

Institution/department: Charles University, Faculty of Pharmacy in Hradec Králové, Department of Social and Clinical Pharmacy

Title of diploma thesis: Rationality of benzodiazepine use in older patients

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Introduction: Benzodiazepines are one of the most commonly prescribed potentially inappropriate drugs (PIMs) in geriatric patients in Europe and are responsible for common problems associated with risky drug prescription in older age (eg, cognitive impairment, falls, orthostatic hypotension, drug dependence, and others). Physiological and pathophysiological changes associated with the aging process, as well as frequent polymorbidity and polypharmacotherapy, are associated with more frequent occurrence of drug-related complications in older age. With the growing proportion of geriatric population, the importance of preventing drug complications in older adults increases. The aim of this study was to compare prescribing habits in the use of BZD and in the use of drug combinations with sedative potential and to determine the association of their use with drug-related risks in geriatric patients in community pharmacy practice in Spain (SP) and the Czech Republic (CZ) and in groups of patients assessed in various healthcare settings in the Czech Republic in the EuroAgeism H2020 project.

Methodology: The analyzed data were obtained by prospective data collection in seniors in the EuroAgeism H2020 project (2018-2022). Data were collected in the Czech Republic in at least 3 regionally different health care settings and in community pharmacy care in the SP. For the purposes of this diploma thesis, data from the Czech Republic (N = 1602) - from acute (N = 589), outpatient (N = 451) and community pharmacy care (N = 450 patients) and data from SP from community pharmacy care (N = 260) were used. The assessment of seniors was performed by trained researchers using standardized questionnaires of the EuroAgeism H2020 research project, based on the prospective CGA assessment method (CGA-Comprehensive Geriatric Assessment). The rationality of benzodiazepine use was analyzed according to explicit criteria of potentially inappropriate drugs in older age (revised Beers 2019 criteria and EU (7) -PIM list) with a focus on dosing and duration of drug use (without taking into account diagnoses and with taking into account some specific indications). For a pilot description of the main characteristics, we used the methods of descriptive statistics using R software (version 4.0.3). Differences in the number of categorized variables (eg, number of drugs) between different types of care in the Czech Republic and between pharmacy care in the Czech Republic and in SP were evaluated by chi-square test (if all expected numbers were > 5) or Fisher's exact test (if at least one expected number was ≤ 5). The association between the number of prescribed sedative drugs or the sedative potential of the drug regimen and the occurrence of negative symptoms and other drug-related risks was assessed using the Kendall's rank correlation tau = 0.9342443, p <0.001. The analysis of categorized variables was adjusted for basic confounding factors (age and gender) by the Cochran-Mantel-Haenszel test. Differences between the observed groups were considered statistically significant if p <0.05.

Results: There were 56.5 % and 78.9 % of women in acute and ambulatory care in the Czech Republic, the average age was 79.07 years +/- 8.11 years (SD) and 82.77 years +/- 8.53 years (SD). In SP and CZ, 62.4 % and 64.6 % of women were represented in community pharmacy care, the average age of the participants was 71.74 years +/- 6.25 years (SD), and 76.61 years +/- 7.15 years (SD). Polypharmacotherapy and excessive polypharmacotherapy were documented in the CZ: 1) in acute care in 45.7 % and 47.4 % of seniors; 2) in ambulatory care in 54.7 % and 22.6 % and in 3) community pharmacy practice in 24.9 % and 3.8 % of seniors ($p < 0.001$). In community pharmacy practice in SP, the prevalence was 41.2 % and 13.1 % (differences between community care in CZ and SP were significant, $p < 0.001$). In SP sample we found an exceptionally high prevalence of BZD use (35.4 % of seniors used at least 1 BZD) compared to 2.4 % in community pharmacy practice in CZ ($p < 0.001$). In CZ, there were 16.7 % of patients in ambulatory care and 18 % of patients in acute care using BZD. The 3 most frequently prescribed BZD in SP were: lorazepam (16.5 %), lorazepam (6.5 %) and alprazolam (4.6 %); in the total sample in CZ: alprazolam (4.1 %), oxazepam (3.6 %) and bromazepam (3.1 %). The most frequent potentially inappropriate prescription of BZD in CZ focused mainly on administration of long-acting BZD for the indication of insomnia (9.6 % of patients in ambulatory care). In SP community pharmacy care this was 31.2 % and another problem was exceeding the maximum recommended daily dose it 6.5 % of patients (for example for lorazepam). In SP sample we found an exceptionally high overall prevalence of use of sedative drugs (41.5 %, $p < 0.001$) in comparison with pharmacy practice in CZ (8.2 %). Sedative drugs were mostly used in acute care in CZ (54.7 % of patients). The most frequently prescribed combination of sedative drugs in CZ was alprazolam and citalopram - 5.7 % (sedative potential- 3, means strong), in SP pharmacy care it was diazepam and citalopram - 12 % (sedative potential - 4, very strong). The results of the association analysis showed a significant correlation between a higher number of sedative drugs and a higher sedative potential drug regimen and the occurrence of negative symptoms and risky complications of sedative treatment.

Conclusion: We found significant differences in the use of BZD (choice of active substances, duration of therapy and drug combinations) and all sedative drugs in geriatric patients in community pharmacies in SP and CZ (with a higher prevalence in SP). At the same time, there were significant differences in these characteristics between different settings of healthcare in the Czech Republic. The results of the associations testing showed a statistically significant correlation between the number of sedative drugs used and sedative potential of drug regimens with higher occurrence of negative symptoms and risky complications of sedative treatment in geriatric patients. Specific measures should be taken, both at the regulatory level and in clinical practice, to better ensure the safety of pharmacotherapy in older age in use of BZD and sedative drugs. According to our results, these measures should be targeted in the Czech Republic of acute care setting and implemented particularly in Spanish clinical practice.

Key words: rationality of geriatric pharmacotherapy, inappropriate prescription of drugs, benzodiazepines, sedative drugs, drug complications, seniors



Support: *This project has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 764632. It was also supported by other projects of the research group “Aging, polypharmacotherapy and changes in the therapeutic value of drugs in old age” of the scientific program PROGRESS Q42- KSKF2 (led by doc. D. Fialová), which include pre-application research focused on innovative drugs and innovative treatment technologies under the name InoMed, co-financed by the European Union (NO.CZ.02.1.01 / 0.0 / 0.0 / 18_069 / 0010046); SVV program 260 551, START project No START / MED / 093 CZ.02.2.69 / 0.0 / 0.0 / 19_073 / 0016935) and ICARE4 OLD Horizon 2020 project ID: 965341.*