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# 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.



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**Title:** 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.

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## 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 that zolpidem be prescribed on special secure prescription pads. The overall impact will be evaluated according to three axes: the impact on the number of consumers, on the type of consumption (chronic use versus occasional use, problematic consumption versus non-problematic use), and on 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 on the one hand via an epidemiological study of the French National Health Insurance data base and on the other hand 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, use of drug not reimbursed will not be observable in the SNDS database, as well as many clinical data that are not routinely gathered.

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

## INTRODUCTION

Zolpidem is a medicinal substance that has been the target of a number of regulatory framework changes in both French national and international spheres. Worldwide, a number of cases of misuse of zolpidem have been described (Europe and 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] and in a ruling of July 15th 2002, zolpidem was placed by the United Nations in the table IV of the Vienna convention which aims to control the abuse and trafficking of psychotropic substances.

In France, the French Addictovigilance network (FAN), piloted by the French National Agency for Medicines and Health Products Safety (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 Centre for evaluation of and information on drug dependence and addiction monitoring (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 are under reinforced surveillance by the ANSM as they are associated with a risk of misuse and addiction. As is the case for zolpidem. 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 this conclusion the Summary of Product Characteristics (SPC) of zolpidem was modified, with notably the addition of a warning with

respect to addiction. In June 2011, an update of data relative to the addictive potential of zolpidem, presented before the National Commission of Narcotics and Psychotropic Substances (CNSP), found the same two consumer groups as in the 2002 survey, with cases of seemingly increasing gravity associated with the consumption of particularly high dosages [8]. In light of these results, the prescription of zolpidem on special secure prescription pads was put forward by the CNSP. In 2012, the FAN tools all, once again, proclaim zolpidem as a problematic substance.

The analytical and surveillance tools of the FAN allow for the identification of the problem of addiction, they also provide transversal data relative to specific population groups, however they do not provide a general population risk profile, nor a comparison to other molecules. A research program based on the French National Health Insurance data base, allowed for the collection of quantitative data in the general population via an analysis of the usage of zolpidem and zopiclone [9]. The results of this research program provided the identification of a number of different clinical profiles of zolpidem consumers: *(i)* « non-problematic » consumers, the largest group; *(ii)* individuals who could have developed a tolerance to the hypnotic effects of zolpidem, for whom the prescription of alternative hypnotic/anxiolytic medication is justified; *(iii)* potential problematic consumers of zolpidem (1%) (high rate of fraudulent behavior, excessive usage, non-respect of guidelines and medical-pharmaceutical nomadism). In 2017, another research program gave insight into the characteristics of the two aforementioned consumer groups via the analysis of reports from health professionals [10].

Following to these results, on the 11th of January 2017, the ANSM decreed that as from April the 10$^{th}$ 2017, the prescription of zolpidem was to be done on secure prescription pads [11]. The ANSM stated that « this measure is taken in order to limit the risk of abuse and misuse » and « to encourage correct usage ». In a country where the consumption of psychotropic drugs is high, a ruling that impacts the most sold hypnotic drug [12, 13] will disrupt not only its' usage but also on a larger scale the overall

prescription of sedative substances. The current project aims to develop a means to measure the impact of this new ruling, in the scope of works of the ANSM, that is to say, in terms of the reduction of the risk of abuse, the improvement of correct use of zolpidem and the change in prescriptions of sedative molecules. This project forms part of the evaluation of zolpidem done by the Nantes CEIP-A, the organization in charge of its follow up. In addition to the tools used by the FAN [5], this project will allow for a longitudinal evaluation of the trajectories of different patients, as well as providing insight into the general population.

## METHODS AND ANALYSIS

### Aim

The objective of the ZORRO study (ZOlpidem and the Reinforcement of the Regulation of prescription Orders) is to evaluate the overall impact of the obligation to use secure prescription pads for zolpidem. We propose a multimodal approach that will provide valuable insight into three key questions: 1) what is the impact of this measure on the number of consumers? 2) What is the impact of this measure on the type of consumption? 3) What is the impact of this measure on the consumption of other sedative molecules?

### Study design

This scientific project is based on a multimodal epidemiological approach, which combines a retrospective cohort study involving the use of the French National Health Information data base (SNDS, formerly known as the French National Inter-schemes Health Insurance data base (SNIIRAM)) [14] and a transversal study involving the gathering in-field of clinical data of different populations: general practitioners that prescribe zolpidem as well as consumers (both patients having consulted a general practitioner and those having recourse to specialized care centers dedicated to drug dependence). To our knowledge, a study of this amplitude does not exist in France.

These two approaches will provide insight into three key areas:

- To evaluate the impact of the measure on the number of consumers, we will estimate via the SNDS data base the prevalence and the incidence of zolpidem consumers in the general population before and after the regulatory framework change.
- To evaluate the impact of the measure on the type of consumption, we will explore the changes in the modes of consumption: occasional use *versus* chronic use and problematic use *versus* non-problematic use. Problematic use is defined as a consumption outside of the SPC guidelines for at least one of the following parameters: the duration of consumption, the dosage, the means of procurement, the routes of administration or the search for an effect other than hypnotic. This evaluation will be done both from SNDS data base for the evaluation of the general population and from the field studies for the evaluation of problematic consumers of zolpidem (patients of general practitioners and users of specialized care centers dedicated to drug dependence).
- To evaluate the impact of the measure on the consumption of other sedative molecules, we will analyze the reporting of prescriptions and the changes observed both in the general population in the SNDS data base as well as among prescribers and problematic consumers of zolpidem (patients of general practitioners and users of specialized care centers for users of specialized care centers dedicated to drug dependence).

**Setting of the study**

The Nantes CEIP-A, is the national investigating center in charge of the management, surveillance and coordination of the entire project. General practitioners, their patients and users of zolpidem will be recruited across France. The gathering and the analysis of data (SNDS data base and field studies) will be centralized by the Nantes CEIP-A.

A multi-disciplinary pilot committee, comprised of pharmacologists, general practitioners, a methodologist bio-statistician, a clinical study technician and of an addictologist psychiatrist, has been

constituted in order to define the research protocol and in order to insure the scientific and methodological validity of the study.

**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 present 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 (CNAMTS). Practitioners specialized in the care of addictions and used to working with the FAN, will also be solicited [15]. All 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)*

Patients of general practitioners will be selected by participating practitioners. Users can also be selected by participating specialized care centers dedicated to drug dependence (addiction care and prevention centers (CSAPA) and drug-user risk reduction centers (CAARUD). All subjects (patients and users) with a problematic usage of zolpidem before the coming into force of the new regulatory framework and who provide their oral consent to participate, will be included in the study. A problematic consumption of zolpidem will be defined according to the DSM 5 criteria of substance use disorder. Under aged or protected individuals as well as subjects with French language difficulties (understanding, reading or writing) incompatible with the filling out of a questionnaire, will not be included in the study.

**Materials**

*Analysis of the SNDS database*

The SNDS data base is described in detail in the publication by Martin-Latry *et al* [14] as well as on related internet sites [16, 17]. The data analyzed will be sociodemographic data of the patients and the medication delivered to them (denomination, quantity, medical specialty of the prescribing practitioner). The access to the data will be done in accordance with current rulings and practice.

*Field study among general practitioners*

Participating general practitioners will reply to short telephone questionnaire, which will gather information on their perceptions and their prescription strategy following to the new regulatory framework (continuation of zolpidem on a secure prescription pad, prescription of a different sedative drug, cease in hypnotic prescriptions). The criteria for their choices will also be explored.

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

Patients and users will fill out a two-part auto-questionnaire. The first part will evaluate the consumption of zolpidem before the coming into force of the new regulatory framework (dosages used, duration, pursued effects and effects felt) and their change or not after the coming into force of the new regulatory framework (cease, change in dosage, relay to another drug or sedative substance). The second part of the questionnaire will be filled out only by patients or users for whom a change is observed and it will gather information pertaining to the favored replacement substance (dosages used, duration, pursued effects and effects felt).

**Study size**

*Analysis of the SNDS database*:

In light of the retrospective nature of the study and of the data bases used, the calculation of a power is not necessary, in accordance with the good practice guidelines of the European Network of Centers for Pharmaco-epidemiology and Pharmacovigilance [18].

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

Three hundred practitioners will be selected in order to insure that at least one hundred practitioners participate in the recruitment of problematic consumers of zolpidem. For feasibility reasons, the number of general practitioner patients to be included depends upon the construction of a convenience sample. This sample is estimated to be about 200 patients. Furthermore, 200 users will be recruited via the specialized care centers dedicated to drug dependence.

**Statistical methods**

All variables will undergo a descriptive analysis. Quantitative variables will be described using usual position (mean or median) and dispersion (standard deviation, interquartile range) parameters. The normality of their distribution will be assessed numerically (normality test) and graphically. For normally distributed quantitative variables, mean and standard deviation will be used. For non-normally distributed variables, median and interquartile ranges will be used. Qualitative variables will be described using number and frequency tables for each parameter. All analysis will be conducted with SAS software. Specific statistical methods will be implemented in order to answer each question adequately.

*Impact of the measure on the number of consumers: estimation of prevalence and incidence of zolpidem users within the SNDS database before and after the regulatory framework change.*

A number of periods will be studied (figure 1). The proportion of patients having received at least one delivery of zolpidem during the period 2 and during the period 4 will be compared using a Mc Nemar test for paired proportion. Patients missing from one of the two periods will be recorded as non-users. The significance threshold will be fixed at 5%. An incident user will be defined as a patient receiving a first delivery of zolpidem without any prior delivery over the preceding 6 months. The number of incident

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

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

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

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

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

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

French good practice guidelines regarding hypnotics, presence of an associated psychiatric disorder. The analysis will be repeated during periods 2 and 4. In order to study the transitions between clusters over time, a latent transition analysis (LTA) will be performed. The choice of the best model will be made considering Bayesian Information Criterion (BIC). The choice of the best model will also be made with consideration to the stability of the model (proportion of convergences among the 5000 iterations), the BIC (lower is better) and the interpretability of the model.

*Within the field observational study among problematic consumers of zolpidem:* A descriptive analysis will be performed. We will compare the number and the distribution of the positives criteria of problematic consumers (patients et users) before (for zolpidem treatment) and after the coming into force of the new regulatory framework (for zolpidem treatment or replacement substances): duration of consumption, dosage, manner in which zolpidem or other substance is obtained, route of administration or pursued effects different from the expected effect of the treatment or substance. Parametric or non-parametric paired-tests will be used for comparisons, according to the distributions of each variable. For each hypothesis test, an alpha risk of 5% will be used. In case of multiple testing, a correction of the significance threshold will be applied to avoid alpha risk inflation (Hochberg's method).

*Impact on the consumption of other sedative molecules: analysis of prescription deferrals and switches*

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

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

zolpidem users have shifted their consumption to other drugs since the change in regulatory framework. Secondly, a sequence analysis will be performed using dedicated tools (TramineR, SeqHMM and arulesSequences packages in R software). This will include a cluster analysis of the sequences, in order to identify typical trajectories in consumption and their modification following to the change in the regulatory framework.

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

*Within the field study among problematic consumers of zolpidem:* A descriptive analysis of the number of molecules tried as a replacement and the molecules that best replaced zolpidem, if applicable, after the change in regulatory framework, will be performed. In patients stopping zolpidem, but switching to another molecule, a univariate analysis of the same variables will be conducted in order to describe the use of zolpidem before the coming into force of the new regulatory framework and the use of other sedative drugs used in place of zolpidem after the coming into force of the new regulatory framework. For each hypothesis test, an alpha risk of 5% will be used. In case of multiple testing, a correction of the significance threshold will be applied to avoid alpha risk inflation (Hochberg's method).

## DISCUSSION

The evaluation of the addictive power of zolpidem by the addictovigilance network, required over the past, above and beyond the tools of the CEIP-A, the implementation of specific research programs. The evaluation of the impact of the change in the regulatory framework will similarly require the implementation of specific research programs. This project offers a design and a methodology which are complementary to the tools of the CEIP-A [4], indispensable to the measurement of the impact, that we believe to be major, of a change in the prescription requirements of the most sold hypnotic in France.

The ZORRO project aims to develop a method to measure the impact of the change in regulatory framework on practitioners' prescriptions of sedative molecules. This evaluation is complex, as in order to be thorough it must precisely measure the different aspects of the consequences of the regulatory framework change, both from a quantitative and qualitative point of view. Rather than doing a single study, we prefer to employ a strategy based on a number of different, and complementary, methodological approaches. We have anticipated some possible bias: for the analysis of information from a data base, we chose the data from the SNDS base as it contains information close to that of the real consumption (more so than the sales figures of pharmaceutical laboratories for example). Concerning the periods of reference BEFORE and AFTER, we have voluntarily chosen periods distant from the times of announcement and the coming into force of the change in regulatory framework in order to minimize bias linked to the transition period. Although, the regulatory framework change came into force in April 2017, the ANSM had published information on the measure as from January 2017. A part of the practitioners that prescribe zolpidem therefore anticipated the change in the regulatory framework and started to change their prescription strategy as from January 2017. One of the limits of the SNDS data base, that justifies our multimodal approach, is the complete absence of clinical information concerning the effects pursued or felt by patients, as well as the modification in routes of administration. Concerning the in-field clinical study, the principal bias is a memory bias of the questioned subjects. The time between the change in the regulatory framework and the implementation of the study is however incompressible as it is necessary to give patients and users sufficient hindsight in order to evaluate the changes in their consumption of zolpidem. In fact, the questions have been formulated in a simplified manner, and our project targets the most problematic consumers, who should remember with little difficulty the changes, having an impact on their daily lives, following to the new regulatory framework. A possible declarative bias does exist among patients and users, although this bias was taken into

account, in order to minimize it, in the conception of the questionnaire. On the one hand the questionnaire is completely anonymous. On the other hand, for patients, the questionnaire is filled-in away from any medical presence and handed back in a sealed envelope that is opened only by the Nantes CEIP-A for data analysis. The subjects recruited via specialized care centers dedicated to drug dependence are used to being questioned on their substance consumption by the CEIP-A personnel, in the framework of their mission of surveillance of cases of addition to and abuse of psychoactive substances. Our personnel have therefore developed an expertise in the realization of projects of this type among the users of specialized care centers dedicated to drug dependence. The strengths of this project lie within its' multimodal approach that allows, on the one hand, to document numerous possible consequences of the regulatory framework change, and on the other hand, to insure the overall coherence of the different studies via the management by an expert team in the field, coordinated by the French national reference center on the addictive potential of zolpidem. This project may very well have a double impact: On the one hand, it will provide additional data essential to the ANSMs' mission of surveillance of the risk relative to overdose, abuse, addiction and misuse of sedative substances ; On the other hand, this project could be the defining point of a series of steps (communication and information campaigns , …) designed to manage the public health issues surrounding zolpidem and to measure their overall impact.

## ETHICS AND DISSEMINATION:

### Ethics approval

The protocol was approved on the 11/06/2018 by the Committee for the Protection of the Population (CPP) and on the 12/04/2018 by the Committee of Expertise in Research, Studies and Evaluations in the Field of Health (CEREES). It was also submitted to the National Commission of Information Technology and Liberties (CNIL).

**Information to participants**

For the epidemiological analysis of the SNDS database: Not applicable

Practitioners: all practitioners will receive clear information regarding the study orally during the telephone interview. Practitioners that participate in the recruitment of patients will also receive written information.

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

**Consent to participate**

For the epidemiological analysis of the SNDS database: Not applicable

Practitioners: oral non-refusal to participate will be sought before delivery of the telephone questionnaire. Practitioners that accept to reply to the telephone questionnaire will be considered as not in opposition of the study. For the recruitment of patients, practitioners that fill in the documents relative to the inclusion of a patient will be considered as agreeing to participate in the study.

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

**Consent for publication**

The written information documents provided to practitioners, patients and users, state that the anonymous information gathered during the study is likely to be used in scientific publications and public communications.

**Availability of data and material**

Not applicable

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**AUTHOR STATEMENT**

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

MR wrote the first draft of the protocol, contributed to the questionnaires development and to the manuscript redaction.

PC designed statistical analysis of the SNDS database and contributed to the manuscript redaction.

MGB provided her expertise in the area of addictology. She contributed to the preparation of the zolpidem problematic consumers' questionnaire and validated their relevance to evaluate problematic use.

PL contributed to the questionnaires development.

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

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

All authors read and approved the final manuscript.

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**COMPETING INTERESTS**

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

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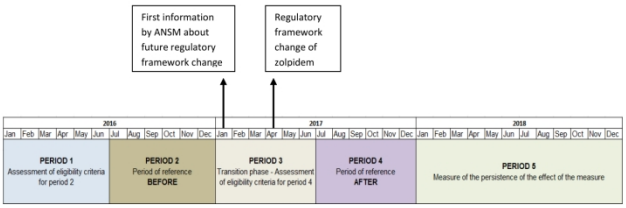
**WORD COUNT**

4258

**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.

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| | |

**Title:** 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.

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**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

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

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

Following to these results, on the 11th of January 2017, the ANSM decreed that as from April the 10th 2017, the prescription of zolpidem was to be done on secure prescription pads [11]. The ANSM stated that « this measure is taken in order to limit the risk of abuse and misuse » and « to encourage correct usage ». In a country where the consumption of psychotropic drugs is high, a ruling that impacts the most sold hypnotic drug [12, 13] will disrupt not only its' usage but also on a larger scale the overall prescription of sedative substances (hypnotics and anxiolytics). The current project aims to develop a means to measure the impact of this new ruling, in the scope of works of

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

## METHODS AND ANALYSIS

### Aim

The objective of the ZORRO study (ZOlpidem and the Reinforcement of the Regulation of prescription Orders) is to evaluate the overall impact of the obligation to use secure prescription pads for zolpidem. We propose a multimodal approach that will provide valuable insight into three key questions: 1) what is the impact of this measure on the number of consumers? 2) What is the impact of this measure on the type of consumption? 3) What is the impact of this measure on the consumption of other sedative molecules?

### Study design

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

These two approaches will provide insight into three key areas:

- To evaluate the impact of the measure on the number of consumers, we will estimate via the SNDS database the prevalence and the incidence of zolpidem consumers in the general population before and after the regulatory framework change.
- To evaluate the impact of the measure on the type of consumption, we will explore the changes in the modes of consumption: occasional use *versus* chronic use and problematic use *versus* non-problematic use. Problematic use is defined as consumption outside of the SPC guidelines for at least one of the following parameters: the duration of consumption, the dosage, the means of procurement, the routes of administration or the search for an effect other than hypnotic. This evaluation will be done both from SNDS database for the evaluation of the general population and from the field studies for the evaluation of problematic consumers of zolpidem (patients of general practitioners and users of specialized care centers dedicated to drug dependence).
- To evaluate the impact of the measure on the consumption of other sedative molecules, we will analyze the reporting of prescriptions and the changes observed both in the general population in the SNDS database as well as among prescribers and problematic consumers of zolpidem (patients of general practitioners and users of drug-user risk reduction centers or specialized care centers dedicated to drug dependence).

**Setting of the study**

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

A multi-disciplinary pilot committee, comprised of pharmacologists, general practitioners, a methodologist bio-statistician, a clinical study technician and of an addictologist psychiatrist, has been constituted in order to define the research protocol and in order to insure the scientific and methodological validity of the study.

**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

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

**Materials**

*Analysis of the SNDS database*

The SNDS database is described in detail in the publication by Bezin *et al* [14] as well as on related internet sites [16, 17]. The SNDS links several existing databases: the SNIIRAM, the nationwide claims database of the French National Healthcare system; the national hospital database (Programme de Médicalisation des Systèmes d'Information; PMSI) and the national death registry (Centre d'épidémiologie sur les causes médicales de Décès; CepiDC). The SNDS covers more than 98% of the French population (66 million people) from birth (or immigration) to death (or emigration), even in case of change in occupation or retirement. Data is individual and anonymous. The SNDS contains a longitudinal record of health encounters, hospital diagnoses and drugs deliveries relative to outpatient medical care claims, including all reimbursed drugs, information from hospital discharge summaries, and date of death.

*Field study among general practitioners*

Participating general practitioners will reply to short telephone questionnaire, which will gather information on their perceptions and their prescription strategy following to the new regulatory framework (continuation of zolpidem on a secure prescription pad, prescription of a different sedative drug, cease in hypnotic prescriptions). The criteria for their choices will also be explored.

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

Patients and users will fill out a two-part auto-questionnaire. The first part will evaluate the consumption of zolpidem before the coming into force of the new regulatory framework (dosages used, duration, pursued effects and effects felt) and their change or not after the coming into force of the new regulatory framework (cease, change in dosage, relay to another drug or sedative substance). The second part of the questionnaire will be filled out only by patients or users for whom a change is observed and it will gather information pertaining to the favored replacement substance (dosages used, duration, pursued effects and effects felt). General practitioners and staff of the CSAPA and CCARUD will return the completed questionnaires to the CEIP-A in Nantes for analysis.

**Study size**

*Analysis of the SNDS database*:

In light of the retrospective nature of the study and of the databases used, the calculation of a power is not necessary, in accordance with the good practice guidelines of the European Network of Centers for Pharmaco-epidemiology and Pharmacovigilance [18].

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

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

of a convenience sample. This sample is estimated to be about 200 patients. Furthermore, 200 users will be recruited via the specialized care centers dedicated to drug dependence.

**Statistical methods**

All variables will undergo a descriptive analysis. Quantitative variables will be described using usual position (mean or median) and dispersion (standard deviation, interquartile range) parameters. The normality of their distribution will be assessed numerically (normality test) and graphically. For normally distributed quantitative variables, mean and standard deviation will be used. For non-normally distributed variables, median and interquartile ranges will be used. Qualitative variables will be described using number and frequency tables for each parameter. All analysis will be conducted with SAS software. Specific statistical methods will be implemented in order to answer each question adequately.

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

A number of periods will be studied (figure 1). The proportion of patients having received at least one delivery of zolpidem during the period 2 and during the period 4 will be compared using a Mc Nemar test for paired proportion. Patients missing from one of the two periods will be recorded as non-users. The significance threshold will be fixed at 5%. An incident user will be defined as a patient receiving a first delivery of zolpidem without any prior delivery over the preceding 6 months. The number of incident users within each period will be compared using a Poisson model. The significance threshold for each coefficient will be fixed at 5%.

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

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

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

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

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

*Within the SNDS database:* A latent class analysis (LCA) will be conducted within each period, including the following variables: age, sex, presence of a chronic disease, poor economic status, prescribing practitioners specialty (only whether or not a general practitioner), number of different prescribing practitioners (doctor shopping), number of dispensing pharmacies (pharmacy shopping), excess use (mean monthly medication possession ratio [19] (MPR) > 1 during the period), adherence to French good practice guidelines regarding hypnotics (encompassing the absence of association with others benzodiazepines), presence of an associated psychiatric disorder (identified by concomitant drug use, i.e opioids substitution treatments, psycholeptic and psychoanaleptic drugs). The analysis will be repeated during periods 2 and 4. In order to study the transitions between clusters over time, a latent transition analysis (LTA) will be performed. The choice of the best model will be made considering Bayesian Information Criterion (BIC). The choice of the best model will also be made with consideration to the stability of the model (proportion of convergences among the 5000 iterations), the BIC (lower is better) and the interpretability of the model.

*Within the field observational study among problematic consumers of zolpidem:* A descriptive analysis will be performed. We will compare the number and the distribution of the positive criteria of problematic consumers (patients et users) before (for zolpidem treatment) and after the coming into force of the new regulatory framework (for zolpidem treatment or replacement substances): duration of consumption, dosage, manner in which zolpidem or other substance is obtained, route of administration or pursued effects different from the expected effect of the treatment or substance. Parametric or non-parametric paired-tests will be used for comparisons, according to the distributions of each variable. For each hypothesis test, an alpha risk of 5% will be used. In case of multiple testing, a correction of the significance threshold will be applied to avoid alpha risk inflation (Hochberg's method).

*Impact on the consumption of other sedative molecules: analysis of prescription deferrals and switches*

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

Firstly, a time series analysis will be performed on aggregated monthly data (proportion of users per month) to compare the changes in the consumption of zolpidem and other sedatives across all the study periods. Cross-correlation between the different time series will be studied in order to identify if zolpidem users have shifted their consumption to other drugs since the change in regulatory framework. Secondly, a sequence analysis will be performed using dedicated tools (TramineR, SeqHMM and arulesSequences packages in R software). This will include a cluster analysis of the sequences, in order to identify typical trajectories in consumption and their modification following to the change in the regulatory framework.

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

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

applicable, after the change in regulatory framework, will be performed. In patients stopping zolpidem, but switching to another molecule, a univariate analysis of the same variables will be conducted in order to describe the use of zolpidem before the coming into force of the new regulatory framework and the use of other sedative drugs used in place of zolpidem after the coming into force of the new regulatory framework. For each hypothesis test, an alpha risk of 5% will be used. In case of multiple testing, a correction of the significance threshold will be applied to avoid alpha risk inflation (Hochberg's method).

**DISCUSSION**

The evaluation of the addictive power of zolpidem by the addictovigilance network, required over the past, above and beyond the tools of the CEIP-A, the implementation of specific research programs. The evaluation of the impact of the change in the regulatory framework will similarly require the implementation of specific research programs. This project offers a design and a methodology which are complementary to the tools of the CEIP-A [4], indispensable to the measurement of the impact, that we believe to be major, of a change in the prescription requirements of the most sold hypnotic in France. The ZORRO project aims to develop a method to measure the impact of the change in regulatory framework on practitioners' prescriptions of sedative molecules. This evaluation is complex, as in order to be thorough it must precisely measure the different aspects of the consequences of the regulatory framework change, both from a quantitative and qualitative point of view. Rather than doing a single study, we prefer to employ a strategy based on a number of different, and complementary, methodological approaches. We have anticipated some possible bias: for the analysis of information from a database, we chose the data from the SNDS database as it contains information close to that of the real consumption. In the absence of available data on the drugs actually taken by patients, this database provides information on the drugs that patients obtain from pharmacies, which is more accurate than sales data for

example. Concerning the periods of reference before and after, we have voluntarily chosen periods distant from the times of announcement and the coming into force of the change in regulatory framework in order to minimize bias linked to the transition period. Although the regulatory framework change came into force in April 2017, the ANSM had published information on the measure as from January 2017. A part of the practitioners prescribing zolpidem therefore anticipated the change in the regulatory framework and started to change their prescription strategy as from January 2017. One of the limits of the SNDS database, that justifies our multimodal approach, is the complete absence of clinical information concerning the effects pursued or felt by patients, as well as the modification in routes of administration. Concerning the in-field clinical study, the principal bias is a memory bias of the questioned subjects. The time between the change in the regulatory framework and the implementation of the study is however incompressible as it is necessary to give patients and users sufficient hindsight in order to evaluate the changes in their consumption of zolpidem. In fact, the questions have been formulated in a simplified manner, and our project targets the most problematic consumers, who should remember with little difficulty the changes, having an impact on their daily lives, following to the new regulatory framework. A possible declarative bias does exist among patients and users, although this bias was taken into account, in order to minimize it, in the conception of the questionnaire. On the one hand the questionnaire is completely anonymous. On the other hand, for patients, the questionnaire is filled-in away from any medical presence and handed back in a sealed envelope that is opened only by the Nantes CEIP-A for data analysis. The CEIP-A personnel are accustomed to interviewing subjects recruited via specialized care centers dedicated to drug dependence on their substance consumption, in the framework of their mission of surveillance of addition and abuse of psychoactive substances. Our personnel have therefore developed an expertise in the realization of projects of this type among the users of specialized care centers dedicated to drug dependence. The strengths of this project lie within its' multimodal approach. It allows, on the one hand, to document numerous possible consequences of the regulatory framework change, and on the other hand, to insure the overall coherence of the

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

**ETHICS AND DISSEMINATION:**

**Ethics approval**

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

**Information to participants**

For the epidemiological analysis of the SNDS database: not applicable

Practitioners: all practitioners will receive clear information regarding the study orally during the telephone interview. Practitioners that participate in the recruitment of patients will also receive written information.

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

**Consent to participate**

For the epidemiological analysis of the SNDS database: not applicable

Practitioners: oral non-refusal to participate will be sought before delivery of the telephone questionnaire. Practitioners that accept to reply to the telephone questionnaire will be considered as

not in opposition of the study. For the recruitment of patients, practitioners that fill in the documents relative to the inclusion of a patient will be considered as agreeing to participate in the study.

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

**Consent for publication**

The written information documents provided to practitioners, patients and users, state that the anonymous information gathered during the study is likely to be used in scientific publications and public communications.

**Availability of data and material**

Not applicable

**Figure legends**

Figure 1: Periods of study of the SNDS database

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**AUTHOR STATEMENT**

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

MR wrote the first draft of the protocol, contributed to the questionnaires development and to the manuscript redaction.

PC designed statistical analysis of the SNDS database and contributed to the manuscript redaction.

MGB provided her expertise in the area of addictology. She contributed to the preparation of the zolpidem problematic consumers' questionnaire and validated their relevance to evaluate problematic use.

PL contributed to the questionnaires development.

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

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

All authors read and approved the final manuscript.

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**COMPETING INTERESTS**

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

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**WORD COUNT**

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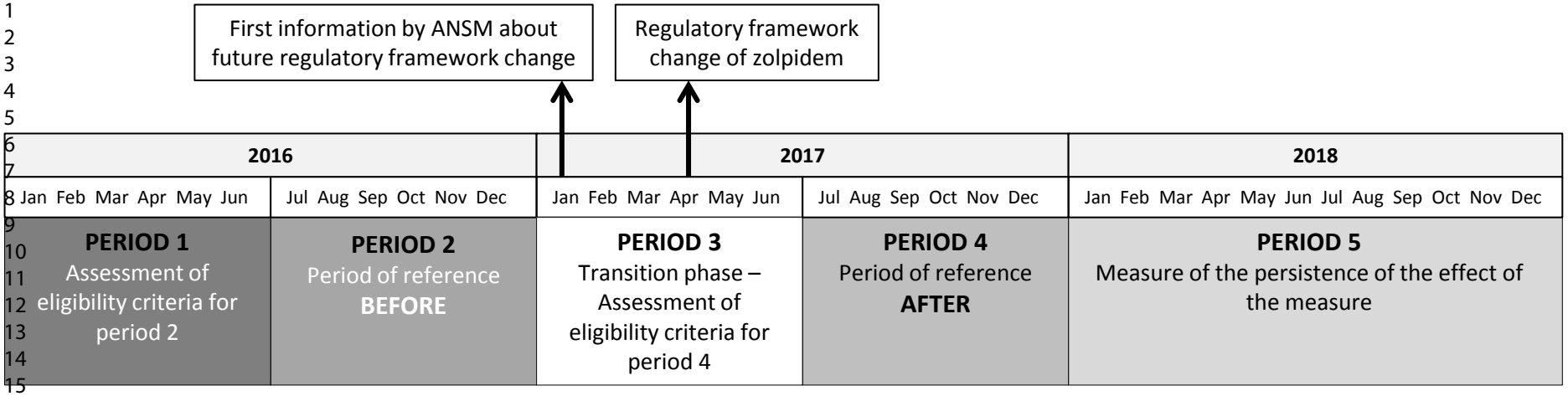
**Figure 1: Periods of study of the SNDS database**




ANSM: French National Agency for Medicines and Health Products Safety

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.

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**Title:** 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.

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**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

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

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

Following to these results, on the 11th of January 2017, the ANSM decreed that as from April the 10th 2017, the prescription of zolpidem was to be done on secure prescription pads [11]. The ANSM stated that « this measure is taken in order to limit the risk of abuse and misuse » and « to encourage correct usage ». In a country where the consumption of psychotropic drugs is high, a ruling that impacts the most sold hypnotic drug [12, 13] will disrupt not only its' usage but also on a larger scale the overall prescription of sedative substances (hypnotics and anxiolytics). The current project aims to develop a means to measure the impact of this new ruling, in the scope of works of

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

## METHODS AND ANALYSIS

### Aim

The objective of the ZORRO study (ZOlpidem and the Reinforcement of the Regulation of prescription Orders) is to evaluate the overall impact of the obligation to use secure prescription pads for zolpidem. We propose a multimodal approach that will provide valuable insight into three key questions: 1) what is the impact of this measure on the number of consumers? 2) What is the impact of this measure on the type of consumption? 3) What is the impact of this measure on the consumption of other sedative molecules?

### Study design

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

These two approaches will provide insight into three key areas:

- To evaluate the impact of the measure on the number of consumers, we will estimate via the SNDS database the prevalence and the incidence of zolpidem consumers in the general population before and after the regulatory framework change.
- To evaluate the impact of the measure on the type of consumption, we will explore the changes in the modes of consumption: occasional use *versus* chronic use and problematic use *versus* non-problematic use. Problematic use is defined as consumption outside of the SPC guidelines for at least one of the following parameters: the duration of consumption, the dosage, the means of procurement, the routes of administration or the search for an effect other than hypnotic. This evaluation will be done both from SNDS database for the evaluation of the general population and from the field studies for the evaluation of problematic consumers of zolpidem (patients of general practitioners and users of specialized care centers dedicated to drug dependence).
- To evaluate the impact of the measure on the consumption of other sedative molecules, we will analyze the reporting of prescriptions and the changes observed both in the general population in the SNDS database as well as among prescribers and problematic consumers of zolpidem (patients of general practitioners and users of drug-user risk reduction centers or specialized care centers dedicated to drug dependence).

**Setting of the study**

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

A multi-disciplinary pilot committee, comprised of pharmacologists, general practitioners, a methodologist bio-statistician, a clinical study technician and of an addictologist psychiatrist, has been constituted in order to define the research protocol and in order to insure the scientific and methodological validity of the study.

**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

dedicated to drug dependence (Centre de Soins, d'Accompagnement et de Prévention en Addictologie; CSAPA) and drug-user risk reduction centers (Centre d'Accueil et d'Accompagnement à la Réduction des risques pour Usagers de Drogues; CAARUD) will select users who presented a problematic use of zolpidem before the coming into force of the new regulatory framework. The inclusion period for patients and users will be the same as for general practitioners (second quarter of 2018 to the end of 2019). Users will be included in the study if they provide their oral consent to participate. The facility staff will provide them with a questionnaire to complete. A problematic consumption of zolpidem is defined according to the Diagnostic and Statistical Manual of Mental Disorders 5$^{th}$ edition (DSM-5) criteria of Substance Use Disorder. Under aged or protected individuals as well as subjects with French language difficulties (understanding, reading or writing) incompatible with the filling out of a questionnaire, will not be included in the study.

**Materials**

*Analysis of the SNDS database*

The SNDS database is described in detail in the publication by Bezin *et al* [14] as well as on related internet sites [16, 17]. The SNDS links several existing databases: the SNIIRAM, the nationwide claims database of the French National Healthcare system; the national hospital database (Programme de Médicalisation des Systèmes d'Information; PMSI) and the national death registry (Centre d'épidémiologie sur les causes médicales de Décès; CepiDC). The SNDS covers more than 98% of the French population (66 million people) from birth (or immigration) to death (or emigration), even in case of change in occupation or retirement. Data are individual and anonymous. The SNDS contains a longitudinal record of health encounters, hospital diagnoses and drugs deliveries relative to outpatient medical care claims, including all reimbursed drugs, information from hospital discharge summaries, and date of death.

*Field study among general practitioners*

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

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

Patients and users will fill out a two-part auto-questionnaire. The first part will evaluate the consumption of zolpidem before the coming into force of the new regulatory framework (dosages used, duration, pursued effects and effects felt) and their change or not after the coming into force of the new regulatory framework (cease, change in dosage, relay to another drug or sedative substance). The second part of the questionnaire will be filled out only by patients or users for whom a change is observed and it will gather information pertaining to the favored replacement substance (dosages used, duration, pursued effects and effects felt). General practitioners and staff of the CSAPA and CCARUD will return the completed questionnaires to the CEIP-A in Nantes for analysis.

**Study size**

*Analysis of the SNDS database*:

In light of the retrospective nature of the study and of the databases used, the calculation of a power is not necessary, in accordance with the good practice guidelines of the European Network of Centers for Pharmaco-epidemiology and Pharmacovigilance [18].

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

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

of a convenience sample. This sample is estimated to be about 200 patients. Furthermore, 200 users will be recruited via the specialized care centers dedicated to drug dependence.

**Statistical methods**

All variables will undergo a descriptive analysis. Quantitative variables will be described using usual position (mean or median) and dispersion (standard deviation, interquartile range) parameters. The normality of their distribution will be assessed numerically (normality test) and graphically. For normally distributed quantitative variables, mean and standard deviation will be used. For non-normally distributed variables, median and interquartile ranges will be used. Qualitative variables will be described using number and frequency tables for each parameter. All analysis will be conducted with SAS software. Specific statistical methods will be implemented in order to answer each question adequately.

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

A number of periods will be studied (figure 1). The proportion of patients having received at least one delivery of zolpidem during the period 2 and during the period 4 will be compared using a Mc Nemar test for paired proportion. Patients missing from one of the two periods will be recorded as non-users. The significance threshold will be fixed at 5%. An incident user will be defined as a patient receiving a first delivery of zolpidem without any prior delivery over the preceding 6 months. The number of incident users within each period will be compared using a Poisson model. The significance threshold for each coefficient will be fixed at 5%.

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

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

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

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

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

*Within the SNDS database:* A latent class analysis (LCA) will be conducted within each period, including the following variables: age, sex, presence of a chronic disease, poor economic status, prescribing practitioners specialty (only whether or not a general practitioner), number of different prescribing practitioners (doctor shopping), number of dispensing pharmacies (pharmacy shopping), excess use (mean monthly medication possession ratio [19] (MPR) > 1 during the period), adherence to French good practice guidelines regarding hypnotics (encompassing the absence of association with others benzodiazepines), presence of an associated psychiatric disorder (identified by concomitant drug use, i.e opioids substitution treatments, psycholeptic and psychoanaleptic drugs). The analysis will be repeated during periods 2 and 4. In order to study the transitions between clusters over time, a latent transition analysis (LTA) will be performed. The choice of the best model will be made considering Bayesian Information Criterion (BIC). The choice of the best model will also be made with consideration to the stability of the model (proportion of convergences among the 5000 iterations), the BIC (lower is better) and the interpretability of the model.

*Within the field observational study among problematic consumers of zolpidem:* A descriptive analysis will be performed. We will compare the number and the distribution of the positive criteria of problematic consumers (patients et users) before (for zolpidem treatment) and after the coming into force of the new regulatory framework (for zolpidem treatment or replacement substances): duration of consumption, dosage, manner in which zolpidem or other substance is obtained, route of administration or pursued effects different from the expected effect of the treatment or substance. Parametric or non-parametric paired-tests will be used for comparisons, according to the distributions of each variable. For each hypothesis test, an alpha risk of 5% will be used. In case of multiple testing, a correction of the significance threshold will be applied to avoid alpha risk inflation (Hochberg's method).

*Impact on the consumption of other sedative molecules: analysis of prescription deferrals and switches*

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

Firstly, a time series analysis will be performed on aggregated monthly data (proportion of users per month) to compare the changes in the consumption of zolpidem and other sedatives across all the study periods. Cross-correlation between the different time series will be studied in order to identify if zolpidem users have shifted their consumption to other drugs since the change in regulatory framework. Secondly, a sequence analysis will be performed using dedicated tools (TramineR, SeqHMM and arulesSequences packages in R software). This will include a cluster analysis of the sequences, in order to identify typical trajectories in consumption and their modification following to the change in the regulatory framework.

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

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

applicable, after the change in regulatory framework, will be performed. In patients stopping zolpidem, but switching to another molecule, a univariate analysis of the same variables will be conducted in order to describe the use of zolpidem before the coming into force of the new regulatory framework and the use of other sedative drugs used in place of zolpidem after the coming into force of the new regulatory framework. For each hypothesis test, an alpha risk of 5% will be used. In case of multiple testing, a correction of the significance threshold will be applied to avoid alpha risk inflation (Hochberg's method).

**DISCUSSION**

The evaluation of the addictive power of zolpidem by the addictovigilance network required over the past, above and beyond the tools of the CEIP-A, the implementation of specific research programs. The evaluation of the impact of the change in the regulatory framework will similarly require the implementation of specific research programs. This project offers a design and a methodology which are complementary to the tools of the CEIP-A [4], indispensable to the measurement of the impact, which we believe to be major, of a change in the prescription requirements of the most sold hypnotic in France. The ZORRO project aims to develop a method to measure the impact of the change in regulatory framework on practitioners' prescriptions of sedative molecules. This evaluation is complex, as in order to be thorough it must precisely measure the different aspects of the consequences of the regulatory framework change, both from a quantitative and qualitative point of view. Rather than doing a single study, we prefer to employ a strategy based on a number of different, and complementary, methodological approaches. We have anticipated some possible bias: for the analysis of information from a database, we chose the data from the SNDS database as it contains information close to that of the real consumption. In the absence of available data on the drugs actually taken by patients, this database provides information on the drugs that patients obtain from pharmacies, which is more accurate than sales data for example. Concerning the periods

of reference before and after, we have voluntarily chosen periods distant from the times of announcement and the coming into force of the change in regulatory framework in order to minimize bias linked to the transition period. Although the regulatory framework change came into force in April 2017, the ANSM had published information on the measure as from January 2017. A part of the practitioners prescribing zolpidem therefore anticipated the change in the regulatory framework and started to change their prescription strategy as from January 2017. One of the limits of the SNDS database, that justifies our multimodal approach, is the complete absence of clinical information concerning the effects pursued or felt by patients, as well as the modification in routes of administration. Concerning the in-field clinical study, the principal bias is a memory bias of the questioned subjects. The time between the change in the regulatory framework and the implementation of the study is however incompressible as it is necessary to give patients and users sufficient hindsight in order to evaluate the changes in their consumption of zolpidem. In fact, the questions have been formulated in a simplified manner, and our project targets the most problematic consumers, who should remember with little difficulty the changes, having an impact on their daily lives, following to the new regulatory framework. A possible declarative bias does exist among patients and users, although this bias was taken into account, in order to minimize it, in the conception of the questionnaire. On the one hand the questionnaire is completely anonymous. On the other hand, for patients, the questionnaire is filled-in away from any medical presence and handed back in a sealed envelope that is opened only by the Nantes CEIP-A for data analysis. The CEIP-A personnel are accustomed to interviewing subjects recruited via specialized care centers dedicated to drug dependence on their substance consumption, in the framework of their mission of surveillance of addition and abuse of psychoactive substances. Our personnel have therefore developed an expertise in the realization of projects of this type among the users of specialized care centers dedicated to drug dependence. The strengths of this project lie within its' multimodal approach. It allows, on the one hand, to document numerous possible consequences of the regulatory framework change, and on the other hand, to insure the overall coherence of the

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

**ETHICS AND DISSEMINATION:**

**Ethics approval**

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

**Information to participants**

For the epidemiological analysis of the SNDS database: not applicable

Practitioners: all practitioners will receive clear information regarding the study orally during the telephone interview. Practitioners that participate in the recruitment of patients will also receive written information.

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

**Consent to participate**

For the epidemiological analysis of the SNDS database: not applicable

Practitioners: oral non-refusal to participate will be sought before delivery of the telephone questionnaire. Practitioners that accept to reply to the telephone questionnaire will be considered as not in opposition of the study. For the recruitment of patients, practitioners that fill in the documents relative to the inclusion of a patient will be considered as agreeing to participate in the study.

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

**Consent for publication**

The written information documents provided to practitioners, patients and users, state that the anonymous information gathered during the study is likely to be used in scientific publications and public communications.

**Availability of data and material**

Not applicable

**Figure legends**

Figure 1: Periods of study of the SNDS database

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**AUTHOR STATEMENT**

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

MR wrote the first draft of the protocol, contributed to the questionnaires development and to the manuscript redaction.

PC designed statistical analysis of the SNDS database and contributed to the manuscript redaction.

MGB provided her expertise in the area of addictology. She contributed to the preparation of the zolpidem problematic consumers' questionnaire and validated their relevance to evaluate problematic use.

PL contributed to the questionnaires development.

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

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

All authors read and approved the final manuscript.

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**COMPETING INTERESTS**

None declared.

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**WORD COUNT**

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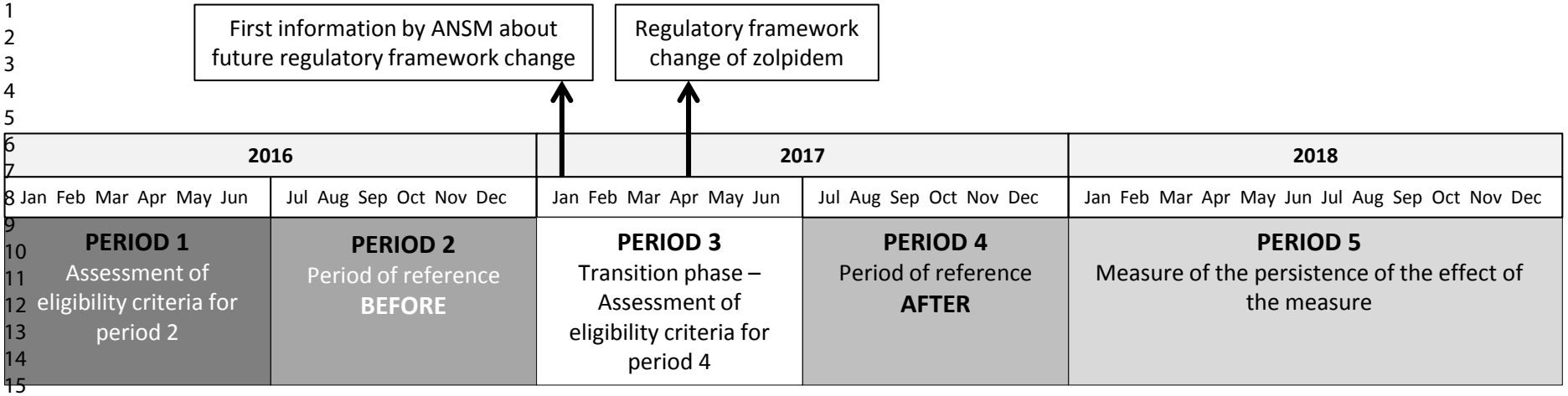
**Figure 1: Periods of study of the SNDS database**




ANSM: French National Agency for Medicines and Health Products Safety