

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Gerardin, Marie; Rousselet, Morgane; Caillet, Pascal; Grall-Bronnec, Marie; Loue, Pierre; Jolliet, Pascale; Victorri-Vigneau, C

VERSION 1 – REVIEW

REVIEWER	Albert Figueras Fundació Institut Català de Farmacologia Universitat Autònoma de Barcelona Spain
REVIEW RETURNED	23-Jan-2019

GENERAL COMMENTS	<p>I have read with interest the manuscript describing the ZORRO protocol.</p> <p>The use and overuse of hypnotic as well as hypnosedant medicines is an urgent public health topic. So, the idea underlying the present study is sound.</p> <p>The main objective is to study the impact of an administrative measure, and this is interesting. The authors propose a multifaceted approach to measure that impact. My suggestions to improve the results obtained by this study are:</p> <ol style="list-style-type: none">1) Regarding the SNDS database, will additional variables be studied (for example, co-treatment with zolpidem + another hypnotic or sedative).2) I'm not sure about the results of the field study with practitioners. Usually telephone questionnaires have limited results and many biases (professionals who follow guidelines and recommendations use to answer more and to lie less).3) The description of field studies in patients and users, which is another important part of the study, should be described in more detail: specific objectives, specific methodology, patients selection, etc.).
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REVIEWER	Mohammad Babaieian School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
REVIEW RETURNED	26-Feb-2019

GENERAL COMMENTS	The study is well-designed and you described everything precisely.
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REVIEWER	Stefania Chiappini University of Hertfordshire, UK
REVIEW RETURNED	07-Mar-2019

GENERAL COMMENTS

The manuscript describes the ZORRO study (Zolpidem and the Reinforcement of the Regulation of prescription Orders), evaluating the overall impact of the new French regulatory framework, requiring zolpidem to be prescribed on special secure prescription pads. The paper would add a picture of the current Zolpidem (and other hypnotics/sedative drugs) abuse in France, with regard to the recent changes related to their consumption. However, it was somewhat difficult to read on some part (see later). I think the manuscript must be reworked for clarification purposes. Specifically, the ENGLISH should be improved, there are typos, spelling and syntactic mistakes. Here are my remarks:

line 40: I suggest to use: far-reaching

line 44: I suggest to use: requiring zolpidem to be prescribed

line 45: I suggest to avoid repetition, and reformulate the sentence (in three lines authors use the word 'impact' three times)

line 52: I suggest here, as in all the manuscript, to avoid long periods. Be clear and concise. Please simplify the sentence.

line 73: could be here a typo for 'lack' (not lake)?

line 77: I suggest to modify the first sentence; it should be of impact for the reader. In this case you write: " Zolpidem is a medicinal substance that has been the target of a number of regulatory framework...", but I wonder when?how?why?could you add references?

line 87: I think "centre" is plural

line 88: please, check and spell all the acronyms CEIP-A. The majority of them are French, so I suggest to explain them in French using the brackets. Others of them are the following: Line141 SNIIRAM; line 184: CNAMTS, CSAPA, CAARUD..

line 89: I suggest " specifically-developed"

line 90: I suggest to reformulate this period: "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"

line 100: Please reformulate the period: "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". It is not clear.

line 106 Simplify the sentence: "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"

line 108 I would reformulate in this way: "However, collecting quantitative data of the usage of zolpidem and zopiclone in the general population [9], a research based on the French National Health Insurance database provided the identification of a number of different clinical profiles of zolpidem consumers"

line 126 Considering "the change in prescriptions of sedative molecules", which type do you mean? Other Z-drugs? hypnotics in general? which type of sedatives?

line 141 data base is one word, please check the manuscript to be consistent.

line 184 I suggest "included" instead of "present"

line 202 I suggest to explain the acronym DSM, the reader may not be a psychiatrist or a psychologist

line 202: I suggest to use capital letter for Substance Use Disorder

	<p>line 210: "The SNDS database is described in detail in the publication by Martin-Latry et al [14] as well as on related internet sites [16, 17]": I would reformulate the sentence in a more technical writing.</p> <p>line 316: I suggest the use of the British "behaviour" instead of the American "behavior"</p> <p>line 340: please consider "database" one word</p> <p>line 341: I suggest to clarify the sentence "more so than the sales figures of pharmaceutical laboratories"</p> <p>line 342: I do not understand why to use capital letter for "BEFORE and AFTER"</p> <p>line 344: after "Although" do not use a comma</p> <p>line 346: I suggest "prescribing" not "prescribed"</p> <p>lines 369-370 "On" do not need capital letter</p> <p>line 371: I would use "for example". I suggest not to use dots.</p> <p>line 410: is there a bracket missing after 1998? Be consistent with references.</p> <p>line 421: I think this reference should be completed.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1) Regarding the SNDS database, will additional variables be studied (for example, co-treatment with zolpidem + another hypnotic or sedative).

We added information regarding variables that will be studied, including other drugs (cotreatment with other benzodiazepines, opioid substitution treatments, psycholeptics and psychoanaleptics).

2) I'm not sure about the results of the field study with practitioners. Usually telephone questionnaires have limited results and many biases (professionals who follow guidelines and recommendations use to answer more and to lie less).

We have extensive experience in conducting pharmaco-epidemiological studies using telephone questionnaires (Gérardin M. et al, 2015). They are a means of interviewing a large number of people and of obtaining a satisfactory response rate. They are also a much more acceptable and less time-consuming method than a paper questionnaire. We chose this method to interview general practitioners because it is the only way to obtain information on their feelings about the change in the regulatory framework around zolpidem. Finally, we inform all participants that data recorded is completely anonymous. From our experience, the majority of respondents provide data without hindrance. That said, the bias related to telephone data collection will be taken into account when interpreting the results.

3) The description of field studies in patients and users, which is another important part of the study, should be described in more detail: specific objectives, specific methodology, patients selection, etc.).

We have modified the manuscript to provide greater clarity with respect to the field studies with patients and users.

Reviewer 3

The paper would add a picture of the current Zolpidem (and other hypnotics/sedative drugs) abuse in France, with regard to the recent changes related to their consumption. However, it was somewhat difficult to read on some part (see later). I think the manuscript must be reworked for clarification purposes. Specifically, the English should be improved, there are typos, spelling and syntactic mistakes.

We have taken your comments on board and the requested adjustments to the manuscript have been reviewed by a native English speaker.

Line 77: I suggest to modify the first sentence; it should be of impact for the reader. In this case you write: " Zolpidem is a medicinal substance that has been the target of a number of regulatory framework...", but I wonder when?how?why?could you add references?
We have modified this passage in order to provide greater clarity.

Line 126: Considering "the change in prescriptions of sedative molecules", which type do you mean? Other Z-drugs? hypnotics in general? which type of sedatives?
The term "sedative molecules" includes all drugs used as hypnotics and/or anxiolytics.

Line 210: "The SNDS database is described in detail in the publication by Martin-Latry et al [14] as well as on related internet sites [16, 17]": I would reformulate the sentence in a more technical writing. This part has been extended as follow: ", 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."
A more recent reference has also been added.

VERSION 2 – REVIEW

REVIEWER	Stefania Chiappini Huniversity of Hertfordshire, UK
REVIEW RETURNED	19-Mar-2019
GENERAL COMMENTS	Aftere the revision the manuscript has really improved. It is interesting, well-written and consistent.