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Title of rigorous thesis: Evaluation of the rationality of pharmacotherapy in geriatric patients in ambulatory and acute care- analyses of pain treatments and use of opioids

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Objectives: The core issue in geriatric treatment is the selection of the most appropriate and the safest drug regimen. Geriatric patients often suffer from multiple disorders and particularly seniors with unresolved pain tend to use polypharmacy, often irrationally. This study focused on the description of pain prevalence and use of opioids in seniors in two settings of care (acute and ambulatory care) in the Czech Republic and on analyses of negative outcomes associated with use of opioids in combined drug regimens.

Methods: Data were collected during 2018-2019 in various healthcare facilities in the Czech Republic as the part of EUROAGEISM H2020 ESR7 project. Prospective study included assessments of 1152 patients who were 65 years or older in acute (N=589) or ambulatory (N= 563) care in 4 cities (Prague, Brno, Hradec Králové and Opava). Data were collected through the standardised questionnaire, using interviews with patients and healthcare professionals or by recording data from medical records. Questionnaires were based on the Comprehensive Geriatric Assessment method and consisted of questions related to sociodemographic and functional status of a geriatric patient, lifestyle, utilization of health services, patient clinical information, laboratory values and pharmacotherapy. Patients who were terminally ill, had speech impairment, suffered from severe hear loss or speaking problems or who scored <10 at MMSE (Mini-Mental State Examination) were excluded from the study. Also, associations between number of ACH drugs used/anticholinergic activity of drug regimen and negative complications were tested. Data were evaluated in statistical software R, version 4.0.5. Descriptive analysis was used to compare observed characteristics of patients and drug prevalence in acute and ambulatory care in the Czech Republic. Continuous variables (e.g. age) were described by average, standard deviation (SD), median, minimum and maximum; discrete variables (e.g. gender) were described by absolute and relative frequency (percentage). Average age of the patients in acute and ambulatory care was compared by t-test. Differences between frequency of discrete variables (e.g. number of drugs) were analysed by chi-squared test if all expected frequencies were at least five, otherwise Fisher's exact test was used. Ordinal regression was applied when evaluating

associations between the number of anticholinergics (or anticholinergic activity of drug regimens) and the number of negative complications. Kendall rank correlation coefficient was used to assess associations between number of anticholinergic drugs used and their anticholinergic activity. Results were concluded as statistically significant if the p-value (attained significance level) was less than 0.05. Not all confounding factors were taken into consideration when conducting analysis – only basic statistical methods were applied. Structure of missing values were not analysed. Presented statistical analysis gained pilot results for further application of other multidimensional statistical methods.

Results: There were 43.5 % of men and 56.5 % of women in acute care while ambulatory care cohort consisted of 21.1 % of men and 78.9 % of women. Pain was experienced by 335 (56.9 %) and 334 (59.3 %) patients in acute and ambulatory care, respectively. There were 191 (16.6 %) patients using opioids in the cohort (in acute care 132 (39.4 %), in ambulatory care 59 (17.7 %)). 150 (13.0 %) were users of weak opioids or their combinations, 34 (3.0 %) users of strong opioids or their combinations and 7 (0.6 %) were taking weak opioids and strong opioids at the same time. There were significant differences in the number of patients suffering from various types of pain in acute and ambulatory care: chronic pain (29.0 %, 55.4 %), acute pain (29.2 %, 8.5 %) and breakthrough pain (7.5 %, 2.0 %). The majority of acute care patients (58.8 %) suffered from pain several times per day while ambulatory care patients (54.8 %) experienced pain mostly at least 2-3 times per week but not on a daily basis. Pain was localized in acute care patients mainly in legs (15.3 %), chest (9.0 %) and back (8.1 %). Ambulatory care patients suffered from pain mainly in knees (19.5 %), spine (14.2 %) and back (12.1 %). The majority of patients experienced pain in acute care because of fractures (8.8 %), neuropathy (6.5 %) and osteoarthritis (5.4 %) and in ambulatory care pain causes included mainly osteoarthritis (26.6 %) and vertebrogenic algic syndrome (VERTAS) (18.1 %). Opioids were mostly used in acute care patients with fractures (22.0 %), neuropathy (12.9 %) and VERTAS (9.1 %). Whereas in ambulatory care, opioids were prescribed to patients with VERTAS (39.0 %), osteoarthritis (37.3 %) and neuropathy (8.5 %). The most common groups of prescribed analgesics in acute and ambulatory care were: pyrazolones: particularly metamizole (29.4 %, 12.4 %) and anilides: particularly paracetamol (11.9 %, 4.4 %). In terms of co-analgesics the most commonly used in acute and ambulatory care were: antipsychotics (21.4 %, 19.4 %), antidepressants (21.2 %, 27.4 %), anticonvulsant (16.6 %, 13.5 %), anxiolytics (15.1 %, 14.6 %) and benzodiazepine derivatives (14.8 %, 14.4 %). 16.8 % of acute care patients and 8.3 % of ambulatory patients used weak opioids in combination

with any anticholinergic or sedative drug. Strong opioids in combination with anticholinergic or sedative medications were observed in 5.9 % and 1.1 % of acute and ambulatory care patients. At least one anticholinergic side effect was experienced by 35.0 % and 37.8 % of acute and ambulatory care patients, respectively. The most frequent side effects were atrial fibrillation at both types of care – acute and ambulatory care (34.1 %, 21.3 %) and constipation (14.6 % and 8.5 %). The majority of acute care and ambulatory care patients took anticholinergic medications – one anticholinergic drug was prescribed to 33.6 % and 26.6 % patients, two anticholinergic drugs to 23.3 % and 23.6 % and more than three anticholinergic drugs to 24.3 % and 21.1 % of patients in above stated settings of care. Mild anticholinergic activity of prescribed drug regimens (0.6-1.4) was confirmed in 31.6 % acute care patients and 24.2 % ambulatory care patients; moderate anticholinergic activity (1.5-2.4) in 21.2 % and 22.2 % of patients in relevant settings of care and strong activity (2.5+) in 27.5 % and 25.0 % of patients. Results of association analyses showed a significant correlation between number of anticholinergic drugs prescribed (or number of anticholinergic activity of drug regimens) and negative complications ($p < 0.001$). There were negligible differences described in association analyses between acute care and ambulatory care, or in relation to gender or opioid use.

Conclusion: We found out that opioid medications were mostly prescribed in older patients in acute care and majority of them were weak opioids or their combinations. The results of association analyses confirmed there was a high correlation between number of anticholinergic drugs prescribed (or anticholinergic activity of drug regimens) and negative complications in older patients. Effective and safe treatment of pain in older adults require continuous monitoring of efficacy and safety of prescribed drug regimens.

Key words: potentially inappropriate medication, seniors, rational pharmacotherapy, acute and ambulatory care, pain, analgesics, opioids, Czech Republic



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