Timing of Concomitant Drug Use in Pharmacoepidemiological Studies


Background
Both antidepressants and benzodiazepines have been associated with an increased risk for hip fracture. However, the hazard function is not constant over exposure time and differs for these two medication classes. In pharmacoepidemiological studies, concomitant use of medication is mostly considered dichotomously (yes/no) in a fixed time exposure window. However, the timing of initiation of co-use will determine the overall hazard function.

Objective
The aim of this study was to describe the timing of initiating benzodiazepine co-medication use among antidepressant users.

Methods
1. Patients from the Information Network of General Practice (LINH) database starting antidepressant use during 2002-2009 were selected.
2. Incident patients (no antidepressant use history in the previous year) were selected.
3. Antidepressant treatment episodes were constructed for each patient assuming the start of a new episode when 90 days elapsed between the theoretical end-date of a prior prescription and the start-date of the next prescription.
4. Within the first antidepressant episode, 3 types of benzodiazepine co-use were defined:
   - Group A: Before starters: first benzodiazepine prescription before the start of antidepressant treatment episode
   - Group B: Simultaneous starters: start of benzodiazepine prescription on the same day as the start of the antidepressant episode and no benzodiazepine prescriptions during 182 days prior to start
   - Group C: After starters: first benzodiazepine prescription after the start of the antidepressant episode

Results
The study population consisted of 16617 patients initiating antidepressant treatment. Among those patients, 28.5% had concomitant benzodiazepine use at some stage. Characteristics of these 3 groups in terms of age, length of co-use, number of benzodiazepine prescriptions and antidepressant poly-therapy were different. The timing of the start of benzodiazepine use is shown in Figure 2.

Conclusion
The timing of the start of benzodiazepine co-use among incident users of antidepressants is heterogeneous. Hence, concomitant users of benzodiazepine and antidepressant medications are expected to have a different overall hazard function for hip fracture, depending on when the co-use occurred. To calculate accurate overall hazard function, for two medications with a known adverse event, it is important to consider the timing of initiation of the co-medication as opposed to defining co-use as constant over time.

Disclosure
The department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, has received unrestricted research funding from the Netherlands Organisation for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private-public funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the EU Innovative Medicines Initiative (IMI), EU 7th Framework Program (FP7), the Dutch Medicines Evaluation Board, the Dutch Ministry of Health and Industry (including GlaxoSmithKline, Pfizer, and others).

The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on outcomes of Therapeutics by a European consortium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency for Pharmaceutical Sciences.

Author affiliations
1. Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, the Netherlands
2. Department of Clinical Pharmacy, University Medical Center Utrecht, the Netherlands
3. Medicines Evaluation Board, Utrecht, the Netherlands