ASSOCIATION BETWEEN EXPOSURE TO BENZODIAZEPINES AND RELATED DRUGS AND SURVIVORSHIP OF TOTAL HIP REPLACEMENT IN ARTHRITIS: A POPULATION-BASED COHORT STUDY OF 246 940 PATIENTS

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BACKGROUND

Total hip replacement (THR) is successful in treating hip arthritis. Prosthetic survivorship may depend on the medications taken by the patient; particularly, the role of benzodiazepines (BZD) and related drugs (Z-drugs) with THR revision has been poorly investigated.

OBJECTIVES

To compare THR short-term survivorship according to level of exposure to benzodiazepines and Z-drugs.

DESIGN, SETTING AND PARTICIPANTS

Patients aged 40 years or older, having undergone unilateral primary THR for osteoarthritis from January 1, 2009, through December 31, 2012 (48 months), according to French national health insurance databases were included in the cohort. Patients having primary THR for trauma or bone cancer, prosthetic revision before the inclusion period, simultaneous bilateral THR, not being reimbursed 6 months after THR or with incoherent coded were excluded (N=164 723).

Outcome of interest was THR revision, including any surgical procedure in which the implant or any component was changed or removed.

Follow-up started the day the primary THR was performed. Observations were right-censored on December 31, 2014, if neither revision nor death had yet occurred.

Exposure of interest was the cumulative defined daily doses per day (cDDD/day) of BZD and Z-drugs dispensed within 6 months before or after inclusion. We defined four exposure groups; cDDD/d = 0: unexposed; <0.08: low exposure;] 0.08–0.38]: medium exposure; >0.38: high exposure.

THR survivorship was assessed according to level of exposure to BZD and Z-drugs in univariate and multivariate Cox models adjusted for patient, THR and implanting center characteristics.

RESULTS

- **Study population:** The entire study cohort comprised 249 597 patients. THR characteristics were missing for 2 657, excluded from subsequent analyses, leaving 246 940; 61 054 were enrolled in 2009, 60 808 in 2010, 62 230 in 2011 and 62 848 in 2012.
- **Patient characteristics:** Mean age was 69.9 years (SD: 10.8). Women (57.9% of enrolled individuals) were significantly older than men (71.6 vs. 67.5, P < .0001). Regarding comorbidities, 9.4% were obese, 5% had dementia and 2.5% Parkinson's disease. Regarding treatments, 18.6% were exposed to antidepressants (significant difference between men and women, 11.7% vs. 23.6%, P < .0001), 27.9% to oral corticosteroids, 8.1% to antiepileptic drugs (non-BZD) and 12.9% to anxiolytic or hypnotic drugs, non-BZD.
- **THR characteristics:** Implantation was performed in a private hospital in 65.7% of cases and nearly half of patients were implanted in centres performing 14 to 38 monthly procedures. Median hospital stay was 8 days (IQR: 7–10). Fixation was uncemented: 73.0%, cemented: 6.1%, hybrid: 19.2% and reverse hybrid: 1.6%. Bearing surfaces were Ceramic on Ceramic (CoC): 40.7%, Metal on Polyethylen (MoP): 34.0%, Ceramic on Polyethylen (CoP): 21.0% and Metal on Metal (MoM): 3.3%.
- **Baseline exposure to BZD:** 48.3% of subjects exposed to BZDs (15.7% highly exposed); 17.5% exposed to anxiolytic-BZDs, 14.8% to hypnotic-BZDs, 9.8% to both anxiolytic and hypnotic-BZDs and 6.2% to other BZDs (antiepileptics or muscle relaxants). Exposed patients received a mean cDDD/d of 0.40, and 5.4 BZDs deliveries on average, within the year around inclusion.
- **Exposure to BZD during follow-up:** exposed patients received on average 4.2 BZDs deliveries yearly and mean received cDDD/d was 0.37. Baseline and follow-up exposure patterns were very similar.

- **Risk of revision according to BZDs exposure**

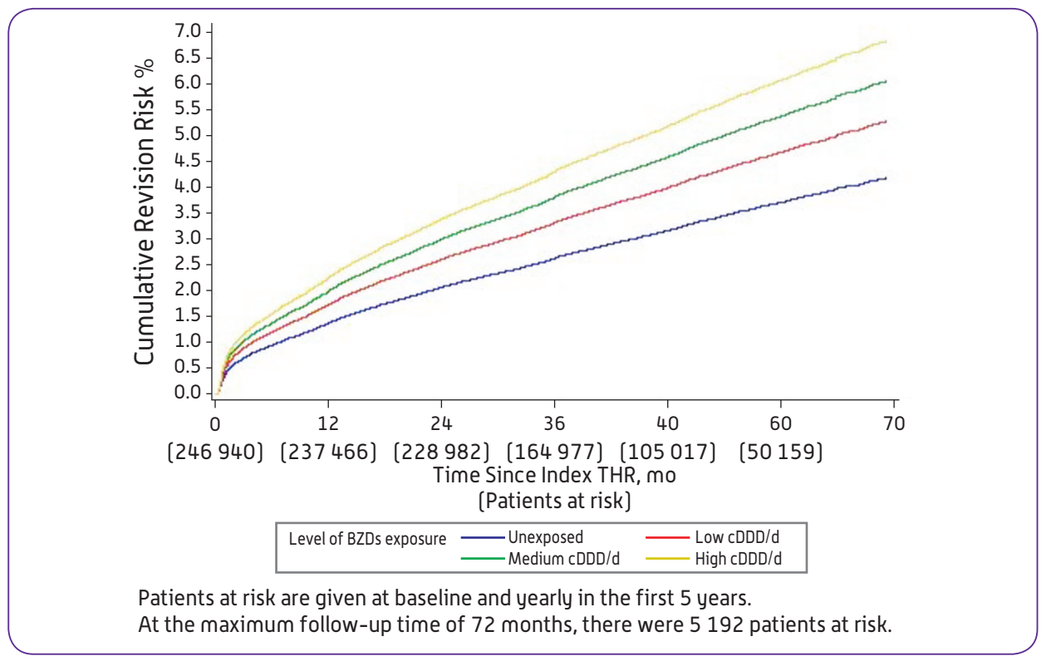

Figure 1: Kaplan Meier Cumulative revision risk according to BZDs exposure

During 45 months follow-up, 9 043 (3.7%) prosthetic revisions were observed. Cumulative revision rates were 3.0% in unexposed, 3.9% in low doses, 4.4% in medium doses and 4.8% in high doses of BZDs) (Fig 1).

Table 1. Associations between exposure level to BZDs and prosthetic revision

		Revisions (N=9 043)	Univariate Cox Model (N=246 940)	Multivariate Cox Model (N=246 940)
	N	%	HR (IC 95%)	aHR[1] (IC 95%)
Unexposed	127 797	3.0	ref	ref
Low	41 196	3.9	1.26 (1.19-1.34)	1.18 (1.12-1.26)
Medium	39 181	4.4	1.45 (1.37-1.53)	1.32 (1.24-1.40)
High	38 766	4.8	1.63 (1.55-1.73)	1.37 (1.29-1.45)

(1) Hazard Ratios were adjusted for: sex, age at implantation, diabetes mellitus, obesity, Parkinson's disease, immunodeficiency, exposure to antidepressant, oral corticosteroid, antiosteoporotics, psychostimulant, antipsychotic, antiepileptic (non-BZD), anxiolytic or hypnotic (non-BZD), public or private sector, center volume of activity, duration of stay, cement type and bearing surface

Univariate and Multivariate analyses gave similar results: adjusted HR, aHR=1.18 (95%CI: 1.12-1.26) for low cDDD/d, aHR=1.32 (95%CI: 1.24-1.40) for medium cDDD/d and aHR=1.37 (95%CI: 1.29-1.45) for high cDDD/d, compared to unexposed patients.

When assessing separately baseline exposure to anxiolytic-BZDs alone, exposure to hypnotic-BZDs alone and exposure to both BZDs, aHR was 1.23 (1.16-1.30) for anxiolytic-BZDs, 1.28 (1.21-1.36) for hypnotic-BZDs and 1.37 (1.28-1.47) for both, (p<0.0001).

In sensitive analysis with BZDs exposure as time-dependant variable, aHR = 1.29 (1.23-1.36) for BZDs-exposed patients, versus unexposed.

DISCUSSION AND CONCLUSION

Exposure to benzodiazepines and Z-drugs is associated with an increased risk of THR revision, with a dose-response relationship. Similar findings were found when stratifying analyses on sex, on age group, on hospital sector or on exposure to antidepressant drugs. The large number of patients, the possibility of comparing prosthetic survivorship according to BZDs exposure in cDDD/d and of adjusting survival analysis for many known and suspected prosthetic revision risk factors in multivariate Cox models are strengths of the study. Exposure to treatment is derived from drug dispensing data instead of effective drug intake. However, the possible classification bias is non-differential and given that BZDs dispensations are regularly renewed overtime, it is reasonable to assume that the drug is ingested. We were unable to identify the direct causes for revision.

Whatever the underlying mechanism, cautious prescribing might be needed as well as careful history examination and assessment of risk for patients with a hip prosthesis.