Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

DIORAMA

Resistant Depression in France,
description from the nationwide claims and hospitalization database

Protocol

Version V1.4, 28 August 2017

Bordeaux PharmacoEpi
Plateforme de recherche en pharmaco-épidémiologie
Service de Pharmacologie médicale, CIC Bordeaux CIC1401
INSERM - Université de BORDEAUX - CHU de Bordeaux - Adera
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STUDY INFORMATION

Title	Resistant Depression in France, description from the nationwide claims and hospitalization database (DIORAMA)
Protocol version identifier	Version 1.4
Date of last version of protocol	28 August 2017
IMPACT study number	NA
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Active substance	Antidepressants (AD) used for Treatment-Resistant Depression (TRD): ATC code N06A
Medicinal product	NA
Product reference	NA
Procedure number	NA
Marketing authorisation holder(s)	Janssen-France
Joint PASS	No
Research question and objectives	**Research question**: To assess the frequency of TRD, the characteristics of the concerned patients, their healthcare consumption and the corresponding costs. **Main objective:** To estimate the incidence and prevalence of TRD in the French population. **Secondary objectives:** To describe the baseline characteristics of incident patients, their healthcare consumption during the TRD episode and within the following 2 years and the corresponding costs.
Country of study	France
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2 LIST OF ABBREVIATIONS

AD	Antidepressants
ATC	Drug classification (*Anatomique, Thérapeutique et Chimique*)
BPE	Bordeaux PharmacoEpi, the Pharmacoepidemiology research platform of the University of Bordeaux - INSERM CIC1401
CNAMTS	French national health insurance fund for salaried worker (*Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés*)
CNIL	French data protection commission (*Commission Nationale de l'Informatique et des Libertés*)
DEP	Data Extraction Plan
DRG	Diagnosis-Related Groups (*or GHM for Groupes Homogènes de Malades*)
ECT	Electroconvulsive Therapy
EGB	1/97th random sample of the national health insurance database (*Echantillon Généraliste de Bénéficiaires*)
HAS	*Haute Autorité de Santé*
ICD-10	International Classification of Diseases, 10th classification
LTD	Long-Term Disease (registration for major chronic diseases with full insurance coverage of all claims related to disease)
MAOI	Monoamine oxidase inhibitors
MPR	Medication Possession Ratio
PMSI	National hospital discharge summary database (*Programme de Médicalisation des Systèmes d'Information*)
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SNIIRAM	National healthcare insurance system database (*Système National d'Information Inter-Régimes de l'Assurance Maladie*)
out of T2A	Specific hospital record of innovative and expensive products not included in DRG cost
SNRI	Serotonin-norepinephrine reuptake inhibitors
SRG	Stay-Related Groups (*or GHS for Groupes Homogènes de Séjours*)
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic antidepressant
TRD	Treatment-Resistant Depression

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4 ABSTRACT

TITLE	**DIORAMA**: Resistant Depression in France, description from the nationwide claims and hospitalization database
RATIONALE AND BACKGROUND	Depression is a common mental illness, which concerns 4.8% of the French population and is associated with a high psychological, social and economic burden. In 15 to 30% of the depressive episodes, the depression becomes resistant to treatment but these estimates are not accurate since the notion of treatment-resistant depression (TDR) is difficult to define precisely. Conventionally, TRD involves depression that fails to improve adequately after the use of 2 AD (whether or not they are from different pharmacological class) at doses and durations that would normally be effective, administered to a patient believed to be adherent (3). Patients suffering from TRD experience a disproportionate burden of illness with significant impairment, increased morbidity, and higher economic costs than those of a treatment responsive depression case (4). The global epidemiological situation and the clinical characteristics of TDR are thus poorly understood and require further study, especially in France. With the development of a new medication for the treatment of TRD, Janssen-France requests that the Bordeaux PharmacoEpi (BPE) platform, CIC Bordeaux CIC1401 of Bordeaux University, carries out a study in France to estimate the frequency of, the risk factors and the costs for TRD using the SNIIRAM nation-wide claims and hospital database. During the regulatory process for SNIIRAM access, a preliminary analysis will be performed using the EGB database (1/97th permanent random sample of the SNIIRAM) to optimize the SNIIRAM analysis.
RESEARCH QUESTION AND OBJECTIVES	**Research question:** To assess the frequency of TRD, the characteristics of the concerned patients, their health care consumption et the corresponding costs. **Main objective:** To estimate the prevalence and incidence of TRD in the French population. **Secondary objectives:** To describe the baseline characteristics of incident patients, their health care consumption during the TRD episode and within the 2 following years after the TDR episode and the corresponding costs.
STUDY DESIGN	The estimate of TDR incidence and prevalence will be carried out using 2 population-based cohorts. A **first cohort** study will be conducted to define TDR algorithm including all patients with at least one AD reimbursement in 2013, a 2-year period of history (2011-2012) and a 2-year period of follow-up (2014-2015), within the French nationwide claims and hospital database. To estimate annual TDR incidence and prevalence, a **second cohort** study will be conducted on TDR incident patients identified from 2012 to 2015 by the pre-defined TDR algorithm (Figure 2).
POPULATION	**Cohort 1 for algorithm identification:** all patients identified in 2013, with a 2-year period of history (2011-2012) and a 2-year period of follow-up (2014-2015) according to the following steps: ***a) Patients extracted from database:***

- 18 years of age or older;
- resident in metropolitan France;
- with at least one AD reimbursement in 2013. The date of the first AD reimbursement in 2013 will be defined as the **initiation date**;
- without any diagnostic of psychotic disorders, Parkinson's disease or dementia within the last 2 years preceding the initiation date;

b) ***Incident patients with AD treatment:*** patients with no AD reimbursement or depression diagnosis within a 6-month period before the initiation date;

c) ***Incident patients with long-term AD treatment:*** incident patients with at least 3 AD reimbursements within a 6-month period following the initiation date;

d) ***Potential incident TRD patients with long-term AD treatment:***. Incident patients treated with long-term AD who have failed of various AD treatment strategies (AD used alone, combination of ADs, potentiation of AD(s) effect by antipsychotic drug, antiepileptic drug, thyroid hormones or lithium) despite good adherence to medication of each treatment strategy (MPR $\geq$ 80%).

e) ***Specification of the algorithm:*** identification of sub-groups of patients who are likely to be treated with AD for other medical conditions than TRD such as:

- chronic psychotic disorders;
- anxiety disorders;
- neuropathic pain;
- current or ancient chronic ethylism.

Cohort 2 for the estimation of TDR incident and prevalent patients: all patients identified in 2012, 2013, 2014 and 2015 with at least a 2-year period of history, a maximum of 3 years of follow-up.

An incident user will be considered as a prevalent user in the years following the TRD episode, if the TRD episode is continued over this same period. A TRD episode will be considered completed if there is no new drug reimbursement of any AD treatment strategy within a 3-month period following the last AD reimbursement identified in the absence of any concomitant hospitalization.

VARIABLES

Index date: date of the first TRD date

Baseline patients' characteristics

Characteristics during the follow-up: patients' characteristics and characteristics of the TRD episodes

Healthcare resources use estimated in euros (€):

- From the Collective perspective taking into account the amounts of healthcare resources paid by the patients;
- From the National Health insurance perspective taking into account the amounts of the healthcare reimbursed by the National Health insurance to the patients.

DATA SOURCES

The SNIIRAM database is the nationwide healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system

(PMSI) and the national death registry, using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires.
The EGB is a permanent 1/97 random sample of the SNIIRAM, with free and full access to certain entities fixed by ministerial order, including accredited INSERM unit.

STUDY SIZE

World Health Organization Depression has estimated the prevalence of depressive disorders in 2015 in France at 4.8%. This concerns thus around 3.2 millions patients in the French population (66.8 millions of persons). In 15 to 30% of the depressive episodes, the depression becomes resistant to treatment. This corresponds to an effective varying from 480 000 to 1 million French individuals – between 4 800 to 10 000 persons in the EGB within a 1-year period.

DATA ANALYSIS

A Statistical Analysis Plan (SAP) will be developed and will be validated by the Scientific Committee before the analysis. The statistical analysis will be performed using the SAS® software (latest current version), following a detailed statistical analysis plan.

The following analyses will be performed for the 2 cohorts:

- A flow chart depicting the number of patients and sequences of treatment available in the database satisfying the inclusion criteria;
- Description of baseline characteristics, comorbidities;
- Description of the TDR episode;
- Description of the TRD prevalence and incidence, averaged per year and age- and sex-standardized to the French population;
- Description of healthcare resources use and their related costs during the TRD episode and during the follow-up period.

MILESTONES

EGB faisability study	**Q2 2017– Q1 2018**
- Synopsis & Protocol	Q2 2017
- Regulatory aspects and data extraction	Q2 2017
- Statistical Analysis Plan	Q2-Q3 2017
- Data management and tatistical analysis	Q3-Q4 2017
- EGB study report	Q1 2018
SNIIRAM study	**Q1-Q3 2018**
- Regulatory aspects and data extraction	Q3-Q4 2017
- Statistical Analysis Plan	Q1 2018
- Data management and statistical analysis	Q1-Q2 2018
- Final report	Q3 2018

5 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason

6 MILESTONES

Milestones	Planned Date
Synopsis EGB & Protocol SNIIRAM	Q2 2017
EGB feasibility study	Q2 2017-Q1 2018
- EGB Data extraction	Q2 2017
- Statistical Analysis Plan (EGB)	Q2-Q3 2017
- Data management and statistical analysis	Q3-Q4 2017
- EGB Study report	Q1 2018
Regulatory aspects and data extraction follow-up with CNAMTS (SNIIRAM)	Q3-Q4 2017
SNIIRAM study	Q1-Q3 2018
- Statistical Analysis Plan (SNIIRAM)	Q1 2018
- SNIIRAM data extraction	Q1 2018
- Data management and statistical analysis (SNIIRAM)	Q1-Q2 2018
- Final report (SNIIRAM)	Q3 2018

7 RATIONALE AND BACKGROUND

According to the World Health Organization, depressive disorders are ranked in 2015 as the largest contributor to non-fatal health loss (1). The proportion of the global population with depression is estimated at that time to be 4.4%, but prevalence varies according to sex and region. Depression is more common among female (5.1% *vs.* 3.6%) and nearly half of the people living with depression reside in the South-East Asia Region and Western Pacific Region. In France, 4.8% of the population is concerned by depressive disorders. Depression is also associated with a high economic burden (2) mostly due to decreased psychosocial function (notably workforce performance), making it a major public health priority.

In 15 to 30% of the depressive episodes, the depression becomes resistant to treatment (3). These estimates are not accurate since the notion of treatment-resistant depression (TRD) is difficult to define precisely. Research literature on the subject reveals a relatively high degree of heterogeneity of definitions, especially in the number or the type of antidepressants (AD) to consider and on the therapeutic strategies to employ. Conventionally, TRD involves depression that fails to improve adequately after the consecutive use of 2 AD (whether or not they are from different pharmacological class) at doses and durations that would normally be effective, administered to a patient believed to be adherent (3). Another less well-documented strategy is based on the combination of 2 individual ADs in case of non-response to a first one (4). Effect of AD may also be potentiated by other medications such as lithium, antiepileptic drugs, antipsychotic drugs or thyroid hormones but level of evidence of these strategies remains heterogeneous (5) Patients suffering from TRD experience a disproportionate burden of illness with significant impairment, increased morbidity, and higher economic costs than those of a treatment responsive depression case (6). The global epidemiological situation and the clinical characteristics of TRD are thus poorly understood and require further study, especially in France.

With the development of a new medication for the treatment of TRD, Janssen-France requests that the Bordeaux PharmacoEpi (BPE) platform, CIC Bordeaux CIC1401 of Bordeaux University, carries out a study in France to estimate the frequency of, the risk factors and the costs for TRD using the SNIIRAM nation-wide claims and hospital database.

During the regulatory process for SNIIRAM access, a preliminary analysis will be performed using the *Echantillon Généraliste de Bénéficiaires* (EGB) database (1/97th permanent random sample of the SNIIRAM) to optimize the SNIIRAM analysis.

8 RESEARCH QUESTION AND OBJECTIVES

The research question is to assess the frequency of TRD, the characteristics of the concerned patients, their healthcare consumption and the corresponding costs.

The main objective is to estimate the prevalence and incidence of TRD in the French population.

The secondary objectives are to describe the baseline characteristics of incident patients, their healthcare consumption during the TRD episode and within the following 2 years and the corresponding costs.

9 RESEARCH METHODS

9.1 STUDY DESIGN

The estimate of TRD incidence and prevalence will be carried out using **2 population-based cohorts.**

A **first cohort** study will be conducted to define TRD algorithm (Figure 1). This cohort will include all patients with at least one AD reimbursement in 2013, a 2-year period of history (2011-2012) and a 2-year period of follow-up (2014-2015), within the French nationwide claims and hospital database.

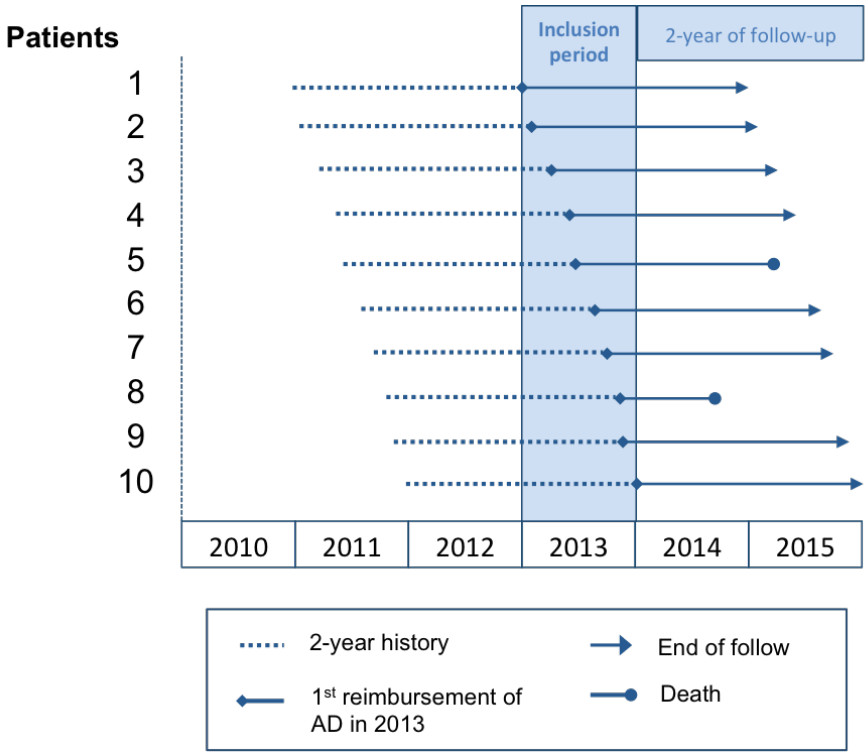

Figure 1. Study design of the main cohort

To estimate annual TRD incidence and prevalence, a **second cohort** study will be conducted on all TRD incident patients identified from 2012 to 2015 by the pre-defined TRD algorithm.

9.2 SETTINGS

9.2.1 Treatments of interest

ADs indicated for TRD (Tricyclic antidepressant, TCA; Monoamine oxidase inhibitors, MAOI; Selective Serotonin Reuptake Inhibitors, SSRI; Serotonin-norepinephrine reuptake inhibitors, SNRI; others ADs) will be identified in the French nationwide claims

and hospital database (SNIIRAM and EGB) according to the corresponding ATC codes (Annex 1).

9.2.2 Population

9.2.2.1 Constitution of the first cohort

The **first cohort** will allow building the identification algorithm of TRD incident patients. This cohort will include all patients identified in 2013 according to the criteria set out below, with a 2-year period of history (2011-2012) and a 2-year period of follow-up (2014-2015).
The procedure of inclusion will be implemented in successive steps;

a) ***Extraction of the population:*** will be extracted from the database, all patients with the following characteristics:

- 18 years of age or older;
- resident in metropolitan France;
- with at least one AD reimbursement in 2013. The date of the first AD reimbursement in 2013 will be defined as the **initiation date;**
- without any diagnosis of chronic psychotic disorders, Parkinson's disease or dementia within the last 2 years preceding the initiation date. Each disease will be identified based on the algorithm provided by the National Health Institute, using specific ICD-10 codes linked to the hospitalizations (in main, related or associated diagnosis) or to the long-term diseases (LTD) registration and specific medications and their related ATC/CIP codes (Annex 2).

b) ***Selection of incident patients with AD treatment:*** Incident patients with AD treatment will be identified and selected from the previous population if they do not have any AD reimbursement or depression diagnosis within a 6-month period before the initiation date. The depression diagnosis will be identified based on the algorithm provided by the National Health Institute, using specific ICD-10 codes linked to the hospitalizations (in main, related or associated diagnosis) or to the LTD registration (Annex 2).

c) ***Selection of incident patients with long-term AD treatment:*** Incident patients with long-term AD treatment will be identified and selected from the previous population if they have at least 3 AD reimbursements within a 6-month period following the initiation date.

d) ***Selection of potential incident TRD patients with long-term AD treatment:*** Potential incident TRD patients with long-term AD treatment will be identified and selected from the previous population if they have failed of various AD treatment strategies despite good adherence to medications of each treatment strategy.

- The possible **AD treatment strategies** are defined here below:

- Treatment strategy n°1: AD used alone (i.e. without prescription at the same date of another individual AD or another TRD medication such as an antipsychotic drug, an antiepileptic drug, thyroid hormones or lithium as listed in Annex 3);
- Treatment strategy n°2: combination of 2 individual ADs prescribed at the same date (4). Other combinations with amitriptyline or with low dose mianserin will be considered as symptomatic treatment and will not be included in this treatment strategy definition;
- Treatment strategy n°3: potentiation of AD(s) effect by another TRD medication (antipsychotic drug, antiepileptic drug, thyroid hormones or lithium) prescribed at the same date as the AD(s) (4). In patients with history of epilepsy or hypothyroidism defined by the presence in the 6 months prior to the prescription date of at least one reimbursement of antiepileptic/thyroid hormones (Annex 3), or of hospitalization/LTD ICD-10 codes for epilepsy (E00-E07)/hypothyroidism (G40, G41), the combination of an AD with an antiepileptic/thyroid hormones will not be considered as potentiation;

- **The initiation date** will be the date of the first AD reimbursement (treatment strategy n°1) or the date of the first reimbursement of the combination of ADs (treatment strategy n°2), or the date of the first reimbursement of the potentiation of AD (treatment strategy n°3). In cases where reimbursement dates are different (treatment strategies n°2 and n°3), the initiation date will be the most recent reimbursement date.

- **TRD definition:**
  - For the treatment strategy n°1, the **AD treatment failure** will be defines as the occurrence of a change in treatment strategy at least 3 weeks after the initiation date. A change in AD treatment strategy may include a switch from an individual AD used alone (treatment strategy n°1) to another individual AD used alone (treatment strategy n°1) or to the addition of another individual AD (treatment strategy n°2) or to the AD potentiation (treatment strategy n°3). In cases where the first treatment failure includes a change to treatment strategies n°1 or 2, then a TRD episode will be defined as the occurrence of 2 successive treatment failures within a period of 3-month (extended up to 6 months in a subsequent sensitivity analysis) after treatment initiation. The **TRD date** will be the date of the second treatment failure (Figure 2a). In cases where the first treatment failure includes a change to treatment strategies n°3, then a TRD episode will be defined as the occurrence of the first treatment failure within a period of 1 to 3-month. The **TRD date** will be the date of the first treatment failure (Figure 2b).
  - The treatment strategies n°2 or n°3 will be considered as a recurrence of a previous TRD episode for the patient concerned. In this case, a TRD episode will be identified as soon as the treatment strategy n°2 or n°3 is

initiated. The **TRD date** will be the initiation date of the treatment strategy (Figure 2c).

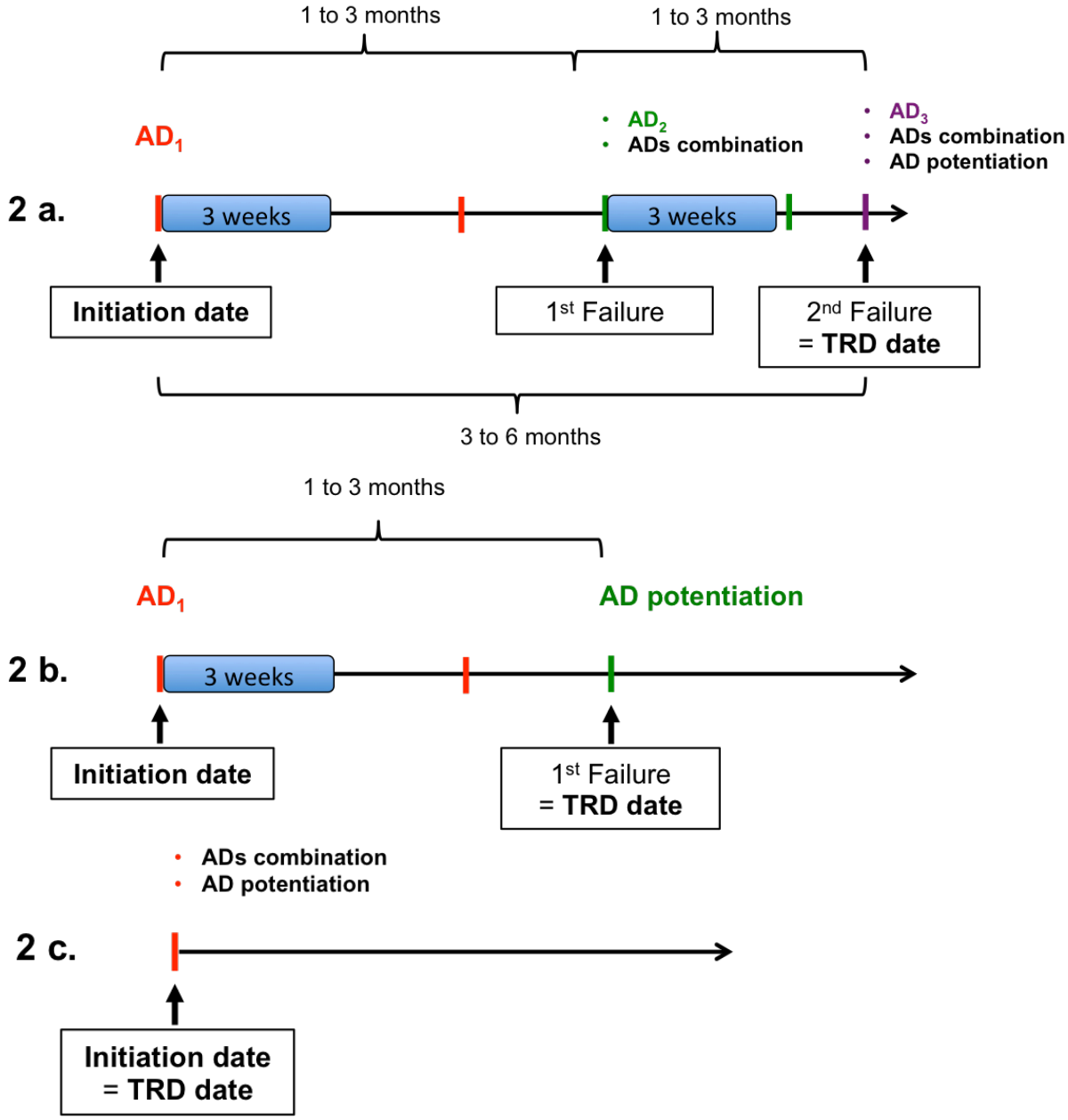

Figure 2. TRD definition considering the various possible treatment strategies

- Patients with a good adherence to medications of each AD treatment strategy. Adherence will be estimated by the calculation of the Medication Possession Ratio (MPR) for the period covered by each treatment strategy taking into account the overlap period between 2 successive reimbursements of the same medication (Figure 3). Considering the French prescription practices, the theoretical period covered by one drug reimbursement will be set at 30 days. A good adherence will be defined by a value of the MPR equal to or greater than 80% for all medications of the treatment strategy. A subsequent sensitivity analysis will be conducted with varying thresholds.

$$\text{MPR (\%)} = \frac{\text{Theoretical number of days covered by the drug reimbursements}}{\text{Total number of days between the first drug reimbursements of 2 successive treatment strategies}}$$

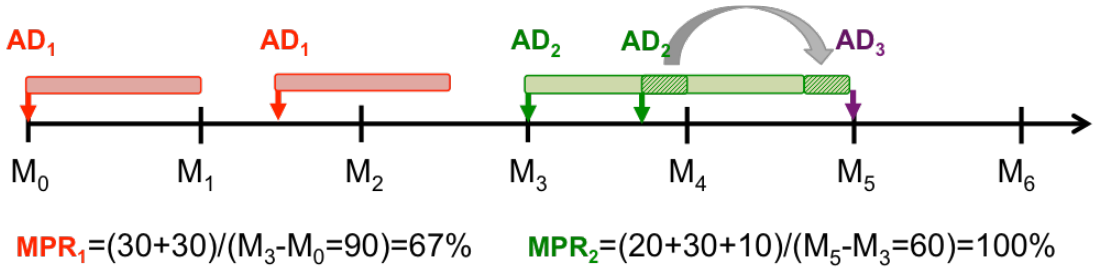

Figure 3. Examples of Medication Possession Ratio (MPR) calculation for 3 successive individual antidepressants (AD) reimbursements

e) ***Specification of the algorithm:*** The definition of the algorithm will be specified from the previous population after the identification of groups of patients who are likely to be treated with AD between the initiation date and the TRD date for other medical conditions than TRD. Groups will be constituted on the basis of the presence of at least one of the following criteria:

- Chronic psychotic disorders, defined by at least one reimbursement or one hospitalization with the ATC or ICD-10 codes listed in Annex 2 during the period from the initiation date to the TRD date;
- Anxiety disorders defined by at least one reimbursement of anxiolytic (*i.e.* all drugs starting with the ATC code N05B) during the period from the initiation date to the TRD date;
- Neuropathic pain defined by at least one reimbursement of opioids used alone or in combination (*i.e.* all drugs with the ATC codes N02A, or lamaline® N02BE51) concomitantly to the reimbursement of tricyclic AD during the period from the initiation date to the TRD date;
- Current or ancient chronic ethylism, defined by at least one reimbursement or one hospitalization with the ATC or ICD-10 codes listed in Annex 2 within the 12-month period prior to the TRD date.

9.2.3 Constitution of the second cohort

The **second cohort** will allow identifying potential TRD incident and prevalent patients from 2012 to 2015 by applying the TRD algorithm defined previously. This cohort will include all potential incident TRD patients identified in 2012, 2013, 2014 and 2015 using the TRD algorithm defined previously.

Patients of this cohort will have at least a 2-year period of history and a maximum of 3 years of follow-up after TRD date. Patients will be followed to the end of 2015 or to death whatever comes first. An incident user will be considered as a prevalent user in the years following the TRD episode, if the TRD episode is continued over this same period (Figure 4). A TRD episode will be considered completed if there is no new drug

reimbursement of any AD treatment strategy within a 3-month period following the last AD reimbursement identified in the absence of any concomitant hospitalization.

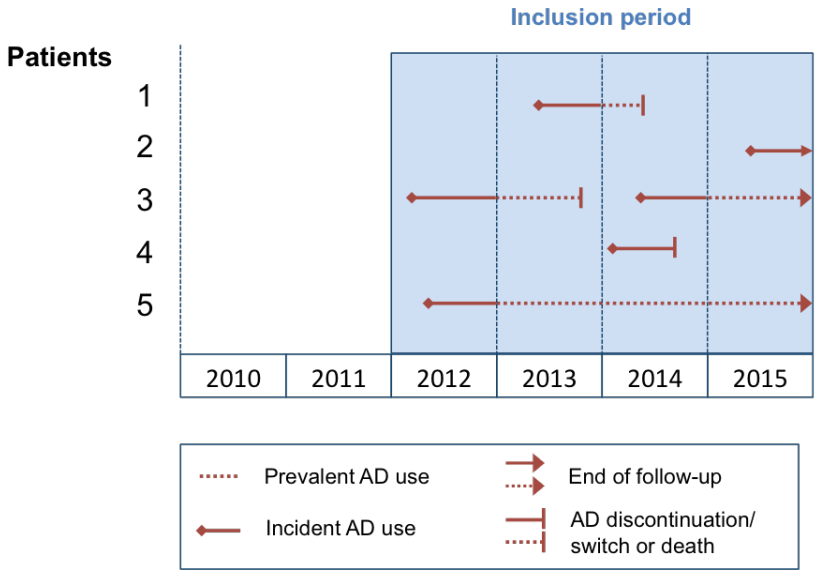

Figure 2. Study design of the second cohort

9.3 VARIABLES

9.3.1 Index date

The index date will be defined as the first TRD date identified in the study period.

9.3.2 Baseline TRD patients' characteristics

Extracted data related to baseline characteristics will be:

- Age at the index date;
- Gender;
- Within the 2-year period before the index date:
  - Psychiatric and non-psychiatric comorbidities identified according to the hospitalizations diagnosis and LTD;
  - Psychiatric and non-psychiatric reimbursed drugs;
  - In- and outpatient psychiatric consultations;
  - In- and outpatient sessions of Electroconvulsive Therapy (ECT);
  - Work stoppages and invalidity especially long-term sick leave (1 year), long-term leave (3 years) and invalidity of level 1 (part-time) and level 2.

9.3.3 TRD patients' characteristics during the follow-up

Extracted data related to follow-up characteristics will be:

- Vital status defined with the date of death (cause of death not available in the database);
- Characteristics of TRD episodes:
  - type and prescribers (psychiatrist or general practitioner) of AD reimbursed;
  - medications of AD treatment strategies reimbursed in the TRD episode;
- Psychiatric and non-psychiatric reimbursed medications;
- Psychiatric and non-psychiatric new comorbidities identified according to the hospitalizations diagnosis and LTD;
- In- and outpatient psychiatric consultations;
- In- and outpatient sessions of Electroconvulsive Therapy (ECT).

9.3.4 Healthcare resources use

Healthcare resources use related to TRD will be defined as:
- Hospitalizations related to TRD;
- Drugs and other non-drug treatments for TRD;
- Specific TRD tests or imaging;
- Medical visits related to the prescription of specific TRD treatment, tests or imaging;
- Transport related to TRD hospitalization or medical visits.

Other healthcare resources use will be classified as:
- Other hospitalizations;
- Other medical visits;
- Other drugs;
- Other lab tests;
- Physiotherapy;
- Nursing acts;
- Transport;
- Sick leave daily allowances;
- Pension and disability allowances;
- Other.

9.4 DATA SOURCE

The SNIIRAM database is the nationwide healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system (PMSI) and the national death registry, using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. The EGB is a permanent 1/97 random sample of the SNIIRAM, with free and full access to certain entities fixed by ministerial order, including accredited INSERM unit.
The SNIIRAM contains individual pseudonymised information on (Tuppin 2010, Bezin 2017):
- General characteristics: gender, year of birth, affiliation scheme, area of residence; deprivation status (CMU-c);

- Date of death for those concerned and very soon cause of death;
- Long-term disease (LTD, or ALD in French, and associated ICD-10 codes) with starting and ending date. LTD mainly concerned costly chronic diseases. LTD registration is obtained at the request of a patient's practitioner and validated by the health insurance system physician. Once registered, patients receive full (i.e. 100%) reimbursement for expenditure related to the LTD. The LTD information is specific for the diagnosis (very low risk of false positives), but not sensitive because not all patients with the disease ask to benefit from a LTD;
- Outpatient reimbursed healthcare expenditures: visits, medical procedures, nursing acts, physiotherapy, medical imageries, lab tests, drugs, medical devices, transports, sick leaves… with prescriber and professional caregiver information (medical or paramedical specialty, private/public practice), dates (prescription and dispensation), and codes (but not the medical indication nor result);
- Hospital-discharge summaries from the PMSI: ICD-10 diagnosis codes (primary, linked and associated diagnosis) for all private and public medical, obstetric and surgery hospitalizations, with the date and duration of hospitalization, medical procedures, and cost coding system, as well as most of very costly drugs. The hospital discharge summary includes the medical unit summaries when the patient is hospitalized successively in several medical units. Data from PMSI psychiatry, and rehabilitation centres are available in the SNIIRAM but not yet in EGB. Primary diagnosis is the health problem that motivated the admission in the hospital. It is determined at hospital discharge. For patients hospitalized successively in several medical units, the primary diagnosis of the hospitalisation, as well as all medical unit primary diagnoses, are generally taken into account to define the occurrence of an outcome in a pharmacoepidemiology study. A linked diagnosis can exist only if the primary diagnosis is a care procedure with a code Z of the ICD-10 classification (e.g. chemotherapy session) for a chronic or LTD disease. It indicates the pathology at the origin of the care procedure. As primary diagnosis, is taken into account to define the occurrence of an outcome in a pharmacoepidemiology study. Associated diagnoses are specified if they represent specific healthcare resources. They are mainly underlying chronic diseases. Associated diagnoses can be used to define chronic diseases but are generally not taken into account to define the occurrence of an outcome in a pharmacoepidemiology study (many being false positives for the studied outcome).

Non-hospital data are updated every month and hospital-discharge summaries yearly at end of Q3 for the previous year. Access to SNIIRAM is regulated and needs approval from the National Institute of Health Data (*Institut National des Données de Santé* - INDS) and French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

9.5 STUDY SIZE

World Health Organization Depression has estimated the prevalence of depressive disorders in 2015 in France at 4.8%. This concerns thus around 3.2 millions patients in the French population (66.8 millions of persons). In 15 to 30% of the depressive episodes, the depression becomes resistant to treatment. This corresponds to an

effective varying from 480 000 to 1 million French individuals – between 4 800 to 10 000 persons in the EGB within a 1-year period.

9.6 DATA MANAGEMENT

Database extraction criteria will be described in a Data Extraction Plan (DEP) approved prior to initiating extraction. Data extraction will be done by the CNAMTS. The BPE data manager in charge of the project will validate the population extracted by the CNAMTS using the EGB data extraction.
Data transformation, including decision rules, disease definition, exposure definition, outcomes, risk factors, healthcare resources and calculated variables will be detailed in a statistical analysis plan (SAP).

9.7 DATA ANALYSIS

9.7.1 Generalities

Statistical analysis will be performed using SAS® software (SAS Institute, latest current version, North Carolina, USA). A Statistical Analysis Plan (SAP) will be developed and will be validated by the Scientific Committee before the analysis.
During the regulatory process for SNIIRAM access, a preliminary analysis will be performed using the *Echantillon Généraliste de Bénéficiaires* (EGB) database (1/97th permanent random sample of the SNIIRAM) to optimize the SNIIRAM analysis.
The BPE team will perform the following analyses for **each cohort**. Other specific statistical analyses could be performed with protocol amendment.

9.7.2 Population description

- A flow chart depicting the number of patients available in the database satisfying the inclusion criteria;
- Description of baseline characteristics and comorbidities.

9.7.3 Within the TRD episode and the 2-year period of follow-up

- Description of the TRD episode in term of:
  - type and sequence of reimbursed medications of AD treatment strategies before AD treatment failure;
  - AD treatment prescribers;
  - alternative treatment strategy adopted in case of AD treatment failure;
  - duration of TRD episodes;
- Description of the healthcare consumption during the follow-up period (reimbursed medications, in- and outpatient consultations, hospitalizations, ECT).

9.7.4 TRD prevalence and incidence

TRD prevalence and incidence will be estimated over the 4-year period of selection accounting for the duration of the TRD episode. Estimates will be averaged per year and will be age- and sex-standardized to the French population.

9.7.5 Healthcare resources use and costs

Healthcare resources cost will be estimated in euros (€):

- From the Collective perspective taking into account the amounts of healthcare resources paid by the patients;
- From the National Health insurance perspective taking into account the amounts of the healthcare reimbursed by the National Health insurance to the patients.

9.8 QUALITY CONTROL

The BPE, INSERM CIC1401, has implemented a quality management system for all its activities. CNAMTS data extraction will be validated using the expected population size estimated using the EGB. An independent double programming will be performed for main criteria and analysis, and the results compared for validation. All statistical logs are kept and can be provided. In the case of interim analysis, the database for the interim analysis is locked and kept for ulterior validation if needed. The statistical analysis report (SAR) is included in the final study report.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The SNIIRAM is a national healthcare claims database linked to the national hospital discharge summaries database that covers about 99% of the French population. It provides a unique opportunity to identify all TRD patients, with exhaustive information about reimbursed treatments out of hospital and use of reimbursed healthcare resources, as well as all hospitalizations. Furthermore, the SNIIRAM has the advantage of any study that use patient records from an existing database that are not impacted by the study, as most of field studies.

This is also the main limit of this claims and hospitalization database that was built for administrative and reimbursement purposes with a lack of clinical data and biological results, including severity or stage of the disease, relapse or recurrence, or some risk factors such as smoking status, body mass index, blood pressure.

TRD patients will be identified using AD reimbursements, which are not specific of the disease and non-TRD patients could thus be erroneously included. Groups of patients who are likely to be treated with AD for other medical conditions than TRD will be identified then described before being potentially excluded, in order to maximize the algorithm specificity.

The algorithm will allow identifying incident TRD patients who might become prevalent in the subsequent years if the TRD episode lasts. Since the study period will be limited to 4 years, the algorithm could not identify long-term prevalent TRD patients and TRD prevalence estimate will thus be underestimated.

9.10 OTHER ASPECTS

None.

10 PROTECTION OF HUMAN SUBJECTS

This project is a database analysis with individual anonymous information for which subject informed consent is not required. Data extraction from the SNIIRAM is regulated and needs approval from Institute of Health Data (*Institut des Données de Santé* - IDS) and French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This project is a database analysis using anonymous individual information without any spontaneous reporting. Study outcomes will be reported in aggregate in the final study report, and no individual or expedited reporting is required, according to the EMA Guideline on good pharmacovigilance practices cited above (GVP IV*), as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

* The latest revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) from EMA (coming into effect 16 Sept 2014) specifies: *For Non-interventional post-authorisation studies based on secondary use of data (VI.C.1.2.1.b): "The design of such studies is characterised by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. For these studies, the reporting of suspected adverse reactions in the form of ICSRs is not required. Reports of adverse events/reactions should be summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting*".

12 PLANS FOR DISSEMINATING AND COMMUNATING STUDY RESULTS

This database analysis will be performed by the BPE, INSERM CIC1401, an academic research organization (ARO), for which scientific communication and publication is a major component of its activities. Study methods and results will be submitted to scientific meetings and for publication in international scientific journals.

13 REFERENCES

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14 ANNEXES

Annex 1 – List of antidepressant drugs of interest and their related Anatomical Therapeutic Chemical (ATC) codes

DCI	ATC code
Tricyclic antidepressants	**N06AA**
Amitriptyline	N06AA09
Amoxapine	N06AA17
Clomipramine	N06AA04
Dosulepine	N06AA16
Doxepine	N06AA12
Imipramine	N06AA02
Maprotiline	N06AA21
Trimipramine	N06AA06
Selective serotonin reuptake inhibitors	**N06AB**
Citalopram	N06AB04
Escitalopram	N06AB10
Fluoxetine	N06AB03
Fluvoxamine	N06AB08
Paroxetine	N06AB05
Sertraline	N06AB06
Serotonin-norepinephrine reuptake inhibitors	**N06AX16 + N06AX17 + N06AX21**
Duloxetine	N06AX21
Milnacipran	N06AX17
Venlafaxine	N06AX16
Monoamine oxidase inhibitors	**N06AF05 + N06AG02**
Iproniazide	N06AF05
Moclobemide	N06AG02
Other antidepressants	**N06AX22 + N06AX03 + N06AX11 + N06AX14 + N06AX12**
Agomelatine	N06AX22
Mianserin	N06AX03 except for drug dose equal to 10 mg (CIP7 codes: 3215043, 3342379, 3573601, 3573699, 3573788, 3574291, 3576628, 3583479, 3613281, 3613909, 3614458, 3586673, 3661835, 3674621)
Mirtazapine	N06AX11
Tianeptine	N06AX14
Bupropion	N06AX12

Annex 2 – List of diseases of interest and their related ICD-10 codes

Disease	ICD-10 code	CIP or ATC codes
Psychotic disorders	**F20-F29**	
Schizophrenia	F20	
Schizotypal disorders	F21	
Persistant delusion disorder	F22	
Induced delusion disorder	F24	At least 3 reimbursements within a year of neuroleptic medications (ATC codes starting with N05A). With the exception of lithium (ATC code N05AN01).
Schizoaffective disorder	F25	
Other non-organic psychotic disorders	F28	
Non-organic psychosis	F29	
Parkinson's disease	**G20 + F02.3**	
Parkinson's disease	G20	At least 3 reimbursements within a year of the following medications: Lisuride® or Dopergine® (CIP7 code 3328439), levodopa (ATC code N04BA02), levodopa + entacapone (ATC code N04BA03), bromocriptine at the dose of 5 and 10 mg (ATC code N04BC01), pergolide (ATC code N04BC02), ropinirole (ATC code N04BC04 limited to CIP codes for medication indicated in Parkinson's disease), N04BC07 (except CIP codes for alcohol dependence), selegiline (ATC code N04BD01), rasagiline (ATC code N04BD02), tolcapone (N04BX01), entacapone (ATC code N04BX02). With the exception of apomorphine, anticholinergic, and medications indicated for Restless Legs Syndrome, neuroleptic-induced Parkinson's syndrom and inhibition of physiological lactation (CIP7 codes 30005943, 3644494, 3644502, 3644525, 3644548, 3914841, 3918394, 3918402, 3918425, 3918448, 3927163, 3927217, 3927269, 3927298, 3933442, 3933502, 3933583, 3933637, 3935079, 3935263, 3935346, 3005943 and CIP13 codes 3400933284398 3328439, 3400936444942 3644494, 3400936445024 3644502, 3400936445253 3644525, 3400936445482 3644548, 3400939183947 3918394, 3400939184029 3918402, 3400939184487 3918448, 3400939271637 3927163, 3400939272177 3927217, 3400939272986 3927298, 3400930059432 3005943).
Dementia of Parkinson's disease	F02.3	

Disease	ICD-10 code	CIP or ATC codes
Dementia	**F00-F03 + G30 +F05.1**	
Dementia of Alzheimer's disease	F00	At least 3 reimbursements within a year of medications with the ATC codes starting with N06DA and with the ATC code N06DX01
Vascular dementia	F01	
Other dementia (except by HIV)	F02 (except F02.4)	
Dementia without specification	F03	
Alzheimer's disease	G30	
Dementia with delirium	F05.1	
Depression	**F32+F33**	
Depressive episode	F32	
Recurring depressive disorders	F33	
Chronic alcoholism		
Alcoholic cardiomyopathy	I42.6	At least 3 reimbursements within a year of medications with the ATC codes starting with N07BB
Mental disorders due to alcohol use	F10	
Alcoholic liver disease	K70	
Chronic alcoholic pancreatitis	K85.2	
Alcoholism supervising	Z71.4	
Cushing syndrome due to alcohol use	E24.4	
Alcohol withdrawal	Z50.2	
Alcoholic neuropathy	G31.2	

Annex 3 –. List of drugs other than antidepressants (AD) used to potentiate AD effects in depressive disorders and their related Anatomical Therapeutic Chemical (ATC) codes

DCI	ATC code
Second generation antipsychotic drugs	**N05AH04 + N05AH03 + N05AX12 + N05AX08**
Quetiapine	N05AH04
Olanzapine	N05AH03
Aripiprazole	N05AX12
Risperidone	N05AX08
Cyamémazine (≤ 150 mg/jr)	N05AA06 (Codes CIP: 3296389; 3191992; 3130329)
Amisulpride (≤ 150 mg/jr)	N05AL05 (Codes CIP: 3638105; 3644695; 4935667; 3649994; 3644347; 3864474; 3636129; 3644241; 3672881; 3674242; 3487474; 3528701, 3644229, 3644726)
Lithium	**N05AN01**
Thyroid hormones	**H03AA**
Antiepileptic drugs	**N03AF01 + N03AX09 + N03AF02 + N03AG01**
Carbamazepine	N03AF01
Lamotrigine	N03AX09
Oxcarbazepine	N03AF02
Valproate/Valproic acid	N03AG01