F, Gerardin M, Jolliet P, Hardouin J-B, Victorri-Vigneau C. The French
12
13 addictovigilance network clinical assessment: Z-drugs, true false twins. *Expert Opin Drug Saf*.
14
15 2017;16:1063–9.
16
17
18 11. ANSM : Agence nationale de sécurité du médicament et des produits de santé. Prescription
19
20 obligatoire du zolpidem sur ordonnance sécurisée - Point d'Information. 2017.
21
22 [http://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-](http://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information)
23
24 [obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information](http://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Prescription-obligatoire-du-zolpidem-sur-ordonnance-securisee-Point-d-Information). Accessed 17 Apr 2018.
25
26
27
28 12. ANSM : Agence nationale de sécurité du médicament et des produits de santé. Etat des lieux en
29
30 2013 de la consommation des benzodiazépines en France - Point d'Information. 2014.
31
32 [http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-de-la-consommation-des-benzodiazepines-en-France-Point-d-Information)
33
34 [de-la-consommation-des-benzodiazepines-en-France-Point-d-Information](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-en-2013-de-la-consommation-des-benzodiazepines-en-France-Point-d-Information). Accessed 17 Apr 2018.
35
36
37
38 13. ANSM : Agence nationale de sécurité du médicament et des produits de santé. Etat des lieux de
39
40 la consommation des benzodiazépines - Point d'Information. 2017. [http://ansm.sante.fr/S-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-Information)
41
42 [informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-Information)
43
44 [benzodiazepines-Point-d-Information](http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Etat-des-lieux-de-la-consommation-des-benzodiazepines-Point-d-Information). Accessed 17 Apr 2018.
45
46
47
48 14. J. Bezin, M. Duong, R. Lassalle, C. Droz, A. Pariente, P. Blin, et al. The national healthcare system
49
50 claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology.
51
52 *Pharmacoepidemiol. Drug Saf.*, 26 (8) (2017), pp. 954-962
53
54
55
56 15. Moracchini C, Orleans V, Miloudi S, Frauger E, Micallef J, Thirion X, et al. [General Practitioners'
57
58 Contribution to Dependence Assessment: the OPEMA Programme]. *Therapie*. 2012;67:397–404.
59
60

1
2
3 16. Accueil | SNDS. <https://www.snds.gouv.fr/SNDS/Accueil>. Accessed 28 Jun 2018.
4
5

6 17. ameli.fr - Sniiram. [https://www.ameli.fr/l-assurance-maladie/statistiques-et-](https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/sniiram/finalites-du-sniiram.php)
7
8 publications/sniiram/finalites-du-sniiram.php. Accessed 28 Jun 2018.
9

10
11 18. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP).
12 Guide on Methodological Standards in Pharmacoepidemiology (Revision 5) EMA/95098. 2010.
13
14 http://www.encepp.eu/standards_and_guidances/. Accessed 17 Apr 2018.
15
16
17

18
19 19. Sattler ELP, Lee JS, Perri M. Medication (re)fill adherence measures derived from pharmacy
20 claims data in older Americans: a review of the literature. *Drugs Aging*. 2013;30:383–99.
21
22
23

24 25 **AUTHOR STATEMENT**

26 MG contributed to the questionnaires development and wrote the first draft of the manuscript.
27
28

29
30 MR wrote the first draft of the protocol, contributed to the questionnaires development and to the
31 manuscript redaction.
32
33

34
35 PC designed statistical analysis of the SNDS database and contributed to the manuscript redaction.
36
37

38 MGB provided her expertise in the area of addictology. She contributed to the preparation of the
39 zolpidem problematic consumers' questionnaire and validated their relevance to evaluate
40 problematic use.
41
42
43
44

45
46 PL contributed to the questionnaires development.
47
48

49 PJ validated the final draft of the protocol and the manuscript.
50

51 CVV is responsible for the project management. She designed the study and finalized the protocol.
52

53 All authors read and approved the final manuscript.
54
55
56
57

58 59 **FUNDING STATEMENT**

60

1
2
3 This work was supported by ANSM grant number AAP-2017-027
4

5 **COMPETING INTERESTS**
6

7 None declared.
8
9

10 **ACKNOWLEDGEMENTS**
11

12 We would like to thank, in addition to the authors, all who have worked on this project in order to
13 make it possible : Marie-Lyne Pinot for her help in the elaboration of the call to tender, Léa Ferrand
14 for her work with the regulatory bodies, all the CEIP-A for their valuable participation in the
15 recruitment of practitioners as well as the specialized care centers dedicated to drug dependence of
16 their respective regions. We would also like to thank the ANSM for the financial support they
17 provided so that this research project may be completed, and the Nantes University Hospital for the
18 payment of publication charges of this manuscript.
19
20
21
22
23
24
25
26
27

28 **WORD COUNT**
29

30 4209
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: Periods of study of the SNDS database

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15

First information by ANSM about future regulatory framework change

Regulatory framework change of zolpidem

2016						2017						2018																							
Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
PERIOD 1 Assessment of eligibility criteria for period 2						PERIOD 2 Period of reference BEFORE						PERIOD 3 Transition phase – Assessment of eligibility criteria for period 4						PERIOD 4 Period of reference AFTER						PERIOD 5 Measure of the persistence of the effect of the measure											

ANSM: French National Agency for Medicines and Health Products Safety

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41