Background:
Acute liver injury (ALI) is a major drug safety issue. Several antidepressants (AD) and anxiolytic-hypnotic (BZ) drugs have been associated with ALI. Objectives: To quantify exposure to antidepressants and anxiolytic-hypnotic drugs prior to hospital admission for acute liver injury (ALI) in the French national healthcare systems database SNDS (6.6 million persons). Methods: Case-control hospital admission for ALI (K71.1, 3, 8, 9, F00.1) and AD (N06A) dispensed from 7 to 60 days before hospital admission to avoid indication and prophylactic biases. Reference populations were a) the whole French population over the study period extrapolated from the 17397 permanent representative sample CEG, b) a case-population analysis, and c) 5 controls per 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 person-years (MPY) or patient-years (MPY) with 95% confidence intervals (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. 3019 cases and 13766 controls had been exposed in any drug with 1460 days treatment (OR 3.1 [2.9-3.4]) 914 cases were exposed to at least one anxiolytic BZ and 429 at least one hypnotic (vs 289 and 1377 controls OR 2.3 [2.0-2.6] and 2.2 [2.0-2.6]) ranging from 241 cases for zolpidem 0.9 to eszazepam. Rates of ALI were 4.6 [3.7-4.7] cases/MPY for any BZ with individual drugs risk from 132 for clobazam (ICD-10 E84) to 190 [169-210] for zolpidem. Sedation was associated with 31 [19-42] cases/MPY. Per MPY rate was 45 [39-51] for all BZ, ranging from chlorazepate 66 [49-94] to meprobamate 26 [20-31]. Zolpidem was associated with 35 [21-51] cases/MPY, alprazolam 28 [24-34], triazolam 30 [26-36], OR ranged from 7.5 [1.2-45] for fluoxetine to 1.3 [1.0-1.9] 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 1690 controls (OR 2.3 [2.0-2.5]) for 158 [38-194] for mianserin to 32 [8-40] for escitalopram; par MPY from 116 [38-275] (fluvoxamine) to 31 [8-27] (escitalopram). OR ranged from excitation 7.8 [1.3-45] or agomelatine 4.9 [2.6-16] to escitalopram 1.8 [1.2-2.2]. Conclusion: Rates associated with most BZ and AD were within the same order of magnitude within each class, with a few outliers, none unexpected.

Methods:

Study design
- Case–population study of adults with a 1st 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 96% of the French population and the EPI3 permanent representative sample of SNDS.

Study population
- Case identified in SNDS among adult patients with a 1st hospital admission from 2010 to 2014 with a diagnosis of ALI (ICD-10 codes K71.1, K71.2, K71.6, K71.0-9) for hepatitis (ICD-10 code K70.0) or hepatitis (ICD-10 code K70.0) (Figure 1).
- Reference population identified in EPI3 among adult patients affiliated at least for one day during the year considered to the national healthcare insurance system for salaried workers (CNAMTS). Extrapolated to the whole French population.
- Control identified in EPI3 among adult patients affiliated with 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 to 1 cases (Figure 2).

Results:

Identification of ALI cases – Case–population analysis

Identification of controls – Case–control analysis

Risk of hospital admission for ALI
- For BZ, OR ranged from 7.5 [1.2-44.8] for fluoxetine 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 [1.2-2.2] for escitalopram.

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

Abstract
Antidepressant And Anxiolytic-hypnotic Exposure Prior To Hospital Admission For Acute Liver Injury
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Declaration of Interest Statement
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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.

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 hundreds. A previous field study (SALT) exhaustively explored the acute liver failure leading to liver transplantation in 7 countries. The EPILAM study was conducted in order to identify drugs with less severe hepatotoxicity, still resulting in hospital admission using the French nationwide claims database.

Methods

Study design
- Case–population study of adults with a 1st 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 96% of the French population and the EPI3 permanent representative sample of SNDS.

Study population
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Risk of hospital admission for ALI
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