




# Antidepressants and Hepatotoxicity: A Cohort Study among 5 Million Individuals Registered in the French National Health Insurance Database

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## Abstract

**Background** Hepatotoxicity may be a concern when prescribing antidepressants. Nevertheless, this risk remains poorly understood for serotonin and noradrenaline reuptake inhibitors (SNRIs: venlafaxine, milnacipran, duloxetine) and ‘other antidepressants’ (mianserin, mirtazapine, tianeptine and agomelatine), particularly in comparison with selective serotonin reuptake inhibitors (SSRIs: fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram), which are by far the most commonly prescribed antidepressants.

**Objective** We quantified the risk of serious liver injury associated with new use of SNRIs and ‘other antidepressants’ compared with SSRIs in real-life practice.

**Methods** Based on the French national health insurance database, this cohort study included 4,966,825 individuals aged 25 years and older with a first reimbursement of SSRIs, SNRIs or ‘other antidepressants’ between January 2010 and June 2015. We compared the risk of serious liver injury within the 6 months following antidepressant initiation according to antidepressant class, with SSRIs as the reference, using an inverse probability-of-treatment-weighted Cox proportional hazard model adjusted for demographic characteristics and risk factors of liver injury.

**Results** We identified 382 serious liver injuries overall (none for milnacipran initiators). Age and gender standardized incidence rates per 100,000 person-years were 19.2 for SSRIs, 22.2 for venlafaxine, 12.6 for duloxetine, 21.5 for mianserin, 32.8 for mirtazapine, 31.6 for tianeptine and 24.6 for agomelatine initiators. Initiation of antidepressants of interest versus SSRIs was not associated with an increased risk of serious liver injury [adjusted hazard ratios (95% confidence interval): venlafaxine 1.17 (0.83–1.64), duloxetine 0.54 (0.28–1.02), mianserin 0.90 (0.58–1.41), mirtazapine 1.17 (0.67–2.02), tianeptine 1.35 (0.82–2.23) and agomelatine 1.07 (0.51–2.23)]. This finding was confirmed by the results of an additional study using a case-time-control design.

**Conclusion** These results do not provide evidence of an increased risk of serious liver injury following initiation of SNRIs or ‘other antidepressants’ compared with SSRIs in real-life practice. This could reflect an inherent lack of difference in risk between the drug classes, or the fact that individuals with higher susceptibility to drug-induced liver injury are not prescribed drugs considered to be more hepatotoxic.

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## Key Points

This cohort study, which included 4,966,825 antidepressant initiators identified in the French national health insurance database, did not identify any significant increased risk of serious liver injury associated with serotonin and noradrenaline reuptake inhibitors and ‘other antidepressants’ compared with selective serotonin reuptake inhibitors.

In real-life practice, the risk of serious liver injury does not seem to differ markedly across antidepressants proposed as first line. This could reflect an inherent lack of difference in risk between the drug classes, or the fact that individuals with higher susceptibility to drug-induced liver injury are not prescribed drugs considered to be more hepatotoxic.

## 1 Background

Drug-induced liver injuries (DILIs) are a leading cause of acute liver failure [1], post-marketing warnings and withdrawal of drugs from the market [2]. DILIs have a reported incidence between 1 and 19 per 100,000 patient years, which is likely to be underestimated [3, 4], the risk emerging only once a drug is widely prescribed [2].

Almost all antidepressants may induce hepatotoxicity, even at therapeutic dose [5]. Injuries can be hepatocellular, cholestatic or mixed [5]. They are usually idiosyncratic, unpredictable, with an apparent lack of relationship to dose and generally appear between several days and 6 months after drug initiation [5]. Among antidepressants initially proposed as first-line therapy for major depressive disorders, the highest risk has been suggested for agomelatine (a recent and novel molecule acting as a melatonin-receptor agonist and a selective serotonin receptor antagonist), duloxetine [a serotonin and noradrenalin reuptake inhibitor (SNRI)] and tianeptine (chemically affiliated to the tricyclic antidepressants, with distinct pharmacological properties) [5]. Selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed antidepressants, might globally have a better safety profile regarding hepatotoxicity [5, 6].

Risk management plans have been developed for agomelatine and duloxetine since their release owing to the possibility of rare and severe liver injuries raised by pre-marketing clinical trials [7, 8]. Notably, these molecules are contraindicated in patients with pre-existing liver disease resulting in hepatic impairment and, to date, agomelatine is the only antidepressant requiring liver monitoring during treatment. Information about antidepressant

hepatotoxicity mainly ensues from clinical trials and pharmacovigilance case reports [5]. Observational studies, tailored to evaluate such a risk in real-life conditions, are scarce, have limited sample sizes and mainly focused on duloxetine [9, 10].

The objective of the present study was to quantify the risk of serious liver injury associated with initiation of SNRIs (venlafaxine, milnacipran and duloxetine) and ‘other antidepressants’ (mianserin, mirtazapine, tianeptine and agomelatine) compared with initiation of SSRIs in real-life practice. Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) were outside the scope of the study because of their particular safety profile, justifying their second-line use for the treatment of major depressive disorders.

## 2 Methods

### 2.1 Data Sources

A cohort study was conducted using the French national health insurance database [Système National d’Information Inter-Régimes de l’Assurance Maladie (SNIIRAM)]. Individuals were enrolled from January 1, 2010 to June 30, 2015. This health insurance database covers almost the entire French population (65.3 million inhabitants) with different affiliation schemes based on types of employment. For the present study, the data relating to beneficiaries of the main scheme (the general scheme covering approximately 77% of the French population) were used. The SNIIRAM comprehensively records the following with corresponding dates: outpatient drugs [Anatomical Therapeutic Classification (ATC) codes] and medical devices prescribed, reimbursed services and procedures, as well as demographic data such as age, sex, area of residence (postcode), complementary universal health insurance (free access to healthcare for people with an annual income < 50% of the poverty threshold) and date of death. The database does not stipulate the medical indication for each reimbursement. However, it includes information on severe and costly long-term disease (LTD) for which health expenses are fully reimbursed; these are coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) and the date of LTD diagnosis is recorded. An anonymous unique identifier for each patient links SNIIRAM information to the national hospital discharge database [Programme de Médicalisation des Systèmes d’Information (PMSI)], which covers all hospitals and provides reasons for admission (in the format of the ICD-10) and surgical procedures. Previous observational studies using the SNIIRAM and the PMSI have been published elsewhere [11–17].

## 2.2 Inclusion and Exclusion Criteria

Individuals aged 25 years and older, affiliated to the general insurance scheme without changes in health plan during the previous 12 months and with a first reimbursement (i.e., no antidepressant reimbursed in the previous 6 months) of antidepressant (except tricyclic or MAOIs) between January 1, 2010 and June 30, 2015 were included in the study. Inclusion date corresponded to the first date meeting those conditions. In order to minimize the collection of non-drug-induced liver injury, individuals with a history of acute or chronic liver disease, pancreatitis, cancer, human immunodeficiency virus infection (HIV), alcohol use disorders identified based upon LTD or hospitalization diagnoses or reimbursements of specific drugs [Appendix Table 1, see electronic supplementary material (ESM)] were excluded due to pre-existing or possible liver conditions. Individuals with reimbursements for antidepressants of several groups (see exposure definition) within 15 days of inclusion were also excluded.

## 2.3 Exposure Definition

Eight groups of antidepressant initiators were identified depending on the molecule used at inclusion among those marketed in France during the study period: (1) SSRIs (ATC code, fluoxetine: N06AB03, citalopram: N06AB04, paroxetine: N06AB05, sertraline: N06AB06, fluvoxamine: N06AB08 or escitalopram: N06AB10), (2) venlafaxine (N06AX16), (3) milnacipran (N06AX17), (4) duloxetine (N06AX21), (5) mianserin (N06AX03), (6) mirtazapine (N06AX11), (7) tianeptine (N06AX14) and (8) agomelatine (N06AX22).

## 2.4 Outcome Definition

The outcome was defined as the occurrence of a serious liver injury possibly related to antidepressant exposure (i.e., acute form of serious liver injuries), resulting in hospitalization within the 6 months following antidepressant initiation. The outcome was identified by using the main or related diagnoses of incident hospital stays registered in the PMSI (ICD-10 codes: K71.0, K71.1, K71.2, K71.6, K71.8, K71.9, K72.0, K75.2, K75.9, K76.2, K76.7, Z94.4, Appendix Table 2, see ESM). A literature search was undertaken to identify ICD-10 codes having a priori the best positive predictive value [18–21]. These codes were then validated by a senior pharmacologist (BB).

## 2.5 Follow-Up

Individuals were followed up for 6 months after antidepressant initiation or up to the first of the following events: serious liver injury, antidepressant discontinuation (follow-up

pursued 3 months after discontinuation), switch to another antidepressant, cancer, HIV infection, viral hepatitis, change in health plan or death.

## 2.6 Covariates

The following covariates were identified at inclusion date: age categories, sex, quintiles of deprivation index of participant's area of residence (reflecting a major part of spatial socioeconomic heterogeneity) [22], complementary universal health insurance, prime-prescriber specialty (general practitioner, private practice psychiatrist or hospital practitioner) and inclusion year. Reimbursements for drugs potentially associated with hepatotoxicity (at least one reimbursement, Appendix Table 3, see ESM) [23, 24], and immunosuppressant drugs (at least two reimbursements, ATC code L04A) were considered respectively in the 6 and 12 months preceding inclusion (including the date of antidepressant initiation).

The following comorbidities were considered on the basis of relevant reimbursed medicines (at least two reimbursements, ATC codes), hospital discharge or LTD reports (ICD-10 diagnosis codes): psychiatric history (based upon psychotropic drug reimbursement or psychiatric disease diagnosis), diabetes mellitus (based upon antidiabetic drug reimbursement or diagnosis related to diabetes and its complications), cardiac failure (based upon related diagnosis), chronic renal failure (based upon related diagnosis), measurable morbid obesity (based upon related diagnosis) in the 12 months preceding inclusion (including the date of antidepressant initiation), measurable history of substance abuse (based upon opiate substitution reimbursement or diagnosis related to substance abuse) and smoking habits (based upon nicotine replacement therapy reimbursement or diagnosis related to tobacco use) in the 36 months preceding inclusion (including the date of antidepressant initiation). Detailed ATC and ICD-10 codes used to identify comorbidities are provided in Appendix Table 4 (see ESM).

Individuals with reimbursement for aminotransferase testing in the month preceding or following inclusion were identified as well as those with initiation of drugs potentially associated with hepatotoxicity, additional antidepressants or aminotransferase testing during the follow-up.

## 2.7 Statistical Analysis

Antidepressant initiators were described according to the distribution of covariates previously mentioned. Sex- and age-standardized incidences of serious liver injury were computed for each group of antidepressant initiators based upon sex and age distribution of SSRI initiators. A univariate Cox proportional hazard model with initiation of antidepressant as the main explanatory variable was first

used to compare the risk of serious liver injury according to initiation of venlafaxine, milnacipran, duloxetine, mianserin, mirtazapine, tianeptine and agomelatine versus SSRIs. To control for confounding, an inverse probability-of-treatment-weighted Cox proportional hazard model for incident liver injuries was then used. Weights were derived from the reciprocal of the propensity scores containing the following characteristics assessed at inclusion: age categories, sex, year of inclusion, deprivation quintiles, complementary universal health insurance, diabetes, heart failure, chronic renal failure, reimbursement for drugs potentially associated with hepatotoxicity, reimbursement for immunosuppressant drugs, measurable history of substance abuse or smoking habits, morbid obesity and aminotransferase testing. To reduce instability induced by large weights, the stabilized weights were computed and then were truncated at the first and 99th percentiles [25]. The standardized differences method for assessing balance in observed baseline covariates between the SSRIs and each antidepressant of interest was applied to compare prevalence of covariates in the stabilized weighted sample. Imbalances below 10% were considered as negligible [26]. An additional adjustment was made on variables strongly linked with exposure (i.e., psychiatric history, prime-prescriber specialty) [27], time-varying covariates (i.e., initiation of drugs potentially associated with hepatotoxicity or other antidepressants, aminotransferase testing during follow-up), and age categories.

## 2.8 Sensitivity Analysis

In a first sensitivity analysis, the code K72.9 ‘hepatic failure unspecified’ was added to the definition of events. Although poorly specific, this code was considered to be compatible with a potential DILI. In a second sensitivity analysis, the follow-up duration was extended to 12 months after antidepressant initiation. In a third sensitivity analysis, the sample was stratified according to the presence or not of aminotransferase testing at inclusion to assess the influence of possible bias ensuing from differential care related to the forthcoming outcome. Finally, a stratification on the number of prescriptions of antidepressant reimbursed during the follow-up (one versus more than one, one reimbursement corresponding to a maximum 30-day supply) was undertaken to control for the bias possibly caused by individuals with a single reimbursement, since they were likely to be non-compliant and therefore not exposed.

## 2.9 Secondary Approach: Study Using a Case-Time-Control Design

A study using a case-time-control design was undertaken as a secondary approach to challenge the conclusions of the main cohort approach and to better control for residual

unmeasured confounding; that is, related to variables not directly recorded in automated databases and considered as unchanged over the study period (e.g., disorders related to alcohol abuse, smoking, morbid obesity etc.). One analysis was performed for each antidepressant of interest compared with SSRIs.

In each analysis, incident cases of serious liver injury occurring between September 1, 2011 and June 30, 2015 were identified using the same criteria as for the main cohort approach. Exposure to antidepressants of interest and SSRIs was measured both during a ‘risk’ and a ‘reference’ period corresponding respectively to the 6 months preceding the liver-related event date and to the period from the 9th to the 15th month before this date, a 3-month wash-out period separating these two time windows.

A conditional logistic regression was used to evaluate whether, comparatively to SSRIs, exposure to the antidepressant of interest was more prevalent during the ‘risk’ period compared with the ‘reference’ period. Antidepressant users considered for analyses were individuals with reimbursements for both (1) SSRIs in the absence of antidepressant of interest during one of the two periods and (2) antidepressant of interest in the absence of SSRIs during the other period (Fig. 1). Odds ratios (ORs), crude and adjusted on covariates prone to vary across the periods (i.e., other antidepressants and drugs potentially associated with hepatotoxicity), were computed.

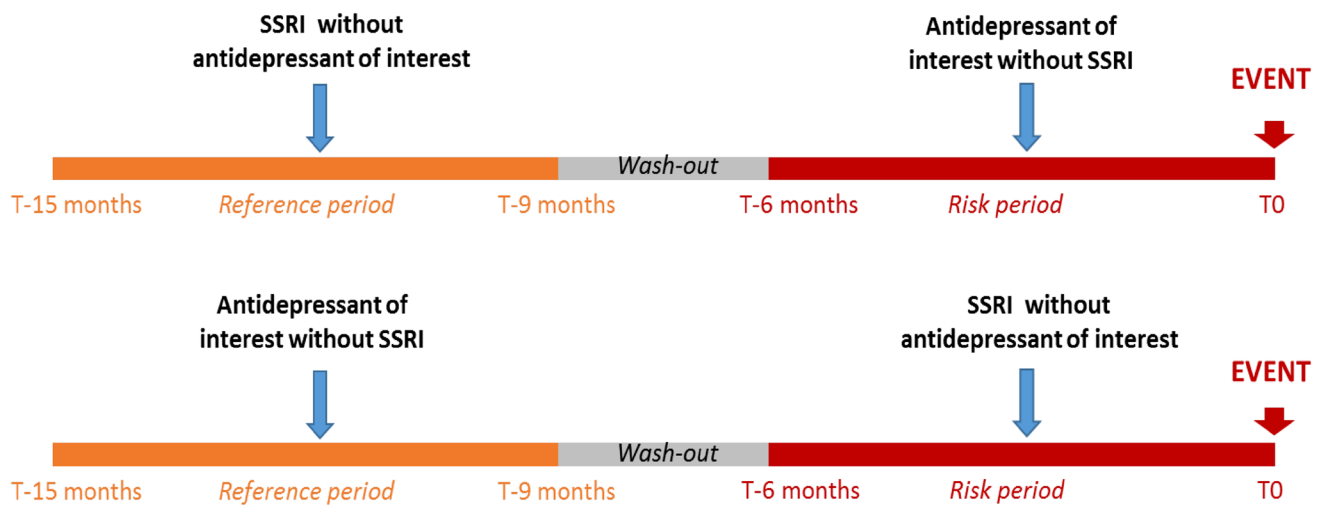
The particularity of the case-time-control design lies in introducing a specific control group to control for temporal biases; that is, when the probability of exposure could be affected by temporal trends independent of the event of interest (e.g., launch of a new drug, introduction of safety warnings, seasonality, etc.). Therefore, for each case, 20 controls of the same sex and age ( $\pm 1$  year) were randomly sampled from the ‘non-case’ population. Exposure was measured as for the matched case, and, taking into account exposure temporal trends, ORs were derived from the coefficient of the interaction between exposure and case or control status introduced in the conditional logistic regressions models [28].

All statistical tests were two-tailed with an  $\alpha$ -risk of 5%. Statistical analyses were performed using SAS Enterprise Guide software, version 7.1 (SAS Institute Inc.).

## 3 Results

### 3.1 Inclusion and Follow-Up Characteristics of Antidepressant Initiators

The study included 4,966,825 antidepressant initiators (Fig. 2). Their characteristics at inclusion are described in Table 1. Women accounted for 68% of the sample. Mean age was



**Fig. 1** Exposure to antidepressants of interest and selective serotonin reuptake inhibitors (SSRIs) for cases and controls included in the case-control design according to study period

52 years, agomelatine initiators were younger and mianserin, mirtazapine and tianeptine initiators were older. Around 8% had complementary universal health insurance. Most of the time the prime prescriber was a general practitioner. For milnacipran, mirtazapine and agomelatine initiators, the proportion of prescriptions initiated by a private practice psychiatrist ranged from 8 to 15% versus <7% for other groups. Aminotransferase testing at inclusion was in place for 35% of agomelatine initiators versus around 20% in the other groups. A history of psychiatric disorders was more frequently found in all groups than among SSRI initiators and was more prevalent in the milnacipran, mianserin, mirtazapine and agomelatine groups. Diabetes was more frequent in duloxetine, mianserin, mirtazapine and tianeptine initiators. Heart failure and chronic renal failure were more often found in mianserin, mirtazapine and tianeptine initiators. Mean follow-up was around 4 months. For 40–50% of initiators, only one reimbursement of antidepressant was retrieved during the follow-up (Appendix Table 5, see ESM).

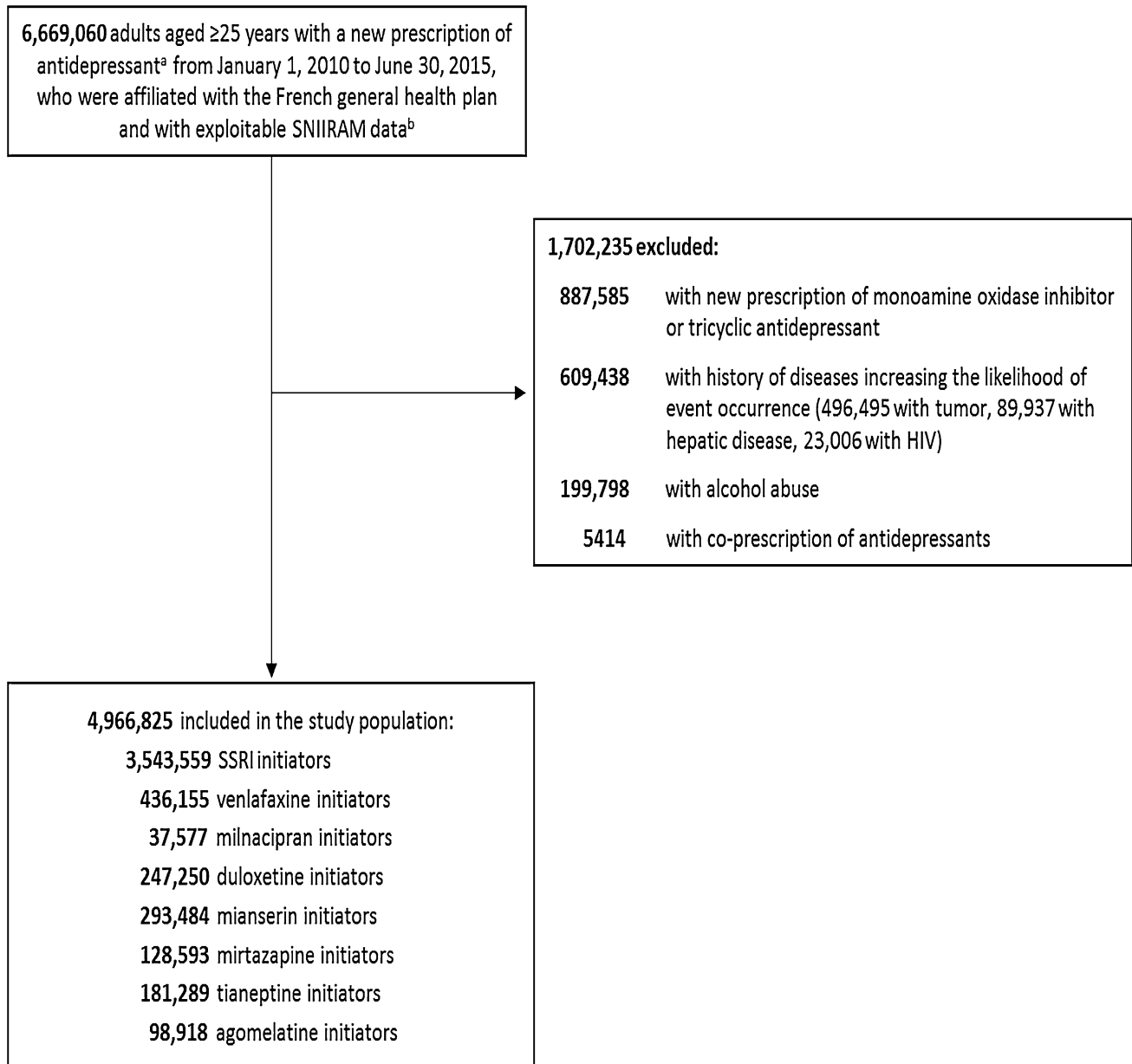
The mean (SD) estimated stabilized weight was 1.00 (0.31), ranging from 0.35 to 2.18. The standard difference in the unweighted model exceeded 10% for 24.9% of the sample. After weighting by the inverse probability of treatment (and stabilization and truncation of the weights), prevalence of qualitative categorical variables was similar between each antidepressant of interest and SSRIs (Appendix Table 6, see ESM).

### 3.2 Main Approach: Association Between Antidepressant of Interest and Serious Liver Injury

A total of 382 serious liver injuries were identified (258 for SSRIs, 36 for venlafaxine, 12 for duloxetine, 29 for mianserin, 15 for mirtazapine, 24 for tianeptine, 8 for agomelatine, see description in Appendix Table 2, ESM) and occurred with a mean delay of 2 months after treatment initiation. No event was identified for milnacipran. Sex- and age-standardized incidence rates per 100,000 person-years were 19.2 for SSRIs, 22.2 for venlafaxine, 12.6 for duloxetine, 21.5 for mianserin, 32.8 for mirtazapine, 31.6 for tianeptine and 24.6 for agomelatine. Initiation of antidepressants of interest was not associated with a significant increased risk of serious liver injury when compared with SSRIs; adjusted hazard ratios (95% CI) 1.17 (0.83–1.64),  $p=0.36$  for venlafaxine; 0.54 (0.28–1.02),  $p=0.06$  for duloxetine; 0.90 (0.58–1.41),  $p=0.64$  for mianserin; 1.17 (0.67–2.02),  $p=0.56$  for mirtazapine; 1.35 (0.82–2.23),  $p=0.24$  for tianeptine and 1.07 (0.51–2.23),  $p=0.86$  for agomelatine. Results are summarized in Table 2.

### 3.3 Sensitivity Analysis

Adding the code K72.9 ‘hepatic failure unspecified’ to the main definition of the outcome (37 incident events added) or



<sup>a</sup> No prescription of antidepressant in the previous 6 months.

<sup>b</sup> 1,072,879 individuals with change in health plan, 351,139 twins and 440 individuals with cancelled antidepressant prescription were not included in the study population.

**Fig. 2** Diagram of inclusion. *HIV* human immunodeficiency virus, *SNIIRAM* Système National d'Information Inter-Régimes de l'Assurance Maladie, *SSRIs* selective serotonin reuptake inhibitors

extending follow-up from 6 to 12 months (116 events added) did not significantly alter the results (Appendix Tables 7 and 8, see ESM). Conclusions remained unchanged in analyses stratified on aminotransferase testing at inclusion and on the number of antidepressant prescriptions during the follow-up (Appendix Tables 9 and 10, see ESM).

### 3.4 Secondary Approach: Study Using a Case-Time-Control Design

In this approach, when comparing exposure during 'risk' and 'reference' periods and using SSRIs as controls, the adjusted ORs (95% CI) for antidepressants of interest were 0.94 (0.51–1.72),  $p = 0.84$  for venlafaxine; 0.86



**Table 1** Characteristics of antidepressant initiators at inclusion

Characteristics	SSRIs (n = 3,543,559)	Venlafaxine (n = 436,155)	Milnacipran (n = 37,577)	Duloxetine (n = 247,250)	Mianserin (n = 293,484)	Mirtazapine (n = 128,593)	Tianeptine (n = 181,289)	Agomelatine (n = 98,918)
Mean age (SD), years	51.1 (17.3)	50.2 (16.1)	50.9 (15.6)	53.1 (16.0)	62.3 (19.5)	58.6 (20.3)	59.3 (19.4)	48.6 (14.6)
Age, years, n (%)								
25–39	1,038,141 (29.3)	124,853 (28.6)	9530 (25.4)	53,421 (21.6)	45,123 (15.4)	27,549 (21.4)	34,301 (18.9)	29,520 (29.8)
40–49	821,693 (23.2)	106,622 (24.4)	9497 (25.3)	56,763 (23.0)	43,238 (14.7)	22,260 (17.3)	31,371 (17.3)	26,545 (26.8)
50–69	1,083,610 (30.6)	145,214 (33.3)	13,562 (36.1)	93,538 (37.8)	85,177 (29.0)	35,029 (27.2)	51,850 (28.6)	33,528 (33.9)
≥ 70	600,115 (16.9)	59,466 (13.6)	4988 (13.3)	43,528 (17.6)	119,946 (40.9)	43,755 (34.0)	63,767 (35.2)	9325 (9.4)
Women, n (%)	2,433,101 (68.7)	294,671 (67.6)	27,306 (72.7)	167,668 (67.8)	197,485 (67.3)	80,810 (62.8)	128,499 (70.9)	66,761 (67.5)
Deprivation index (fifths), n (%)								
First fifth (least deprived)	682,496 (19.3)	87,530 (20.1)	5406 (14.4)	37,485 (15.2)	57,341 (19.5)	15,837 (12.3)	28,538 (15.7)	15,533 (15.7)
Second fifth	712,878 (20.1)	85,668 (19.6)	7198 (19.2)	45,674 (18.5)	54,553 (18.6)	25,009 (19.4)	32,765 (18.1)	17,699 (17.9)
Third fifth	694,538 (19.6)	83,135 (19.1)	7544 (20.1)	48,931 (19.8)	55,513 (18.9)	28,409 (22.1)	35,584 (19.6)	20,080 (20.3)
Fourth fifth	694,946 (19.6)	85,594 (19.6)	7808 (20.8)	51,758 (20.9)	57,877 (19.7)	29,041 (22.6)	37,579 (20.7)	19,569 (19.8)
Fifth fifth (most deprived)	705,691 (19.9)	88,370 (20.3)	9156 (24.4)	57,292 (23.2)	64,837 (22.1)	28,498 (22.2)	40,736 (22.5)	21,273 (21.5)
Missing data	53,010 (1.5)	5858 (1.3)	465 (1.3)	6110 (2.5)	3363 (1.2)	1799 (1.4)	6087 (3.4)	4764 (4.8)
Complementary universal health insurance, n (%)	283,099 (8.0)	35,111 (8.1)	3511 (9.3)	23,390 (9.5)	21,818 (7.4)	13,920 (10.8)	13,163 (7.3)	10,828 (10.9)
Prescriber, n (%)								
General practitioner	2,929,581 (82.7)	350,920 (80.5)	25,003 (66.5)	176,656 (71.4)	225,490 (76.8)	81,761 (63.6)	154,469 (85.2)	67,894 (68.6)
Hospital practitioner	293,607 (8.3)	42,361 (9.7)	5,469 (14.6)	37,733 (15.3)	45,371 (15.5)	32,590 (25.3)	12,938 (7.1)	13,814 (14.0)
Private practice psychiatrist	219,627 (6.2)	30,058 (6.9)	3765 (10.0)	13,659 (5.5)	12,236 (4.2)	10,810 (8.4)	8249 (4.6)	14,988 (15.2)
Other or missing data	100,744 (2.8)	12,816 (3.0)	3340 (8.8)	19,202 (7.8)	10,387 (3.6)	3432 (2.7)	5633 (3.1)	2222 (2.3)
Clinical characteristics, n (%)								
Psychiatric history <sup>a</sup>	1,490,307 (42.1)	200,642 (46.0)	19,170 (51.0)	111,575 (45.1)	156,919 (53.5)	73,257 (57.0)	86,237 (47.6)	52,186 (52.8)
Diabetes <sup>a</sup>	232,970 (6.6)	26,231 (6.0)	2540 (6.8)	33,808 (13.7)	32,364 (11.0)	12,712 (9.9)	18,112 (10.0)	5741 (5.8)
Heart failure <sup>a</sup>	48,122 (1.4)	4705 (1.1)	394 (1.0)	3299 (1.3)	12,070 (4.1)	4924 (3.8)	5570 (3.1)	675 (0.7)
Chronic renal failure <sup>a</sup>	26,204 (0.7)	2588 (0.6)	209 (0.6)	2102 (0.9)	6786 (2.3)	2934 (2.3)	2522 (1.4)	432 (0.4)
Measurable history of smoking <sup>b</sup>	285,243 (8.0)	35,522 (8.1)	3279 (8.7)	23,259 (9.4)	24,838 (8.5)	12,048 (9.4)	15,148 (8.4)	8597 (8.7)
Morbid obesity <sup>a</sup>	49,472 (1.4)	5898 (1.4)	648 (1.7)	6950 (2.8)	5398 (1.8)	2331 (1.8)	2944 (1.6)	1471 (1.5)
Measurable history of substance abuse <sup>b</sup>	23,554 (0.7)	3613 (0.8)	303 (0.8)	1527 (0.6)	3461 (1.2)	2736 (2.1)	912 (0.5)	1080 (1.1)
Use of drugs potentially associated with hepatotoxicity <sup>c</sup>	1,454,984 (41.1)	172,691 (39.6)	17,281 (46.0)	129,046 (52.2)	141,553 (48.2)	57,982 (45.1)	86,439 (47.7)	41,382 (41.8)

Table 1 (continued)

Characteristics	SSRIs (n = 3,543,559)	Venlafaxine (n = 436,155)	Milnacipran (n = 37,577)	Duloxetine (n = 247,250)	Mianserin (n = 293,484)	Mirtazapine (n = 128,593)	Tianeptine (n = 181,289)	Agomelatine (n = 98,918)
Immunosuppressant drug use <sup>e</sup>	16,776 (0.5)	2112 (0.5)	379 (1.0)	2304 (0.9)	1326 (0.5)	616 (0.5)	747 (0.4)	488 (0.5)
Aminotransferase testing, n (%) <sup>d</sup>	663,476 (18.7)	77,877 (17.9)	7169 (19.1)	50,090 (20.3)	57,240 (19.5)	24,867 (19.3)	37,632 (20.8)	34,669 (35.0)
Inclusion year, n (%)								
2010–2011	1,601,684 (45.2)	198,444 (45.5)	23,216 (61.8)	117,552 (47.6)	124,297 (42.4)	51,767 (40.2)	141,315 (77.9)	22,965 (22.4)
2012–2013	1,186,834 (33.4)	143,281 (32.9)	9823 (26.1)	77,866 (31.5)	98,049 (33.4)	43,863 (34.1)	34,103 (18.8)	45,969 (46.5)
2014 to June 2015	755,041 (21.3)	94,430 (21.6)	4538 (12.1)	51,832 (20.9)	71,138 (24.3)	32,963 (25.7)	5871 (3.3)	29,984 (30.3)

SD standard deviation, SSRIs selective serotonin reuptake inhibitors

<sup>a</sup>Measured up to 1 year before inclusion

<sup>b</sup>Measured up to 36 months before inclusion

<sup>c</sup>Measured up to 6 months before inclusion

<sup>d</sup>Measured at inclusion ± 1 month

(0.12–5.98),  $p = 0.88$  for milnacipran; 1.15 (0.53–2.53),  $p = 0.72$  for duloxetine; 0.91 (0.42–1.97),  $p = 0.82$  for mianserin; 1.13 (0.43–3.00),  $p = 0.80$  for mirtazapine; 1.06 (0.40–2.82),  $p = 0.91$  for tianeptine and 0.87 (0.12–6.34),  $p = 0.89$  for agomelatine (Table 3).

## 4 Discussion

This large prospective observational study conducted in an extensive and representative sample of the French population did not identify any increased risk of serious liver injury associated with the use of SNRIs (venlafaxine, milnacipran and duloxetine) or ‘other antidepressants’ (mianserin, mirtazapine, tianeptine and agomelatine) when compared with SSRIs in real-life practice. This conclusion was supported by the results of a case-time-control analysis conducted as a secondary approach.

Most of the data concerning antidepressant hepatotoxicity ensue from pharmacovigilance and published case reports. Some observational studies of limited sample size have provided information about the hepatotoxicity of duloxetine and agomelatine as they were subjected to risk management plans. Two observational studies specifically designed to evaluate duloxetine hepatotoxicity suggested a higher incidence of liver injuries other than hepatic-related death or liver failure with this molecule compared with several other antidepressants, but the conclusions were hampered by insufficient statistical power [9, 10]. Interestingly, our main analysis suggests a trend toward a lower hepatotoxicity of duloxetine when compared with SSRIs but this result was both non-significant and not confirmed by the secondary case-time-control approach. Two observational studies conducted to assess agomelatine safety did not highlight any serious case of hepatotoxicity [29, 30], even though they did not specifically focus on hepatotoxicity and were not comparative. Similarly, our study does not support the existence of a higher risk of serious hepatotoxicity for agomelatine initiators when compared with SSRIs in real conditions of use.

There is clearly a lack of observational studies concerning the potential hepatotoxicity of non-SSRI antidepressants. Possible hepatotoxicity of non-SSRI antidepressants was deduced from a rise in aminotransferase over the normal threshold or rarely by the occurrence of a clinical liver injury during pre-marketing clinical trials or post-approval studies [6, 31, 32] or in published case reports [33–39].

Several interpretations can be put forward to explain the absence of a significant difference in the risk of serious hepatotoxicity between the antidepressants of interest and SSRIs in real-life settings. The first and most obvious is that the antidepressants suspected of conveying the highest risks of hepatotoxicity are not prescribed to individuals believed to present higher susceptibility to DILI (e.g.,



**Table 2** Association between initiation of antidepressants of interest versus selective serotonin reuptake inhibitors (SSRIs) and hospitalization due to serious liver injury (main definition of event, follow-up 6 months)

Antidepressant	Initiators ( <i>n</i> = 4,966,825)	Events ( <i>n</i> = 382)	Event incidence (per 100,000 person-years) <sup>a</sup>	Hazard ratio (95% CI)	
				Crude	Adjusted <sup>b,c</sup>
SSRIs	3,543,559	258	19.2	1.00 [Reference]	1.00 [Reference]
Venlafaxine	436,155	36	22.2	1.15 (0.81–1.63)	1.17 (0.83–1.64)
Milnacipran	37,577	0	0.0		
Duloxetine	247,250	12	12.6	0.70 (0.39–1.24)	0.54 (0.28–1.02)
Mianserin	293,484	29	21.5	1.43 (0.97–2.10)	0.90 (0.58–1.41)
Mirtazapine	128,593	15	32.8	1.65 (0.98–2.77)	1.17 (0.67–2.02)
Tianeptine	181,289	24	31.6	1.93 (1.27–2.94)	1.35 (0.82–2.23)
Agomelatine	98,918	8	24.6	1.18 (0.58–2.38)	1.07 (0.51–2.23)

CI confidence interval, SSRIs selective serotonin reuptake inhibitors

<sup>a</sup>Standardized on sex and age categories (< 50 or ≥ 50 years), SSRI initiators served as the reference group

<sup>b</sup>Inverse probability of treatment weighting considering the following covariates: inclusion year, sex, age, deprivation index and complementary universal health insurance at inclusion; diabetes, heart failure, chronic renal failure, measurable history of smoking, morbid obesity and measurable history of substance abuse up to 12–36 months before inclusion; reimbursements for drugs potentially associated with hepatotoxicity and immunosuppressant drugs up to 6–12 months before inclusion; aminotransferase testing at inclusion ± 1 month

<sup>c</sup>Additional adjustment on age categories, prescriber specialty at inclusion; psychiatric history in 12 months before inclusion; drugs potentially associated with hepatotoxicity, other antidepressants and aminotransferase testing reimbursed during follow-up

**Table 3** Odds ratios for hospitalization due to serious liver injury associated with antidepressant of interest versus selective serotonin reuptake inhibitors (SSRIs) in each case-time-control study performed by antidepressant of interest

Antidepressant of interest in each case-time-control study <sup>a</sup>	Cases		Odds ratio (95% CI)	
	Reference period ( <i>n</i> ) <sup>b</sup>	Risk period ( <i>n</i> ) <sup>c</sup>	Crude	Adjusted <sup>d</sup>
Venlafaxine	21	28	1.00 (0.56–1.81)	0.94 (0.51–1.72)
Milnacipran	5	2	0.43 (0.08–2.36)	0.86 (0.12–5.98)
Duloxetine	13	18	1.09 (0.52–2.30)	1.15 (0.53–2.53)
Mianserin	16	21	1.07 (0.54–2.11)	0.91 (0.42–1.97)
Mirtazapine	11	13	0.93 (0.40–2.18)	1.13 (0.43–3.00)
Tianeptine	17	7	0.94 (0.37–2.36)	1.06 (0.40–2.82)
Agomelatine	5	4	0.69 (0.18–2.69)	0.87 (0.12–6.34)

CI confidence interval, SSRIs selective serotonin reuptake inhibitors

<sup>a</sup>Eligible profiles in each case-time-control study performed by antidepressant of interest: individuals with reimbursements for both (1) antidepressant of interest in the absence of SSRIs during one of the two periods (i.e., risk or reference) and (2) SSRIs in the absence of antidepressant of interest during the other period

<sup>b</sup>Number of cases with reimbursements for both (1) antidepressant of interest in the absence of SSRIs during the reference period and (2) SSRIs in the absence of antidepressant of interest during the risk period

<sup>c</sup>Number of cases with reimbursements for both (1) antidepressant of interest in the absence of SSRIs during the risk period and (2) SSRIs in the absence of antidepressant of interest during the reference period

<sup>d</sup>Adjusted for variations in drugs potentially associated with hepatotoxicity and other antidepressant reimbursement between reference and risk periods

elderly, individuals with diabetes, heart failure, chronic renal failure etc.). This is particularly the case for products involved in risk management plans such as agomelatine and duloxetine, thanks to the information about their hepatotoxicity provided to prescribers. Second, for particular risk situations or if evocative symptoms are identified, it is likely that aminotransferases would be monitored and the treatment

stopped before the occurrence of a serious outcome. However, this hypothesis is not supported by the fact that stratifying on liver monitoring at inclusion did not significantly alter the results. Finally, it is worth recalling that this study was designed to assess the risk of serious hepatotoxicity, so it did not consider infra-clinical or non-serious events, as

was the case for previous observational studies conducted for duloxetine [9, 10].

To our knowledge, the present study is the first to compare the risk of the hepatotoxicity of antidepressants both in real life and on the basis of such a large (5 million treatment initiators) representative nationwide sample. Its sample size warranted identifying rare outcomes such as serious, including fatal, DILIs. The study also utilized the large amount of information provided by the SNIIRAM database to control for the main potential confounders by means of propensity scores, thereby providing more reliable estimates compared with classic multivariate models in the event of rare outcomes [40]. It is also likely that using an active comparator minimized the influence of measured and unmeasured differences in patient characteristics linked with both antidepressant use and the risk of hepatotoxicity [41]. Moreover, the conclusions remained unchanged in several sensitivity analyses testing the effect of a broader event definition, longer follow-up (i.e., 12 months, even if liver-related events generally appear in the 6 months after drug initiation), liver monitoring or excluding patients with a single reimbursement of antidepressant. Finally, the case-time-control design used as a secondary approach to better control for potential unmeasured invariant confounders confirmed the conclusions.

This study also has several limitations. The data were fully anonymized so accessing the original medical files to complement and ascertain clinical information on cases of liver injury was not possible. Therefore, the predictive positive value of the ICD-10 codes used to identify these cases without clinical validation could be debated [19] and the incidence rates obtained may not reflect true incidence rates of DILI. However, given the type of hepatotoxicity considered—serious cases leading to hospitalization or death—and the fact that making the definition broader did not alter the results, it is likely that this bias, if any, did not have a marked influence on the results. Moreover, it would apply the same way in each comparison group and would not have masked a significant excess risk of hepatotoxicity in users of the antidepressants of interest compared with SSRIs.

## 5 Conclusion

This study conducted on almost 5 million antidepressant initiators did not provide any evidence of an increased risk of serious liver injury associated with SNRIs (venlafaxine, milnacipran and duloxetine) or ‘other antidepressants’ (mianserin, mirtazapine, tianeptine and agomelatine) when compared with SSRIs in real-life settings. These findings could reflect an inherent lack of difference in risk between the drug classes, or the fact that individuals with higher susceptibility to drug-induced liver injury are not prescribed drugs considered to be more hepatotoxic.

**Author Contributions** CC, SB, RD and MZ contributed to the conception and design of the study. CC, SB and TL did the statistical analyses. All authors contributed to interpretation of the results. SB drafted the manuscript. All authors critically revised the manuscript for important intellectual content. SB and CC have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RD and MZ supervised the study. All the authors made a significant contribution to the research and the development of the manuscript and approved the final version for publication. SB and CC are guarantors.

## Compliance with Ethical Standards

**Conflict of interest** S Billioti de Gage, C. Collin, T. Le-Tri, A. Pariente, B. Bégaud, H. Verdoux, R. Dray-Spira and M. Zureik have no conflicts of interest to disclose.

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