

Pregabalin abuse in France: A national cohort study

Research Protocol

Principal Investigator:

Lapeyre-Mestre Maryse
Pharmacoepidemiologie, UMR-INSERM 1027
Universite Paul Sabatier - Toulouse 3
CEIP-Addictovigilance de Toulouse
Service de Pharmacologie Clinique, CHU de Toulouse
Faculte de Medecine
37 Allee Jules Guesde
31000 Toulouse France

37, allées Jules Guesde
31000 Toulouse
France

Project Information	
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Institution	University Toulouse III, Toulouse University Hospital UMR INSERM 1027
Project Director	Maryse Lapeyre-Mestre
Contract email	maryse.lapeyre-mestre@univ-tlse3.fr

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Scientific contact	
Last Name	Lapeyre-Mestre
First Name	Maryse
Address	37, allées Jules Guesde
City	Toulouse
Postcode	31000
Country	France
Phone number	0033-561145960
Alternative phone number	0033-561145606
Fax number	0033-561145928
Email address	maryse.lapeyre-mestre@univ-tlse3.fr

CONTACTS

Coordinating/Principal Investigator

Name and Contact details of the coordinating/principal investigator

LAPEYRE-MESTRE Maryse

Department of Clinical Pharmacology

UMR-INSERM 1027

Faculté de Médecine

37, allées Jules Guesde

31000 Toulouse

France

Phone number: 0033-561145960

Fax number: 0033-561145928

Email address: maryse.lapeyre-mestre@univ-tlse3.fr

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List of Acronyms:

ALD : *Affection de Longue Durée* (Chronic Disease Condition)

ANSM : *Agence Nationale de Sécurité du Médicament* (National Medicine Security Agency)

ATC : Anatomical Therapeutic Chemical classification system

CIP : *Code Identifiant de Présentation* (Identification Code of Presentation)

DDD : Defined Daily Dose

EGB: *Echantillon Généraliste de Bénéficiaires* (General Sample of Beneficiaries)

EMA: European Medicine Agency

EMCDDA: European Monitoring Centre for Drugs and Drug Addiction

ENCePP : European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

GABA: Gamma-Amino-Butyric Acid

INSEE : *Institut national de la statistique et des études économiques* (National Institute of Statistics and Economic Research)

ICD-10 : International Statistical Classification of Diseases and Related Health Problems 10th Revision

INSERM : *Institut National de la Santé et de la Recherche Médicale* (National Institute for Health and Medical Research)

PMSI : Programme Médicalisé des Systèmes d'Information (Medicalised Information System Program)

SPC: Summary of Product Characteristics

WHO : World Health Organisation

I. SUMMARY

Principal Investigator	LAPEYRE-MESTRE Maryse 37, allées Jules Guesde 31000 Toulouse France maryse.lapeyre-mestre@univ-tlse3.fr
Title	Pregabalin abuse in France: a national cohort study
Justification/context	<p>Pregabalin is a psychoactive drug indicated in neuropathic pain, generalized anxiety disorder and partial epilepsy. It modifies neuronal activity, binding $\alpha 2\delta 1$ presynaptic voltage-dependent calcic channel receptor, which is responsible for its psychotropic action. Neuropsychiatric adverse drug reactions, such as euphoria, have been described.</p> <p>Pregabalin abuse has been suggested in a few toxicological studies, pharmacovigilance studies with discrepancies in their results, and small population-based survey among opioid users or treated by opiate maintenance drugs in some European countries. Despite signals of abuse in few Nordic (??) European countries, no data suggest a potential for pregabalin abuse in France, and no study has ever compare pregabalin abuse to other drug used in the same indication. Searching a possible pregabalin abuse seems all the more relevant as its consumption increases in France and in Europe.</p>
Objectives	<p>Primary objective: to assess pregabalin abuse and its frequency in the French general population, in comparison with other drugs used in similar indications.</p> <p>Secondary objective: to determine the factors associated with pregabalin abuse.</p>
Study Design	Pharmacoepidemiological retrospective and comparative cohort study
Inclusion criteria	<ul style="list-style-type: none"> - New users of medications of interest since first pregabalin reimbursement in the database (15th June 2006): pregabalin, and its two comparators, gabapentin and duloxetine) - Aged 18 or more - At least two deliveries of the drug of interest.
Exclusion criteria	<ul style="list-style-type: none"> - Gabapentin exposure before inclusion date - Clonazepam exposure before patient inclusion.

Exposure of interest	<ul style="list-style-type: none"> - Pregabalin - Two comparators : <ul style="list-style-type: none"> ➤ Gabapentin (similar molecular structure and similar indications to pregabalin) ➤ Duloxetine (similar indications)
Other data collected	<ul style="list-style-type: none"> - Demographic data : gender, age, date of death. - Drug prescription characteristics: quantity, duration, number of distinct prescribers, and medical specialty of prescribers. - Comorbidities and diseases the year before inclusion. - Other psychoactive drug exposures before inclusion: opiate analgesic, addiction drugs, antidepressants, benzodiazepines, antipsychotics, psychostimulants antiepileptics, and muscles relaxant drugs.
Event of interest	Occurrence of abuse defined as a daily dose above that recommended.
Sample size	Around 15.000 subjects.
Data source	EGB (Echantillon Généraliste des Bénéficiaires – <i>General Sample of Beneficiaries</i>)
Duration of the study	2006-2014
Statistical analysis	<p>Analysis of the outcome: survival model (Kaplan-Meier) and Log-rank comparison test.</p> <p>Analysis of associated factors: univariate and multivariate analysis with a Cox proportional hazard regression model with time dependent covariates.</p>
Expected results	<p>We expect a frequency of abusers within pregabalin group at least equivalent to that showed in Sweden¹, around 8%. We also expect a higher frequency than in the control groups (gabapentin and duloxetine). We expect that some predictive factors should be identified, as suggested in other studies, such as group age, history of abuse, male gender, and treatment with opiate maintenance drugs. Comparing factors associated with abuse in the three groups of drug abusers could allow identification of different profiles of drug abusers (according to our definition of daily dose above that recommended), in the 3 groups and the potential motivations for abuse.</p>

¹ Bodén et al., « Factors Associated with Pregabalin Dispensing at Higher than the Approved Maximum Dose », février 2014.

II. ABSTRACT

Background and rational: Pregabalin is a psychoactive drug indicated in neuropathic pain, generalized anxiety disorder and partial epilepsy. It modifies neuronal activity, binding $\alpha\delta 1$ presynaptic voltage-dependent calcic channel receptor, which is responsible for its psychotropic action. Neuropsychiatric adverse drug reactions, such as euphoria, have been described. Pregabalin abuse has been suggested in from some case reports and pharmacovigilance studies, and from a small population-based survey among opioid users. Despite signals of abuse in few Nordic European countries, no data suggest a potential for pregabalin abuse in the general population in France, whereas searching a possible pregabalin abuse seems all the more relevant as its consumption increases in France and in Europe. Finally, no study has ever investigate abuse of pregabalin in comparison with other drugs with similar indications.

Objective: Our main objective will be to assess pregabalin abuse and its frequency in the French general population, in comparison with other similarly indicated drugs. Our secondary objective will to determine the factors associated with drugs abuse.

Patients and Method: A cohort study will be set from the EGB : Echantillon Généraliste des Bénéficiaires (*General Sample of Beneficiaries*), a national 1/97th representative sample of the French insured population, including new users of pregabalin, compared to 2 control groups of new users of gabapentin or duloxetine. Outcome will be abuse of the cohort study drug, defined as a daily abuse above the maximum recommended dose. Abuse will be investigated through a Kaplan-Meier survival model. Factors associated with abuse were investigated through a Cox proportional hazard regression model with time dependent covariates.

Expected results: We expect a frequency of abusers within pregabalin group at least equivalent to that observed in Sweden², around 8%. We also expect a higher frequency than in the control groups (gabapentin and duloxetine). We expect that some predictive factors should be identified, as suggested in other studies, such as group age, history of abuse, male gender, and treatment with opiate maintenance drugs. Comparing factors associated with abuse in the three groups of drug abusers could allow identification of different profiles of drug abusers (according to our definition), in the 3 groups and the potential motivations for abuse.

² Ibid.

III. CONTEXT

A. Background and rational

Pregabalin is a psychoactive drug indicated in neuropathic pain, generalized anxiety disorder and partial epilepsy. Although pregabalin presents molecular analogy with gamma-aminobutyric acid (GABA), it does not bind to GABA receptors but to $\alpha 2\delta 1$ presynaptic voltage-dependent calcic channel receptor³. It modifies neuronal activity which is responsible for its psychotropic action. Its pharmacological mechanism is not fully elucidated. Withdrawal syndrome and potential for abuse was identified through preclinical and clinical studies, and lead the labelling of potential for abuse in USA. In Europe, European Medicine Agency (EMA) had not retained this potential for abuse in the early labelling. Euphoria has also been most frequently reported with pregabalin in comparison with placebo in a meta-analysis of randomized control trials⁴. Since it was marketed in 2004, pregabalin sales have increased constantly in Europe⁵. In France, it remains among the twenty most sold prescribed drugs in 2013⁶.

In early pharmacovigilance data in France (2006-2009) no case of drug misuse or addiction was reported⁷. That was the same in EudraVigilance®, the European public pharmacovigilance database, among adverse drug reactions reported directly by patients⁸. Nonetheless in this study, cases of pregabalin withdrawal syndromes were found, and 30% of every CNS drug reports concerned pregabalin. Most of the reports were tolerance to the drug, and neuropsychiatric adverse reactions. First reports of abuse and diverted use of pregabalin have been published from 2010, and a study on the Swedish pharmacovigilance database reported a signal of abuse in 2010⁹. Due to these reports, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) noticed pregabalin as a new substance in its 2010 report¹⁰. Substance abuse and

³ Taylor, Angelotti, et Fauman, « Pharmacology and mechanism of action of pregabalin ».

⁴ Zaccara et al., « The Adverse Event Profile of pregabalin ».

⁵ Lapeyre-Mestre et Dupui, « Drug Abuse Monitoring: Which Pharmacoepidemiological Resources at the European Level? ».

⁶ Agence Nationale de Sécurité du Médicament (ANSM), « Analyse des ventes de médicaments en France en 2013 ».

⁷ Fuzier et al., « Adverse Drug Reactions to Gabapentin and Pregabalin ».

⁸ Aagaard et Hansen, « Adverse Drug Reactions Reported by Consumers for Nervous System Medications in Europe 2007 to 2011 ».

⁹ Schwan et al., « A Signal for an Abuse Liability for Pregabalin--Results from the Swedish Spontaneous Adverse Drug Reaction Reporting System ».

¹⁰ EMCDDA, « Annual report on the state of drugs problem in Europe ».

misuse risk was added the same year in the Summary of Product Characteristics (SPC) by the EMA¹¹.

In Germany, a pharmacovigilance study found an increasing of cases of pregabalin addiction 2008¹².

Besides, an increasing number of cases of death in context of substance abuse, with pregabalin screened, was assessed in toxicological post-mortem studies in Finland and in Germany¹³. In a Finnish study, 5% of blood samples from drivers arrested under the influence of substances were positive to pregabalin, often associated with anxiolytic drugs, opioids, and psychostimulants¹⁴.

Some studies have assessed pregabalin abuse in population with risk of substance abuse. Described as an “*ideal psychotropic drug*”, in particular, associated with other drugs (opioids, benzodiazepines, etc.) pregabalin misuse was assessed through online reports searched between 2008 and 2010 among 200 websites¹⁵. In 2013, ten pregabalin cases were identified among drug misusers study in the Emergency department of Belfast Royal Victoria Hospital (United Kingdom)¹⁶. Finally, pregabalin abuse among methadone patients was assessed in 2 studies in addiction care centres in Scotland and Germany¹⁷.

Few epidemiological studies have examined pregabalin abuse in general population. In an online survey in United Kingdom in 2013, prevalence of pregabalin misuse in entire life was estimated 0.5% among a sample of 1500 subjects¹⁸. Abusers obtained pregabalin from relatives prescribed pregabalin or internet. Between 2006 and 2009, a Swedish prescription database study reported a half of opioid drug users and a half of sedative drug users among pregabalin prescribed patients¹⁹. Most patients were prescribed pregabalin out of marketing authorisation

¹¹ European Medicine Agency (EMA), « Lyrica – Procedural steps taken after authorisation. »

¹² Schwan et al., « A Signal for an Abuse Liability for pregabalin--Results from the Swedish Spontaneous Adverse Drug Reaction Reporting System »; Gahr et al., « Pregabalin Abuse and Dependence in Germany ».

¹³ Launiainen et al., « Nicotine, Alcohol, and Drug Findings in Young Adults in a Population-Based Postmortem Database »; Häkkinen et al., « Profiles of pregabalin and Gabapentin Abuse by Postmortem Toxicology »; Lottner-Nau S, Övgüer B, Paul L, Graw M, Sachs H, Roeder G., « Abuse of pregabalin -results of the post-mortem toxicology from 2010 to 2012 ».

¹⁴ Kriikku et al., « Pregabalin Serum Levels in Apprehended Drivers ».

¹⁵ Schifano et al., « Is There a Recreational Misuse Potential for pregabalin? ».

¹⁶ Millar et al., « Lyrica Nights--Recreational pregabalin Abuse in an Urban Emergency Department ».

¹⁷ Grosshans et al., « pregabalin Abuse among Opiate Addicted Patients »; Baird, Fox, et Colvin, « Gabapentinoid Abuse in Order to Potentiate the Effect of Methadone ».

¹⁸ Kapil et al., « Misuse of the Γ -Aminobutyric Acid Analogues Baclofen, Gabapentin and pregabalin in the UK ».

¹⁹ Wettermark et al., « pregabalin Is Increasingly Prescribed for Neuropathic Pain, Generalised Anxiety Disorder and Epilepsy but Many Patients Discontinue Treatment ».

indications. In the Swedish prescription database, pregabalin abuse in general population was evaluated: 8.5% of subjects had a pregabalin prescription higher than the maximum daily dose recommended²⁰. Factors associated to this abuse were male gender, young age, low socio-economic level, epilepsy and current substance abuse (31%) or history of substance abuse (20%).

Despite signals of abuse in few Nordic European countries, no data suggest a potential for pregabalin abuse in France in general population, and no study has ever compare pregabalin abuse to other similar drug abuse. Searching a possible pregabalin abuse seems all the more relevant as its consumption increases in France and in Europe.

B. Hypothesis

Firstly, we hypothesised that the probability to observe pregabalin abuse in France was comparable to that reported in Sweden. This hypothesis seems all the more likely as some pregabalin users report pleasant effects and that its consumption is increasing. Secondly, we hypothesised that factors associated with drug abuse would be history of drug abuse, benzodiazepine abuse, and opiate maintenance treatment, as suggested in other European countries.

C. Justification of the methodological approach adopted

A cohort study will be set from the EGB : Echantillon Généraliste des Bénéficiaires (*General Sample of Beneficiaries*), a national 1/97th representative sample of the French insured population, including new users of pregabalin, compared to 2 control groups of new users of gabapentin or duloxetine.²¹ This database seems to be one of the most relevant in France to assess drug exposure in general population within a cohort study set among a large representative sample of the French general population. As an insurance reimbursement database, EGB seems more relevant to use than prescription database, since prescriptions data might not be representative of real drug exposure, particularly in case of falsified prescriptions (above all in substance abuse studies) or undelivered prescriptions. Besides, one study showed the consistency between drug reimbursement data and chronically consumed drug self-report²². Even if EGB does not contains primary care diagnosis, illegal drugs, tobacco or alcohol

²⁰ Bodén et al., « Factors Associated with Pregabalin Dispensing at Higher than the Approved Maximum Dose ».

²¹ Moulis et al., « French Health Insurance Databases ».

²² Noize et al., « Validity of Chronic Drug Exposure Presumed from Repeated Patient Interviews Varied according to Drug Class ».

consumptions or diagnosis associated with drug delivery, it contains diagnosis associated with hospitalisations, diagnosis associated with specific National Health Insurance program for invalid or chronically ill people, or occupational diseases. We will also be able to have access to any other primary care drug exposure, such as psychoactive drugs, opioid substitution drugs, which should be essential to identify subjects with past substance abuse. Finally, we chose to compare pregabalin to 2 other drugs with similar indications: gabapentin (similar indications and molecular structure) and duloxetine (similar indications). This approach was never done before and would enable us to assess a particular usage profile of pregabalin among comparable drugs used in the same indications or similar molecular structure.

D. Expected results

We expect a frequency of abusers within pregabalin group at least equivalent to that observed in Sweden²³, around 8%. We also expect a higher frequency than in the control groups (gabapentin and duloxetine). We expect that some predictive factors should be identified, as suggested in other studies, such as group age, history of abuse, male gender, and treatment with opiate maintenance drugs. Comparing factors associated with abuse in the three groups of drug abusers could allow identification of different profiles of drug abusers (according to our definition of daily dose above that recommended, in the 3 groups and the potential motivations for abuse).

²³ Bodén et al., « Factors Associated with Pregabalin Dispensing at Higher than the Approved Maximum Dose », février 2014.

IV. OBJECTIVE

The main objective of this study will be to assess pregabalin abuse and its frequency in the French general population, in comparison to other drugs with similar indications (gabapentin and duloxetine), in a pharmacoepidemiological, observational, French national retrospective cohort study.

The secondary objective is to determine the factors associated with abuse of each drug.

V. POPULATION AND METHOD

A. Study Design

A retrospective, French national cohort study on newly exposed adult subjects to pregabalin compare to newly exposed subjects to gabapentin or duloxetine will be set. We will use the EGB, a national representative sample of subjects of the French population, to select our 3 different drugs groups. Depending on the first medication reimbursed in the EGB, patient group will be designate. To be included, each patient will have to be delivered at least two times his group medication.

We will observe the number of pregabalin abusers occurring in time (survival model) in pregabalin group, compared to gabapentin and duloxetine abusers, respectively in gabapentin and duloxetine groups. We will then explore the association between drug abuse and covariables studied.

Patients will be included from the date of first delivery of pregabalin in the EGB, the 15th June 2006, until the 31th December 2012, in order to insure m a two-year minimum follow-up until 31th December 2014.

B. Data source: the EGB sample

The EGB sample, a permanent representative sample of French beneficiaries affiliated with the French health insurance scheme, covering approximately 700,000 beneficiaries in 2015, will be used. EGB is obtained by 1/97th random sampling with control for distribution of age, gender and area of residence²⁴. These beneficiaries are issued from the General Scheme (*Régime Général* - 86% of the French population²⁵), covering salaried workers and the universal health care coverage scheme (CMUC), attributed to the unemployed and low income insured, from agricultural workers and farmers scheme and from self-employed workers and retirees scheme. Thus, 97% of French population is represented. Public sector employees, students, migrants are not represented in the EGB sample.

²⁴ Moulis et al., « French Health Insurance Databases »; Tuppin et al., « French National Health Insurance Information System and the Permanent Beneficiaries Sample ».

²⁵ Tuppin et al., « French National Health Insurance Information System and the Permanent Beneficiaries Sample ».

The EGB has been linked since 2008 with another large-scale information system containing data from hospitalization stays (PMSI). Retrospective collection of data from PMSI has enabled the link with these data since 2005. The accessible data concern medicine, surgery and obstetric hospital stays²⁶.

The EGB includes the following data:

- Sociodemographic: a unique patient anonymous code, gender, year of birth, date of death and area of residence.
- Medico-administrative: 31 major chronic diseases fully covered by National Health Insurance scheme called “Affection de Longue Durée” (ALD) are recorded, also Invalidity and Occupational diseases. All of them are coded according to the International Classification of Diseases (ICD-10²⁷), or specific codes (Occupational disease “tables” or one of the 31 ALD number (see appendix 1)).
- All reimbursements of medical and paramedical expenses are available: medical consultations, visits, physiotherapist, medical transport, with act code, date of the act, price etc. For medication, date of delivery, medication identification (identified by the Anatomical Therapeutic Chemical (ATC) classification system²⁸ and CIP code (*Code Identifiant de Presentation*, Identification Code of Presentation) dosage and quantity dispensed. For every act, data on prescribers (specialty, anonymous identification code) are available.
- Hospitalisation data are available (from PMSI): date, duration, technical acts and diagnosis according to ICD-10 are available. Nevertheless, no data on delivered drugs during hospital stay are available.
- Date of death (provided indirectly by the National Institute of Statistics and Economic Research (INSEE). The cause is not recorded.

²⁶ Moulis et al., « French Health Insurance Databases ».

²⁷ World Health Organization, *International Classification of Diseases Version 10 (ICD-10)*.

²⁸ WHO Collaborating Centre for Drug Statistics Methodology, « Guidelines for ATC Classification and DDD Assignment - 2013 ».

C. Study population

1. Target population

French adult population of both gender, naive of any study medication or medication used in the same indication with abuse potential, will be targeted. In order to be able to widely extrapolate our future results, minimizing potential selection bias, no specific exclusion criteria, based on clinical and other sociodemographic characteristics, have been retained.

2. Inclusion and exclusion criteria

Will be included:

- subjects aged 18 or more,
- new users of pregabalin, gabapentin or duloxetine between the first date of inclusion (15th of June 2006) and until 31st December 2012 (to grant a two-years minimum follow-up),
- Subjects being reimbursed at least two delivery of medication group, at different dates (two delivery or more the same day, only once, will be considered as single time user).

Will be excluded:

- patients who were delivered gabapentin or clonazepam before the starting date of inclusion (15th June 2006) for gabapentin, and before individual date of inclusion for clonazepam, to ensure that every patient would not have been delivered any medication related to pregabalin indication (neuropathic pain, epilepsy). Duloxetine was marketed in France in 2008, so no patient could have received it before. Clonazepam is a benzodiazepine drug indicated in epilepsy. On the one hand, it was widely used in France, out of the indication of its marketing authorisation, to treat neuropathic pains²⁹. On the other hand, its potential for abuse is high³⁰. Consequently, the number of pills by package was limited to 28 in 2008, and treatment initiation was restricted to neurologists and paediatricians in 2012³¹. We hypothesised that excluding patients previously exposed to clonazepam would guarantee naivety of subjects to a medication

²⁹ Agence Nationale de Sécurité du Médicament (ANSM), « Lettre aux Prescripteurs - RIVOTRIL® : Informations importantes sur le bon usage - Réduction du conditionnement des comprimés ».

³⁰ Frauger et al., « [Misuse of clonazepam (Rivotril) »; Frauger et al., « Evidence of Clonazepam Abuse Liability ».

³¹ « Clonazépam (RIVOTRIL®) per os utilisé hors AMM (notamment dans la douleur, les troubles anxieux et du sommeil) : Pourquoi et comment arrêter ? - Mise au point ».

with proved potential for abuse and used in the same indications than pregabalin or comparators.

- patients in other insurance schemes than the General Scheme (*Régime Général*) i.e. self-employees and agricultural workers, for whom data are only available in the EGB since 2011, making impossible the implementation of a long-term follow-up. Nonetheless, the General Scheme covers 86% of the French population³².

No other exclusion criteria will be applied in order to be able to widely extrapolate our future results

3. Groups selection, method and rationale

A dynamic cohort of new users of pregabalin, gabapentin and duloxetine was selected in the EGB. Gabapentin and duloxetine were chosen as control group. Gabapentin molecular structure is close to pregabalin structure (GABA core), and has similar indication (epilepsy and neuropathic pain). Duloxetine is an antidepressant drug (a noradrenaline, serotonin recapture inhibitor) indicated, as pregabalin is, in diabetic neuropathic pain and general anxiety disorder. We did not choose clonazepam as a positive control: restriction of prescription in initiation occurred during the follow-up time of our study and clonazepam sales have widely decreased ever since (–decrease of 70% of consumption between 2011 and 2012, both in initiating patients and current consumers³³). Imipraminic antidepressants are also indicated in neuropathic pain, but we did not choose them, due to the amount of different medications in this class and their main use in depression.

The cohort inclusion will start the 15th June 2006, date of the first reimbursement of pregabalin in the EGB database, and end the 31st December 2012. Follow-up will be performed until the last data available in 2015 (i.e. December 2014). Depending on the first medication registered in time, the patient group will be designated, whatever the prescription patterns would become (switch to one of the other study drug, for instance, a patient switching from pregabalin to gabapentin, would remain in pregabalin group).

³² Tuppin et al., « French National Health Insurance Information System and the Permanent Beneficiaries Sample ».

³³ Agence Nationale de Sécurité du Médicament (ANSM), « État des lieux de la consommation des benzodiazépines en France ».

D. Exposure definition to group medication

1. Medication identification in database, exposure dose definition

Users of pregabalin, duloxetine and gabapentin will be identified in EGB database thanks to ATC codes of each drug, which are the following³⁴.

N03AX16 : pregabalin

N03AX12 : gabapentin

N06AX21 : duloxetine

Subjects exposed to clonazepam before potential inclusion date will be defined with reimbursed drugs recorded in EGB under the ATC code N03AE01 (clonazepam).

Any subject being reimbursed gabapentin before the 15th June 2006 was identified with ATC code N03AX12 in order to be excluded.

Every drug group deliveries will be then extracted. Index date will be the date of the first prescription of one of the 3 study's medications, from the 15th June 2006. Number of packages, quantity of drug by pack (units, as pills for instance), and dose by unit (in milligram) will be selected to measure the total amount of drug delivered by pharmacists.

Each dose delivered will be transformed in DDD (Daily Defined Dose, standardised international unit defined by WHO for each drug listed³⁵):

Dose delivered (mg) = *umber of packs* × *number of unit by pack* × *dose by unit (mg)*

DDD delivered =
$$\frac{\text{number of packs} \times \text{number of unit by pack} \times \text{dose by unit}}{\text{drug DDD}}$$

The DDD of each drug (with ATC code) are the following³⁶ :

- Pregabalin (N03AX16) : 300 mg
- Gabapentin (N03AX12) : 1800 mg
- Duloxetine (N06AX21) : 60 mg

³⁴ WHO Collaborating Centre for Drug Statistics Methodology, « Guidelines for ATC Classification and DDD Assignment - 2013 ».

³⁵ Ibid.

³⁶ Ibid.

2. *Exposition duration to drug: the drug exposure cycle method.*

As already mentioned, real consumption is unknown, in particular along time, since we only know a drug amount delivered at one date. In order to better evaluate drug exposure, we need to formulate some hypotheses: we will use an exposure approximation method by calculating cycles of drug exposure. Several authors, working on similar databases in drug abuse studies, have already been using such methods³⁷.

In France, study drugs are registered on a list of products having a high risk for health and toxicity (“Liste I”): they have to be prescribed by a physicians, and the maximum treatment duration is limited to 6 months. These prescriptions are not renewable, unless the physician writes it down. For these drugs, the quantity dispensed in pharmacies is for a maximum of four weeks. To continue their treatment, patients have to return to a pharmacy to be dispensed the quantity for the next 4 weeks. The date of dispensing, identification of the speciality and quantity dispensed is then automatically recorded and transmitted to health insurance information system to enable reimbursement (and, consequently, in the EGB database). We will define a cycle as an uninterrupted period of delivery (patient coming regularly every month to be given his medication). If the next record for the same substance exceeds fixed number of days, the treatment is considered interrupted (beyond the 4 weeks). A new cycle starts then to the next delivery. We will define an uninterrupted drug exposure by duration of 28 days plus a tolerance of 7 days (i.e. 35 days) between two deliveries. Beyond 35 days between two deliveries, a new cycle starts.

Examples to illustrate exposure cycle definition are given in figure 1.

The duration of a cycle was calculated from the date of first delivery, to the last date of delivery plus its last number of DDD delivered, hypothesising that patient would use one DDD by day at this last delivery (maximum bias).

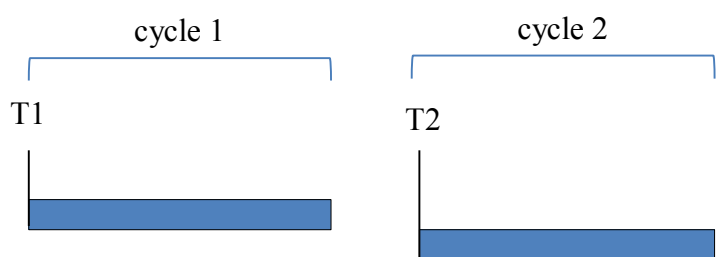
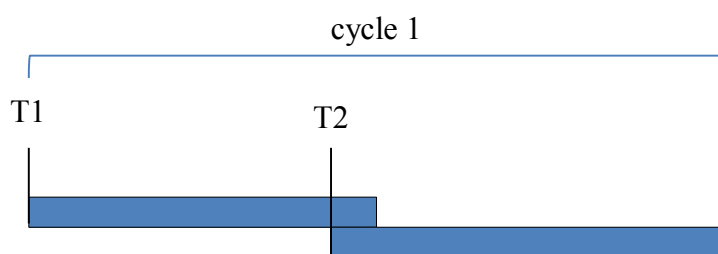
$$\text{Cycle duration (in days)} = (\text{last delivery date} - \text{first delivery date}) + \text{last DDD number}$$

The quantity of exposed drug will be calculated by addition of all DDD delivered during the cycle, whether there are overlapping between two deliveries or not. We calculated a mean daily DDD exposure dividing total DDD dispensed during the cycle by the total cycle duration.

³⁷ Cornish et al., « Risk of Death during and after Opiate Substitution Treatment in Primary Care »; Pradel et al., « Assessment of Doctor-Shopping for High Dosage Buprenorphine Maintenance Treatment in a French Region »; Dupouy et al., « [Opiate substitution treatment’s cycles in a five-year followed-up cohort in ambulatory practice] ».

$$\text{Daily DDD} = \frac{\text{Total number of DDD delivered during the cycle}}{\text{Cycle duration (in days)}}$$

Figure 1: Exposure cycle definition – examples



E. Events of interest: study outcome

1. Incidence of the main outcome

Occurrence of drug abuse along time will be the main outcome (abuse of pregabalin in pregabalin group, etc.). The abuse will be defined by the exceeding of maximum daily dose recommended (???). For every 3 drugs studies, this maximum corresponds to 2 daily DDD³⁸. Details on correspondence between dose in mg and DDD are given table 1.

Table 1: Correspondence between medication, ATC code, DDD, doses in mg, maximum daily dose recommended

Drug	ATC code	1 DDD	2 DDD (maximum daily dose recommended)
Pregabalin	N03AX16	300 mg	600 mg
Gabapentin	N03AX12	1800 mg	3600 mg
Duloxetine	N06AX21	60 mg	120 mg

DDD: Daily Defined Dose - ATC: Anatomical Therapeutic Chemical classification system

Thus, our main outcome occurs at the date of beginning of a cycle where daily drug exposure is above 2 DDD (maximum daily dose recommended).

2. Factor associated to the occurrence of the main outcome

Factors associated with outcome in the three cohorts will be explored through a Cox proportional hazard regression model with time dependent covariates.

We will select and study several covariables of interest, available in EGB. Details on covariables choice, selection, and rational for use is given bellow in paragraph F.

³⁸ WHO Collaborating Centre for Drug Statistics Methodology, « Guidelines for ATC Classification and DDD Assignment - 2013 ».

F. Data collection, covariables studied

Several covariables will be studied, to characterise population, compare groups, and investigate factors associated with abuse.

Covariables studied will be the following:

1. Sociodemographic

Are available in EGB (variable name in EGB between parentheses):

- A unique identification code by subject, securely encrypted to maintain anonymity (BEN_NIR_IDT),
- Gender (BEN_SEX_COD),
- Year of birth (BEN_NAI_ANN),
- Year and month of death (BEN_DCD_AME).

Only year of birth and year and month of death are available to ensure anonymity. Age at inclusion will be calculated at inclusion, considering individuals being born in the middle of their year (15th June), subtracting inclusion date to this birthday approximation date to calculate the age at inclusion. We will consider day of death as the 15th of the month of death and look death during follow-up and up to one year after the last group drug delivery.

2. Lifestyle

As an anonymous reimbursement database, no data are available about marital status, alcohol, tobacco or any illegal drug consumptions, weight, height and body mass index for instance.

3. Comorbidities the year before inclusion

Indication for drug prescription and patient medical history are not recorded in the EGB. Comorbidities will be identified by crossing several variables available in EGB (medico-administrative status and hospitalization data):

- Beneficiaries of ALD scheme (code “41” in variable IMB_ETM_NAT) will be identified, counted, and diseases associated to this ALD status (ICD-10 code, given by variable MED_MTF_COD or ALD code, given by IMB_ALD_NUM) isolated. The list of ALD numbers is given in Appendix.

- Disability (due to chronic disease or disabling disease) can also be identified (code “13” in variable IMB_ETM_NAT) with an associated diagnosis ICD-10 code, given by the variable MED_MTF_COD.
- Occupational diseases are also identified and benefit special status (code “12” in variable IMB_ETM_NAT) with an associated “occupational disease table” code (IMB_MLP_TAB) identifying specific fields of diseases. Two tables will be considered as responsible for chronic pain: Table 57, concerning “peripheral joint diseases occasioned by certain gestures and work postures”, and table 98 concerning “Chronic lumbar spine diseases occasioned by manual handling of heavy loads”.
- Every hospitalisation stays (PMSI) are available, with ICD-10 codes for primary diagnosis associated with each hospital stay (DGN_PAL) or associated diagnosis to hospitalisation (DGN_REL; ASS_DGN).

Every administrative status, every hospitalisation has a beginning and ending date. We will identify comorbidities profiles for each patient in the year before inclusion thanks to these dates, considering the disease status positive if a medico-administrative status or a hospital stays was occurring or still running during the year before inclusion.

Diseases identified by data crossing of these different variables are given in table 2, below.

Table 2: Identification table of diseases

Diseases	ICD-10 Code	ALD number	Occupational disease table
Cancer	C00-97	ALD 30	
Diabetes	E10-11	ALD 8	
Joints pathologies	M05-19	ALD 22	table 57
Spine pathologies	M40-54	ALD 26, ALD 27	table 98
Multiple Sclerosis	G35	ALD 25	
Neuropathy / Neuropathic pain	G50, G53.0, G54, G55-58, G60-64, G95, M89.0, M79.2		
Epilepsy	G40-41		
Substance abuse	F10-19 , T42-43		
Schizophrenia	F20-29		
Depressive disorders	F32-39		
Bipolar disorders	F31		
Anxiety disorders	F40-41		
Personality disorders	F60		

ALD : Chronic Disease Condition; ICD-10 : International Classification of Diseases - 10th Revision

4. Psychoactive drugs the year before inclusion

Psychoactive drugs reimbursed within the year before each subject inclusion will be isolated through ATC code (PHA_ATC_C07 variable). No data on delivered medications in hospital are available. Delivery date (EXE_SOI_DTD variable) will enable to determine exposure the year before inclusion.

Table 3 details pharmaco-therapeutic classes with their ATC codes. Classes of drugs will be the same than those used by Bodén et al.³⁹.

Table 3: Pharmaco-therapeutic classes with their ATC code

Pharmaceutical classes	ATC code
Addiction drugs	
Tobacco dependence drugs	N07BA
Alcohol dependence drugs	N07BB
Opiate substitution drugs	N07BC
Buprenorphine	N07BC01
Methadone	N07BC02
Analgesic drugs	
Strong opioids	N02AA-B-D-F-G other AC et AX
Weak opioids	N02AA08-58-59-79 ; N02AC04-54-74 ; N02AE01 ; N02AX02-52
Other psychoactive drugs	
Benzodiazepines	N05BA ; N05CD ; N05CF
Antidepressant drugs	N06A
Imipraminic antidepressant drugs	N06AA
Psychostimulants drugs	N06B
Other antiepileptic drugs	N03A
Antipsychotic drugs	N05A
Muscle relaxant drugs	
Tetrazepam	M03BX07
Baclofen	M03BX01
Dantrolen	M03CA01

³⁹ Bodén et al., « Factors Associated with Pregabalin Dispensing at Higher than the Approved Maximum Dose », février 2014.

5. *Exposure characteristics of the 3 studied drugs*

We will characterise several covariables from the three studied drugs:

- Specialty of initiating physician (variable PSP_SPE_COD) and any prescriber afterward,
- Care courses : prescription by the attending physician (called “*médecin traitant*” : every subject in French population has a chosen physician which have the role of “gatekeeper”),
- Number of different distinct prescribers for each drug studied,
- Initial quantity delivered (in DDD),
- Mean duration of exposure to drug group,
- Exposure cycle description: mean number, duration of cycles, drug exposure mean quantity.

G. **Statistical analysis**

1. *Missing data*

In EGB, there are no missing data regarding drug exposure. Quality checking is performed before loading data.

2. *Descriptive analysis*

Comparative analysis of variables available between groups will be performed.

Qualitative variables will be presented as number and percentage. Quantitative variables will be described by mean and standard deviation.

Chi2 test will be used to compare qualitative variables between groups. If this test is not applicable (theoretical numbers of subjects above 5), an exact Fisher test will be applied. Student T test will be used to compare quantitative variables. If this test is not applicable (distribution not normal and variances inhomogeneous) a non-parametric test will be used (Wilcoxon).

Significance p-value chosen will be equal to 0.05.

3. *Main outcome measure*

Outcome occurrence in time (survival model) will be modelled by a Kaplan-Meier method. A log-rank test will be used to compare outcome between groups (survival curves). The last

delivery date, or date of death, will be chosen as censoring date (when risk of abuse can be definitely excluded).

4. *Factors associated with outcome*

We will study, in a multivariate analysis, factors associated to outcome occurrence with a Cox proportional hazard regression model with time dependent covariates.

We will select into the multivariate model:

- Covariables significant in Cox model univariate analysis (with p-value bellow 0.20)
- Covariables identified in Bodén et al study⁴⁰.

We will exclude intermediate factors such as medical specialty of prescribers, medico-administrative status which are linked to medical conditions (diseases).

We will include variables into the final model after verifying:

- Log-linearity hypothesis (for continuous quantitative variables),
- Proportional risk hypothesis (testing variables interaction with time),
- Absence of collinearity between variables.

If log-linearity is not verified, we will transform continuous variables in discontinuous variables to include them in the final model. In case of interaction with time, we will discuss stratification. In case of collinearity, we will discuss the interest to keep one of the collinear variables.

Once conditions for multivariate model will be checked, we will perform a backward stepwise Cox proportional hazards model to select variables, retained in the final model with a p-value <0.05. Proportional hazards assumption will be tested for all covariates. The estimation of the crude and adjusted Hazard Ratio and their 95% confidence interval will be provided.

Analysis will be performed on SAS Enterprise Guide version 4.3 software (Copyright © 2006 - 2010, SAS Institute Inc., Cary, NC, USA) available on Health Insurance server to access EGB database.

⁴⁰ Ibid.

VI. LIMITATIONS OF THE STUDY DESIGN, DATA SOURCES

A. Potential for selection bias

In EGB, no data are available for some insured patients: civil servants, teachers and students. Some of these populations might be more at risk of abuse or more likely to present specific characteristics of drug consumption and disease.

However, only few people are not insured by National Insurance Scheme in France. Most needy people are covered by a specific scheme called universal health care coverage scheme (CMUC) which is under General Scheme management.

Despite these weaknesses, EGB remains a good representative sample of French general population⁴¹.

B. Potential for information bias

For some covariates, data crossing will be used. We must expect information bias due to this approach which can provide underestimated comorbidities profile, since diseases will be determined with hospitalisation and medico-administrative data. We will miss primary care diagnosis. However, some coprescribed drugs, for example opiate maintenance drugs, represent a robust proxy for opiate addictions (in France, most of these patients are cared in the ambulatory context).

C. Potential for measurement bias

In EGB, only reimbursement data are available. Thus, illegally obtained drugs cannot be captured in EGB, which is more likely to occur when studying drug abuse. Moreover, one study showed that most of pregabalin abusers obtained drug from relative's treatments or internet⁴². Nonetheless, such reimbursement databases have been widely used in pharmacoepidemiology⁴³, including drug abuse studies⁴⁴. Besides, the use of prescription database would not enable us to see prescription falsifications or to wrongly include undelivered prescriptions. Finally,

⁴¹ Tuppin et al., « French National Health Insurance Information System and the Permanent Beneficiaries Sample »; Moulis et al., « French Health Insurance Databases ».

⁴² Kapil et al., « Misuse of the Γ -Aminobutyric Acid Analogues Baclofen, Gabapentin and Pregabalin in the UK ».

⁴³ Moulis et al., « French Health Insurance Databases »; Pariente et al., « Factors Associated with Persistence of Cholinesterase Inhibitor Treatments in the Elderly ».

⁴⁴ Pradel et al., « Assessment of Doctor-Shopping for High Dosage Buprenorphine Maintenance Treatment in a French Region ».

matching between reimbursement data and self-declared consumption of chronic disease medications (such as the 3 drugs of our study) has been demonstrated to be good⁴⁵.

D. Potential for confounding bias

We can expect several confounding bias: we will not have data about alcohol, tobacco, and illegal drug consumptions. No data will be available also about primary care diagnosis, diagnosis associated to drugs prescriptions etc.

E. Potential for attrition bias/follow-up bias

In EGB, lost to follow-up cannot occur, limiting attrition bias, since follow-up is continue. Once a subject is included in the database, whenever his scheme changes, his follow-up is ensured through every reimbursed health cares. Even if subject move abroad, some reimbursement scheme, depending on the country, may still continue.

Besides, minimum follow-up of two-years is ensured since inclusion will stop the 31th December 2014.

F. Disputable definition of abuse

Definition of abuse can be discussed. Misuse can occur with a lower dose than 2 DDD by day, such as occasional and recreational uses.

⁴⁵ Noize et al., « Validity of Chronic Drug Exposure Presumed from Repeated Patient Interviews Varied according to Drug Class ».

VII. ETHICAL AND REGULATORY CONSIDERATIONS

A. Ethical considerations

National Institute for Health and Medical Research (INSERM) agreement for the research protocol was given in May 2014. Neither ethic committee authorisation nor request to national commissions for individual data protection (CNIL or CCTIRS) is required according to French law to access this kind of anonymous and restricted access databases⁴⁶.

B. Confidentiality

All data are anonymous in EGB databases. Access to server is secured and authorisation is given individually. Identification code of included EGB subjects is given by an unknown double encrypted algorithm⁴⁷. The database is built in order not to be able to join sensitive data (birthday, date of death, living area, date of cares). Thus, identification of subjects from these data is not possible.

Access to EGB data is limited to authorised users only. Consequently, data obtained in this study could not be shared with other parties.

Datasets will be stored on a secured server on the EGB, dedicated to researchers authorised to access EGB.

C. Amendments to the protocol

Any substantial modification, i.e. any modification that would significantly impact the conditions of validity and the results of the study, would be submitted to National Institute for Health and Medical Research in France (INSERM).

⁴⁶ Journal Officiel de la République Française, *Arrêté du 11 juillet 2012 relatif à la mise en œuvre du système national d'information interrégimes de l'assurance maladie*.

⁴⁷ Moulis et al., « French Health Insurance Databases ».

VIII. REPORTING: PLAN FOR DISSEMINATION OF REPORTS

Study results will be presented to the French Medicine Agency (ANSM), and will be added to the data of the French addictovigilance survey of pregabalin. This study will be submitted for communication in national and international congress, and will be submitted for publication to international independent scientific journal.

IX. QUALITY CONTROL: AUDIT AND INSPECTION

Not applicable

X. RULES FOR PUBLICATION

This study will follow the requirements for publication of the study results for ENCePP Seal Studies. In particular, publication will be undertaken in accordance with ENCePP rules for transparency⁴⁸.

⁴⁸ European Medicine Agency (EMA) et al., « How to apply for the ENCePP Study Seal – Guide ».

XI. APPENDIX

ALD disease number

- 1 - Disabling stroke
- 2 - Aplastic anaemia and other chronic cytopenias
- 3 - Chronic arteriopathies with ischaemic manifestations
- 4 - Complex schistosomiasis
- 5 - Severe heart failure, arrhythmias, valvular cardiomyopathy, congenital cardiomyopathy
- 6 - Active chronic diseases of the liver and cirrhoses
- 7 - Primary severe immunodeficiency requiring long-term treatment, infection by HIV virus
- 8 - Diabetes type 1, diabetes type 2
- 9 - Severe forms of neurological and muscular conditions (of which myopathy), serious epilepsy
- 10 - Chronic severe constitutional and acquired haemoglobinopathies, haemolysis
- 11 - Haemophilia and constitutional conditions of severe haemostasis
- 12 - Severe arterial hypertension
- 13 - Coronary heart disease
- 14 – Severe Chronic Respiratory Failure
- 15 - Alzheimer's disease and other dementias
- 16 - Parkinson's disease
- 17 - Hereditary metabolic conditions requiring long-term specialized treatment
- 18 - Cystic fibrosis
- 19 - Chronic nephropathy and primary nephrotic syndrome
- 20 - Paraplegia
- 21 - Polyarteritis nodosa, acute disseminated erythematous lupus, generalized progressive scleroderma
- 22 - Severe evolutive rheumatoid polyarthritis
- 23 - Long-term psychiatric conditions
- 24 - Ulcerative colitis and evolutive Crohn's disease
- 25 - Multiple sclerosis
- 26 - Evolutive structural scoliosis (the angle of which is equal to or over 25 degrees) until rachidian maturation
- 27 - Severe ankylosing spondylarthritis
- 28 - Organ transplant sequelae
- 29 - Active tuberculosis, leprosy
- 30 - Malignant tumours, malignant lymphatic or haematopoietic tissue