

## Abstract

**Background:** Acute liver injury (ALI) is a major drug safety issue. Several antidepressant (AD) and anxiolytic-hypnotic (BZ) drugs have been associated with ALI. **Objectives:** To quantify exposure to AD/BZ prior to hospital admission for acute liver injury (ALI) in the French National healthcare systems database SNDS (66 million persons). **Methods:** All hospital admissions for ALI (K71.1, 2, 6, 9, K72.0) over 2010-2014 were identified in SNDS. Cases with specific diagnoses of liver disease/injury were excluded. Exposures of interest were BZ (ATC codes N05B, N05C) and AD (N06A) dispensed from 7 to 60 days before hospital admission to avoid indication and protopathic biases. Reference populations were a) the whole French population over the study period extrapolated from the 1/97<sup>th</sup> permanent representative sample EGB, in a case-population analysis; b) 5 controls/case from the same database matched on age and sex using the same index date for the case-control analysis. Results are provided as a) number of cases per million users (MP) or patient-years (MPY) with 95% confidence intervals [95%CI] b) Odds Ratios (OR) [95%CI] compared to non-exposure. **Results:** 4807 cases with hospital admission for ALI were identified matched to 24035 controls. 3619 cases and 12796 controls had been exposed to any drug within 7-60 days preadmission (OR 3.1 [2.9-3.4]). 914 cases were exposed to at least one anxiolytic BZ and 495 to at least one hypnotic (vs. 2289 and 1207 controls (OR 2.3 [2.1-2.5] and 2.2 [2.0-2.5])); ranging from 244 cases for zolpidem to 5 for estazolam. Rates of ALI was 43 [37-47] cases/MPY for any BZ with individual drugs risk from 132 for clonazepam [62-244] or hydroxyzine [113-153] to 32 [18-51] for lorazepam. Zolpidem was associated with 55 [47-62] cases/MPY. Per MP rate was 45 [41-51] for all BZ, ranging from clonazepam 68 [49-94] to prazepam 26 [21-33]. Zolpidem was associated with 36 [31-41] cases/MP, alprazolam 28 [24-32], bromazepam 30 [26-35]. OR ranged from 7.5 [1.2-45] for flunitrazepam to 1.5 [1.2-1.9] for lorazepam, with 2.1 [1.8-2.5] for zolpidem and 1.7 [1.5-2.0] for bromazepam. 732 cases were exposed to AD vs. 1809 controls (OR 2.3 [2.1-2.5]) from 137 for escitalopram to 5 for fluvoxamine. Event rates/MPY ranged from 115 [88-146] for mianserin to 32 [26-40] for escitalopram; per MP from 118 [38-275] (fluvoxamine) to 31 [26-37] (escitalopram). OR ranged from moclobemide 7.5 [1.2-45] or agomelatine 6.36 [2.9-14] to escitalopram 1.8 [1.5-2.2]. **Conclusion:** Risks associated with most BZ or AD were within the same order of magnitude within each class, with a few outliers, none unexpected.

1. Gulmez SE, et al. Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen): the multinational case-population SALT study. *Drug Saf.* 2013;36(2):135-44.  
2. Gulmez SE, et al. Risk of hospital admission for liver injury in users of NSAIDs and nonoverdose paracetamol: Preliminary results from the EPIHAM study. *Pharmacoepidemiol Drug Saf.* 2018;27(11):1174-81.

## Declaration of Interest Statement

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## Background

- Acute Liver Injury (ALI) is a major source of drug-induced regulatory action, drug-induced hospital admissions and burden of care.
- To our knowledge, hepatotoxicity studies were based on identification of individual cases and concerned a few hundred cases.
- A previous field study (SALT) exhaustively explored the acute liver failure leading to liver transplantation in 7 countries. The EPIHAM study was conducted in order to identify drugs with less severe hepatotoxicity, still resulting in hospital admission using the French nationwide claims database.

## Objectives

To quantify exposure to antidepressant (AD) and anxiolytic-hypnotic (BZ) prior to hospital admission for ALI in the French National healthcare systems database SNDS.

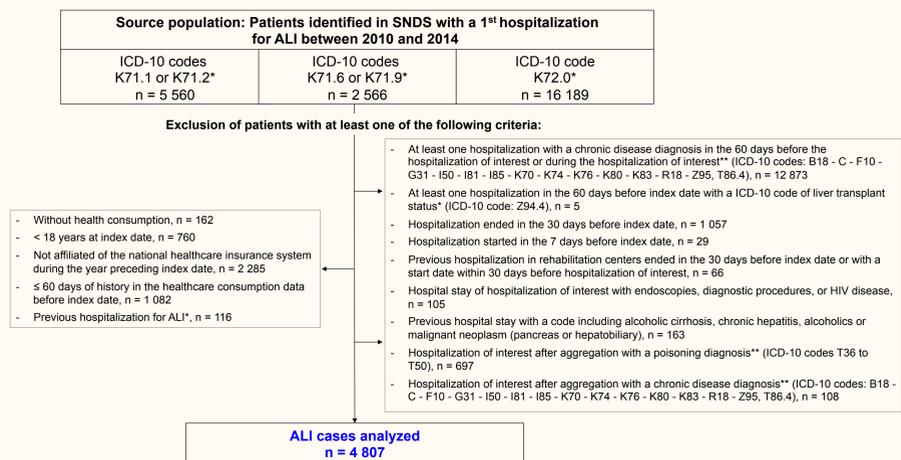
## Methods

- Study design**
  - Case-population study of adults with a 1<sup>st</sup> hospitalization for ALI from 2010 to 2014.
  - Case-control study of adults exposed to interest drugs from 2010 to 2014.
- Data source:** the SNDS French nationwide claims database which covers 99% of the French population and the EGB 1/97<sup>th</sup> permanent representative sample of SNDS.
- Study population**
  - Case** identified in SNDS among adult patients with a 1<sup>st</sup> hospital admission from 2010 to 2014 with main diagnosis of acute toxic liver injury (ICD-10 codes K71.1, K71.2, K71.6, K71.9) or hepatic failure (ICD-10 code K72.0) (Figure 1).
  - Reference population** identified in EGB among adult patients affiliated at least one day for each year considered to the national healthcare insurance system for salaried workers (CNAMTS), extrapolated to the whole French population.
  - Control** identified in EGB among adult patients affiliated to the CNAMTS and hospitalized between 2010 and 2014 for a reason other than ALI. Control were matched on age and gender using the same index date with a ratio of 5 controls / case identified (Figure 2).

- Index date:** Date of first hospital admission for ALI.
- Exposure**
  - Case:** AD (ATC code N06A) and BZ (ATC codes N05B, N05C) dispensing between 7 and 60 days preceding the date of 1<sup>st</sup> hospital admission for ALI (to avoid indication and protopathic bias).
  - Reference population:** number of patients with at least one interest drug dispensed over the study period (2010-2014), extrapolated to the whole French population.
  - Control:** AD (ATC code N06A) and BZ (ATC codes N05B, N05C) dispensing in the same period as the identified cases.
- Data analysis**
  - Incidence rate of ALI: number of exposed cases over the study period per million users (MP) or patient-years (MPY) with 95% confidence intervals (*case-population analysis*).
  - Risk of ALI in exposed patients (Odds Ratio – OR, conditional logistic regression) compared to non-exposed patients (*case-control analysis*).

## Results

### Identification of ALI cases – Case-population analysis



\* Main diagnosis; \*\* Main, associated or related diagnosis; \*\*\* Hospitalizations with a duration of 0 day or with a release "at home" were excluded from the aggregation  
Figure 1. Identification procedure of ALI cases in SNDS between 2010 and 2014

### Exposure of adult ALI cases

- 19% of cases were exposed to at least one anxiolytic BZ and 10% to at least one hypnotic. Exposure ranged from 244 cases for zolpidem to 5 cases for estazolam (Table 1).
- Exposure to AD (17%) ranged from 137 cases for escitalopram to 5 cases for fluvoxamine.

### Incidence of hospitalization for ALI

- For BZ, event rates per MPY ranged from 132 [62-244] for clonazepam to 32 [18-51] for lorazepam and per MP from 68 [49-94] for potassium clonazepam to 13 [9-17] for etifoxin.
- For AD, event rates per MPY ranged from 115 [88-146] for mianserin to 32 [26-40] for escitalopram and per MP from 118 [38-275] for fluvoxamine to 31 [26-37] for escitalopram.

Table 1. BZ and AD exposure of adult ALI cases within 7 and 60 days preceding the index date and incidence of hospitalizations for ALI between 2010 and 2014

Drugs dispensed within	Case	Case / million patients	Case / million patients-year	7-60 days before index date	
				n = 4 807	[95% CI] <sup>1</sup>
<b>N05B - Anxiolytics, n (%)</b>	<b>914 (19.0)</b>	<b>41.48 [36.94; 46.16]</b>	<b>56.57 [51.10; 62.05]</b>		
N05BA12 - Alprazolam	215 (4.5)	27.77 [23.88; 32.05]	74.43 [65.70; 87.60]		
N05BA08 - Bromazepam	189 (3.9)	29.94 [25.58; 34.77]	63.16 [54.75; 73.00]		
N05B01 - Hydroxyzine	166 (3.5)	26.80 [22.72; 31.36]	132.02 [113.15; 153.30]		
N05BA04 - Oxazepam	127 (2.6)	49.09 [40.84; 58.49]	54.43 [43.80; 65.70]		
N05BA06 - Lorazepam	104 (2.2)	62.78 [51.29; 76.08]	43.42 [36.50; 51.10]		
N05BA11 - Prazepam	75 (1.6)	26.47 [20.82; 33.18]	74.15 [58.40; 91.25]		
N05BX03 - Etifoxine	51 (1.1)	12.69 [9.44; 16.68]	66.18 [47.45; 87.60]		
N05BA05 - Potassium clonazepam	39 (0.8)	68.48 [48.69; 93.60]	63.17 [43.80; 87.60]		
N05BA01 - Diazepam	36 (0.7)	29.01 [20.31; 40.16]	40.42 [29.20; 54.75]		
N05BA09 - Clonazepam	22 (0.5)	40.09 [25.13; 60.69]	68.67 [43.80; 102.20]		
N05BA16 - Nordazepam	11 (0.2)	45.48 [22.70; 81.37]	72.73 [36.50; 131.40]		
N05BA21 - Clonazepam	10 (0.2)	17.18 [8.24; 31.59]	132.12 [62.05; 244.55]		
N05BC01 - Meprobamate	9 (0.2)	26.07 [11.94; 49.48]	74.31 [32.85; 142.35]		
N05BC51 - Meprobamate, combinations	8 (0.2)	24.88 [10.73; 49.01]	91.18 [40.15; 178.85]		
N05BE01 - Buspirone	6 (0.1)	20.96 [7.68; 45.62]	81.84 [29.20; 178.85]		
<b>N05C - Hypnotics and sedatives, n (%)</b>	<b>495 (10.3)</b>	<b>46.55 [41.08; 52.30]</b>	<b>47.13 [40.15; 54.75]</b>		
N05CF02 - Zolpidem	244 (5.1)	36.19 [31.29; 41.54]	54.85 [47.45; 62.05]		
N05CF01 - Zopiclone	163 (3.4)	34.55 [29.26; 40.47]	53.57 [43.80; 62.05]		
N05CD06 - Lormetazepam	67 (1.4)	53.08 [41.14; 67.42]	36.31 [29.20; 47.45]		
N05CD11 - Loprazolam	19 (0.4)	30.63 [18.44; 47.83]	31.95 [18.25; 51.10]		
N05CX - Hypnotics and sedatives in combination (excl barbiturates)	5 (0.1)	37.56 [12.17; 87.66]	61.18 [18.25; 142.35]		
N05CD04 - Estazolam	5 (0.1)	37.56 [12.17; 87.66]	61.18 [18.25; 142.35]		
<b>N06 - Psychoanaleptics, n (%)</b>	<b>798 (16.6)</b>	<b>59.35 [52.77; 66.15]</b>	<b>41.71 [36.50; 47.45]</b>		
N06AB10 - Escitalopram	137 (2.9)	31.26 [26.16; 37.04]	32.35 [25.55; 40.15]		
N06AB05 - Paroxetine	117 (2.4)	43.30 [35.78; 51.94]	43.22 [36.50; 51.10]		
N06AX16 - Venlafaxine	99 (2.1)	53.52 [43.49; 65.15]	51.39 [40.15; 62.05]		
N06A03 - Fluoxetine	75 (1.6)	44.41 [36.50; 54.75]	44.41 [36.50; 54.75]		
N06AA09 - Amitriptyline	65 (1.4)	35.08 [27.08; 44.72]	105.37 [80.30; 135.05]		
N06AX03 - Mianserin	64 (1.3)	51.37 [39.56; 65.60]	114.81 [87.60; 146.00]		
N06AB04 - Citalopram	51 (1.1)	46.31 [34.48; 60.90]	44.56 [32.85; 58.40]		
N06AX21 - Duloxetine	49 (1.0)	49.19 [36.39; 65.03]	60.15 [43.80; 80.30]		
N06AA06 - Sertraline	33 (0.7)	32.01 [27.75; 36.62]	32.99 [21.90; 47.45]		
N06AX11 - Mirzapine	29 (0.6)	40.16 [26.90; 57.68]	58.63 [40.15; 83.95]		
N06AX14 - Tianeptine	28 (0.6)	40.46 [26.89; 58.48]	64.42 [43.80; 94.90]		
N06AA04 - Clomipramine	26 (0.5)	63.85 [41.70; 93.54]	74.74 [47.45; 109.50]		
N06AX22 - Agomelatine	14 (0.3)	41.23 [22.53; 69.17]	75.16 [40.15; 127.75]		
N06AX17 - Milnacipran	11 (0.2)	51.78 [25.74; 92.28]	66.19 [32.85; 116.80]		
N06AB08 - Fluvoxamine	5 (0.1)	117.94 [38.21; 275.27]	78.72 [25.55; 182.50]		

<sup>1</sup> Taking into account the extrapolation of patient number for the reference population in the EGB database between 2010 and 2014

### Identification of controls – Case-control analysis

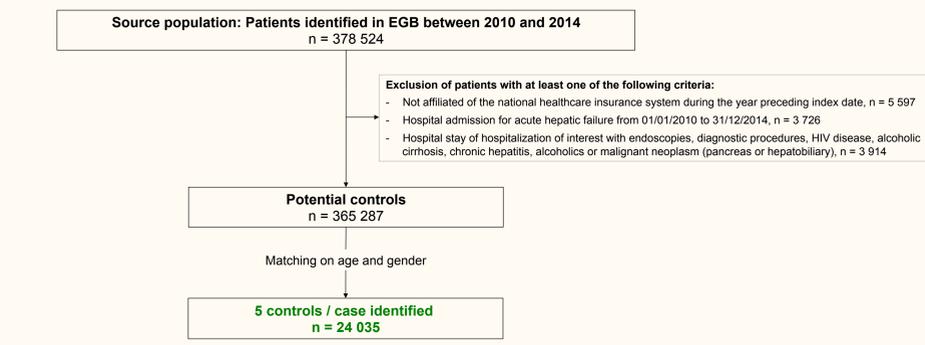


Figure 2. Identification procedure of controls in EGB between 2010 and 2014

### Risk of hospital admission for ALI

- For BZ, OR ranged from 7.5 [1.2-44.8] for flunitrazepam to 1.5 [1.2-1.9] for lorazepam, with an OR of 2.1 [1.8-2.5] for zolpidem and 1.7 [1.5-2.0] for bromazepam (Figure 3).
- For AD, OR ranged from 7.5 [1.2-44.8] for moclobemide or 6.4 [2.9-14.0] for agomelatine to 1.8 [1.5-2.2] for escitalopram.

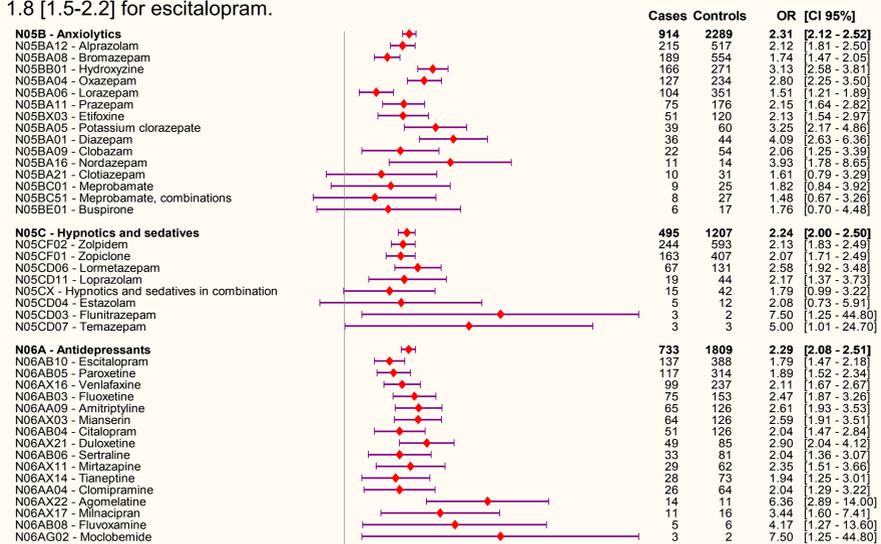


Figure 3. Risk of hospital admission for ALI between 2010 and 2014

## Conclusion

- The hospitalization risk for ALI was within the same order of magnitude for benzodiazepines and antidepressants (2.3 for anxiolytics, 2.2 for hypnotics, and 2.3 for AD).
- Some extreme values were observed, none of them were unexpected (as flunitrazepam or agomelatine).