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Background: The association between benzodiazepines (BZD) and hip fractures has been estimated in several observational studies in different countries or regions, using diverse methodologies and definitions limiting comparability.

Objectives: To estimate the risk of hip/femur fractures associated with BZD prescribing in 3 European primary care databases, using a common protocol, and minimizing inter-database variation through harmonization of definitions and coding.

Methods: A new user cohort study examining BZD and related drug prescribing, and the risk of hip/femur fracture between 2001 and 2009, was performed within 3 primary care databases from the Netherlands (Mondriaan), Spain (BIFAP) and the UK (CPRD). Age, comorbidity and comedication were considered as covariates. Incidence Rates (IRs) were calculated. Hazard ratios (HRs) and 95% confidence intervals (CI) were also estimated for current use versus past use using time-dependent multivariable Cox proportional hazard models.

Results: We observed an increase in IRs by age, across all exposure categories and among all databases. The increase by age was much higher in females than in males in BIFAP and CPRD. Crude HRs for current use of BZD were similar for all databases and ranged from 2.83 (CI: 2.60-3.09) in BIFAP to 3.32 (CI: 3.10-3.56) and 3.32 (CI: 2.31-4.75) in CPRD and Mondriaan, respectively. Adjusted HRs were however disparate: namely, 1.19 (CI: 1.08-1.30) in BIFAP; 1.52 (CI: 1.41-1.63) in CPRD, and 2.03 (CI: 1.40-2.94) in Mondriaan.

Conclusions: Applying the same protocol to estimated risk of hip/femur fractures associated to BZD resulted in different estimates in the 3 databases. The most important confounder was age in all 3 databases, while the effect of other factors was minimal. This study allowed a comparison across countries following a common methodology.

Our findings might be explained by intrinsic differences between populations and pattern of use of BZD.

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716. No Impact of Adjusting for Lifestyle Factors or General Practice on Risk Estimates for the Association between Antidepressants and Hip/Femur Fracture

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Background: Routinely collected data from electronic health record databases often lack information on relevant risk factors, like lifestyle-factors (LSF, smoking, alcohol use, body mass index) or socioeconomic factors that may be needed for confounder adjustment in epidemiological studies.

Objectives: In the context of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project, the impact of confounder adjustment on the risk of antidepressant (AD) use on hip/femur fracture (HF) and compared results across three primary care databases was assessed.

Methods: We conducted a case-control study nested within 3 new AD user cohorts of adult patients (2001-2009) in three databases (Spanish BIFAP, Dutch Mondriaan and UK THIN). Cases were defined as a first HF during the study period. Up to 4 controls were matched by sex, age (+/- 2 years) and time since cohort entry (+/- 6 months). Exposure to AD was classified into current, recent and past use. We adjusted for comedication and comorbidities, using same models for all data sources. The impact of matching on practice (marker for socioeconomic factors) and additional adjustment for LSF was done in THIN. Odds ratios

(OR) were estimated using conditional logistic regression analysis.

Results: Current use of AD was associated with an significantly increased risk of HF in all data sources. Adjusted ORs were 1.52 in BIFAP (1535 cases), 1.59 in THIN (3756 cases) and 3.32 in Mondriaan (79 cases). In BIFAP/THIN, adjustment resulted in <10% change of crude ORs. In Mondriaan, a 36% change is probably explained by violation of model assumptions by including too many variables. Further adjustment for LSF in THIN did not yield different estimates compared to the model without: OR 1.59. Results were similar after including GP practice in the matching algorithm: adjusted OR 1.64.

Conclusions: Matching on GP-practice and adjustment for LSF had no impact on adjusted risk estimates, suggesting that non-availability of such data does not necessarily lead to bias. This could be reassuring for datasets lacking such data or struggling with sample size issues.

717. Antidepressant Use and the Risk of Hip Fracture: A Self-Controlled Case Series Approach in Two Primary Care Databases

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Background: The use of antidepressants (AD, selective serotonin reuptake inhibitors, SSRI, or tricyclic antidepressants, TCA) has been associated with hip fractures (HF) in observational studies. However, it has been suggested that such results may be confounded by unmeasured patient characteristics.

Objectives: To assess the effect of AD use on the risk of HF using self-controlled case series design.

Methods: A self-controlled case series study was conducted in two primary care databases among patients with a first HF and a prescription for AD at

any time during observation. Data were extracted from the UK THIN and the Dutch Mondriaan GP databases of the period 2001-2009. The incidence rate ratio (IRR) of HF for periods of AD use versus no AD use was estimated using conditional Poisson regression.

Results: There were 6,632 and 136 HF patients for analysis in THIN and Mondriaan, respectively. After adjustment for age, an increased risk of HF was observed during the 30 day period after AD initiation: IRR 1.57 (95% CI, 1.39-1.78) in THIN and 3.22 (1.51-6.84) in Mondriaan. The increased risk was also observed during the next six months of AD use: IRR 1.52 (1.39-1.65) in THIN and 2.76 (1.69-4.50) in Mondriaan. In the period after six months, the risk remained higher in THIN (IRR: 1.47; 1.31-1.65) but not significant in Mondriaan (IRR 1.94; 0.84-4.47). Furthermore, an increased risk of HF was observed during the 30 day period prior to AD initiation (IRR 1.22; 1.06-1.41) in THIN and (IRR 2.51; 1.00-6.33) in Mondriaan. In both THIN and Mondriaan, when cases were censored at the event times (HF) there appeared to be a substantial bias in IRR in all the periods: IRR during the 30 day period after AD initiation: 3.07 (2.66-3.54) in THIN and 12.34 (2.13-71.54) in Mondriaan. The risk of HF was higher in SSRI users than TCA users (4.39; 2.42-7.99 vs. 1.39; 0.58-2.41) in Mondriaan but was similar in THIN (1.49; 1.36-1.63 vs. 1.49; 1.33-1.66).

Conclusions: The incidence rate of hip fractures was higher in the periods both immediately after the start of AD use and during the first six months of AD use compared to periods of no use, although the magnitude of the risk varied between databases.

718. Evaluation of “Pre-Treated” Bipolar Disorder Patients Receiving Atypical Antipsychotics in the UK Using an Electronic Health Record Database

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Background: The clinical practice of initiating therapy with atypical antipsychotics (AAs) while the diagnostic evaluation of a patient (pt) proceeds over a period of time is common. These pts are not strictly “on” or “off” label, but classified as “pre-treated”.