DATA MINING: PHARMACOVIGILANCE SIGNALS OF BENZODIAZEPINES AND SKIN AND SUBCUTANEOUS TISSUE DISORDERS

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BACKGROUND
Pharmacovigilance uses data mining algorithms on spontaneous reporting databases, to assess significant associations between adverse drug reactions (ADR) and drugs. These pharmacovigilance databases provide early warnings of hazards that were missed before marketing a drug, mainly because of the limitations of clinical trials. In July 2013, tetrazepam marketing was suspended, after four decades in the market, due to serious skin and subcutaneous tissue disorders ADR (SSTD-ADR).

PURPOSE
We tried to detect possible pharmacovigilance signals between SSTD-ADR and benzodiazepines, by applying data mining on American Pharmacovigilance Database (FAERS), whose data were public.

MATERIAL & METHODS
We calculated data mining algorithms (PRR: Proportional Reporting Ratio; ROR: Reporting Odd Ratio; IC: Information Component, and EBGM: Empiric Bayesian Geometric Mean) on spontaneous reports of SSTD-ADR due to benzodiazepines commercialized in USA, registered into FAERS. All statistical algorithms were calculated from 2x2 contingency tables, according to literature: PRR – 1.96SE (standard error) (with Chi2 and P value associated), ROR – 1.96SE, IC – 2SD (standard deviation), and EBGM – 2SD precision algorithms were calculated. A signal was considered when: PRR ≥ 2 (with Chi2 value≥4); lower bound of 95% two-sided confidence interval (CI95%) of ROR>1; CI95% two-sided of IC>0; or CI95% one-sided of EBGM≥2. All calculations by using Excel® 2011 14.4.1.

RESULTS
We found 3,957 SSTD-ADR (3.05% of all benzodiazepines ADR reports). ROR yielded signals for eight drugs (clobazam, clonazepam, clorazepate, midazolam, oxazepam, quazepam, tetrazepam and triazolam), PRR and IC for four (clobazam, midazolam, quazepam and tretrazepam), while EBGM detected only a signal for tetrazepam. Midazolam, Clobazam and Quazepam originated a signal by 3 algorithms. Tetrazepam was the only which generated a signal by 4 algorithms. Clobazam originated a signal for Stevens-Johnson Syndrome and Blister; midazolam for Toxic Epidermal Necrolysis, DRESS Syndrome, and Erythema; quazepam for Erythema Multiform and Drug Eruption; and tetrazepam for Dermatitis Bullous, Toxic Skin Eruption, Rash Maculopapular and Rash Erythematous. (All these terms are “Preferred Term” level of MedDRA classification).

CONCLUSION
Our pharmacovigilance data mining reveal the existence of potential signals for BZD and SSTD-ADR. However, to stablish causality, larger studies providing new clinical evaluation on these associations will be required.