Summary

Objectives: Benzodiazepines and related drugs are indicated either for the short-term treatment of moderate or severe anxiety or insomnia. These drugs could be involved directly in fatal outcomes, such as in mixed drug overdose, car crashes, or suicide attempts, even if the ways by which these drugs can lead to an increased mortality are not entirely elucidated. This study intended to investigate the impact of anxiolytic or hypnotic drug exposure on all-cause and cause-specific mortality

Design: Retrospective exposed unexposed cohort study

Setting: two large healthcare databases: the CPRD (Clinical Practice Research Datalink) in UK and the EGB (General Sample of Beneficiaries) in France

Participants: Subject aged 18 years or older, meeting sufficient quality standard, and registered in the database for at least one year, were eligible. Exposed patients were those beneficing at least one prescription for any medication containing at least one benzodiazepine. Exposed patients were matched to one control in each of the 2 control groups (new users of antidepressants/non benzodiazepine sedatives in cohort 1, new GP consultants in cohort 2) according to birth year, gender, and practice.

Primary outcome measures: All-cause mortality at one year

Results: Among 643,893 patients recorded in the EGB database, 354,928 met inclusion criteria. After matching for age and sex, the final population comprised 57,287 patients in each group. Among the 14,673,617 patients in the CPRD, 294,552 met inclusion criteria for exposed group, the final population comprised 89,841 in each group. Female were respectively 63% and 57% in the EGB and CPRD cohorts. Population from EGB was younger than CPRD cohort (47.5 (18.3) vs. 57.8 years (18.6)). At baseline, alprazolam, bromazepam, zolpidem and zopiclone represented the most frequently recorded drug in the exposed group in the EGB. In the CPRD, new users of diazepam, zopiclone, and temazepam, were mainly represented. For the main endpoint, 12 months all-cause mortality was found to be significantly higher among those exposed to benzodiazepine in the CPRD , based on the group [HR: 5.91 ,95% CI 5.51-6.34 , $p < .001$] or on benzodiazepine exposure as a time dependant covariate [HR: 3.38, 95% CI 2.82-4.06, $p < .0001$]. In the EGB, patients assigned to the exposed group also demonstrated higher all-cause mortality risk at 12 months [crude hazard ratio (HR):1.99, 95% CI 1.74-2.29 P <.0001] compared to control group 1 and 2 (reference). After adjustment on clinical variables, this effect remained significant in the CPRD [adjusted HR 1.45, 95% CI 1.15-1.84, p<. 0.002], but not in EGB [adjusted HR: 1.24, 95% CI 0.99-1.54, p<0.0605].

Conclusions: This study enables to bring additional evidence on the relation between benzodiazepine use and all-cause mortality and exhibits a significant but moderate effect persisting event after controlling for additional factors in the UK CPRD, but not retrieved in the French EGB.

Registration: This study was commissioned and funded by the European Medicines Agency (Procurement Procedure No. EMA/2012/20/PV). Study protocol has been approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research. This study received the ENCePP Study Seal on April 8, 2013