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RIGOROUS THESIS

EVALUATION OF THE RACIONALITY OF PHARMACOTHERAPY IN GERIATRIC PATIENTS IN AMBULATORY AND ACUTE CARE – ANALYSES OF PAIN TREATMENT AND USE OF OPIOIDS

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Declaration:

I declare that this thesis has been composed by myself under the supervision of Assoc. Prof. Daniela Fialová, PharmD, Ph.D. and that the work has not be submitted for any other degree or professional qualification. I confirm that the work submitted is my own work to which my supervisor and statistician contributed. As well as complete lists of all tested anticholinergic and sedative medications have been worked out by other students and collaborators in the research group entitled "Ageing, Polypharmacy and Changes in the Therapeutic Value of Drugs in the Age" chaired by Assoc. Prof. Daniela Fialová. All relevant works have been cited in this rigorous thesis.

In London, 21.06.2022 Adriana Slaná, MSc.

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ABSTRACT

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 coanalgesics 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 derivates (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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ABSTRAKT (CZECH)

Úvod: Závažným problémem geriatrické léčby je výběr nejvhodnějšího a nejbezpečnějšího lékového režimu. Geriatričtí pacienti často trpí mnohými zdravotními problémy a zejména senioři s nekompenzovanou bolestí mají sklon k polyfarmakoterapii, většinou iracionální. Tato studie popisuje prevalenci bolesti a užívání opioidů ve dvou prostředích zdravotní péče (akutní a ambulantní) v České republice a analyzuje negativní důsledky spojené s užíváním opioidů v kombinovaných lékových režimech.

Metodika: Data pro rigorózní práci byla sbírána mezi lety 2018-2019 v odlišných zdravotnických zařízeních v České Republice v rámci výzkumného projektu EUROAGEISM H2020 ESR7. Výzkumu se zúčastnilo 1152 pacientů ve věku 65 let a více, kteří byli vyšetřeni v nemocničních (N=589) nebo ambulantních (N=563) ve větších zdravotnických zařízeních ve 4 městech (Praha, Brno, Hradec Králové a Opava). Data byla zaznamenávána s pomocí strukturovaného dotazníku po rozhovoru s pacientem, personálem nebo po nahlédnutím do zdravotní dokumentace. Formulář projektu byl založen na prospektivní vyšetřovací metodě CGA (z angl. Comprehensive Geriatric Assessment - Komplexní geriatrické vyšetření) a obsahoval otázky týkající se sociodemografických charakteristik, funkčního stavu, životosprávy pacienta, využití zdravotních služeb, klinických ukazatelů, laboratorních hodnot a farmakoterapie. Pacienti, kteří byli v terminálním stádiu nemoci, trpěli poruchou řeči nebo sluchu nebo měli výsledné skóre MMSE (Mini-Mental State Examination) vyšetření <10 byli ze studie vyřazeni. Další část výzkumu zahrnovala hodnocení asociací mezi počtem užívaných ACH léčiv/anticholinergní aktivitou lékového režimu a negativními ACH symptomy. Data byla zpracována ve statistickém softwaru R, verze 4.0.5. Základní deskriptivní analýza s pomocí deskriptivní statistiky se zaměřila na porovnání základních charakteristik pacientů a prevalencí léčiv mezi pacienty v akutní a ambulantní péči. Spojité proměnné (např. věk) byly popsány průměrem, směrodatnou odchylkou (SD), mediánem, minimem a maximem a kategorizované proměnné (např. pohlaví) absolutními a relativními četnostmi (procenty). Průměrný věk pacientů v akutní a ambulantní péči se porovnával dvourozměrným t-testem. Rozdíly v četnostech kategorizovaných proměnných (např. počet léčiv apod.) byly vyhodnoceny chí-kvadrát testem (pokud všechny takzvané očekávané četnosti byly větší než pět), nebo Fisherovým exaktním testem (pokud alespoň jedna očekávaná četnost byla menší nebo rovna pěti). Pro hodnocení závislosti počtu anticholinergik (a anticholinergní aktivity lékového režimu) a počtu anticholinergních symptomů byla použita ordinální logistická regrese. Asociace mezi počtem anticholinergik a jejich aktivitou byla vyhodnocena Kendallovým korelačním koeficientem. Výsledky byly považovány za statisticky významné, pokud dosažená hladina významnosti *p* byla nižší než 0.05. Při analýze nebyly zohledněny všechny zavádějící faktory a byly použity jen

základní statistické metody. Struktura chybějících hodnot nebyla analyzována. Prezentovaná statistická analýza je základem pro formulování dalších statistických hypotéz a aplikaci složitějších vícerozměrných statistických metod.

Výsledky: V akutní péči bylo v souboru zařazeno 43.5 % mužů a 56.5 % žen, v ambulantní péči 21.1 % mužů na 78.9 % žen. Bolest se vyskytovala u 335 (56.9 %) pacientů v akutní péči a 334 (59.3 %) pacientů v ambulantní péči. V analyzovaném souboru užívalo opioidy 191 (16.1 %) pacientů (v akutní péči 132 (39.4 %), v ambulantní péči 59 (17.7 %)). 150 (13.0 %) seniorů užívalo slabé opioidy nebo jejich kombinace, 34 (3.0 %) užívalo silné opioidy nebo jejich kombinace a 7 (0.6 %) jedinců bylo zahrnuto v obou skupinách, jelikož užívali jak slabé, tak silné opioidy. Významné rozdíly byly zaznamenány v zastoupení různých typů bolesti v akutní a ambulantní péči: chronická bolest (29.0 %, 55.4 %), akutní bolest (29.2 %, 8.5 %) a průlomová bolest (7.5 %, 2.0 %). Většina pacientů v akutní péči (58.8 %) trpěla bolestí několikrát za den, zatímco v ambulantní péči většina pacientů (54.8 %) uváděla bolest minimálně 2-3x za týden, ale ne každý den. Lokalizace bolesti byla vyhodnocena v akutní péči následovně: v oblasti nohou (15.3 %), hrudníku (9.0 %) a zad (8.1 %). Mezitímco v ambulantní péči byla bolest nejvíce lokalizována v kolenou (19.5 %), páteři (14.2 %) a v zádech (12.1 %). Příčinou bolesti v akutní péči byly nejčastěji zlomeniny (8.8 %), neuropatie (6.5 %) a osteoartritida (12.1 %); v ambulantní péči se nejčastěji jednalo o osteoartritidu (26.6 %) a vertebrogenní algický syndrom (VERTAS) (18.1 %). Opioidy byly nejčastěji používány v akutní péči u pacientů na bolesti související se: zlomeninami (22.0 %), neuropatiemi (12.9 %) a VERTAS (9.1 %). V ambulantní péči se jednalo o pacienty s: VERTAS (39.0 %), osteoartritidou (37.3 %) and neuropatií (8.5 %). V analyzovaném souboru byla předepsána u pacientů s bolestí v akutní a ambulantní péči nejčastěji tato analgetika: pyrazolony: zejména metamizol (29.4 %, 12.4 %) a anilidy: zejména paracetamol (11.9 %, 4.4 %). Co se týče koanalgetik, nejčastěji se vyskytovaly v souboru akutní a ambulantní péče antipsychotika (21.4 %, 19.4 %), antidepresiva (21.2 %, 27.4 %), antikonvulsiva (16.6 %, 13.5 %), anxiolytika (15.1 %, 14.6 %) a BZD (14.8 %, 14.4 %). 16.8 % pacientů v akutní péči a 8.3 % ambulantních pacientů užívalo slabé opioidy v kombinaci s anticholinergním nebo sedativním léčivem. Silné opioidy byly předepsány v kombinaci s anticholinergním nebo sedativním léčivem u 5.9 % seniorů v akutní a 1.1 % v ambulantní péči. Alespoň jeden nežádoucí anticholinergní účinek byl nalezen u 35.0 % a 37.8 % pacientů v akutní a ambulantní péči. K nejčastějším potenciálním nežádoucím účinkům patřila fibrilace síní v obou typech péče (34.1 % akutní, 21.3 % ambulantní) a zácpa (14.6 %, 8.5 %). Většina akutních a ambulantních pacientů užívala některý z anticholinergních léků – alespoň jeden anticholinergní lék byl předepsán v akutní a ambulantní péči u 33.6 % a 26.6 % pacientů, dva anticholinergní léky byly předepsány u 23.3 % a 23.6 % pacientů a více než tři anticholinergní léky

u 24.3 % a 21.1 % pacientů. Slabá anticholinergní (ACH) aktivita lékového režimu (0.6-1.4) byla potvrzena u 31.6 % a 24.2 % pacientů; střední ACH aktivita (1.5-2.4) u 21.2 % a 22.2 % a silná (2.5+) u 27.5 % a 25.0 % akutních a ambulantních pacientů. Výsledky asociační analýzy poukázaly na významnou korelaci mezi anticholinergními léky/anticholinergní aktivitou lékového režimu a výskytem anticholinergních symptomů ($p < 0.001$). Minimální rozdíly byly zaznamenány mezi akutní a ambulantní péčí, ale i mezi pohlavními nebo v závislosti na užití opioidů v lékovém režimu.

Závěr: Zjistili jsme, že většina opioidních analgetik byla předepsána seniorům v akutní péči a zpravidla se jednalo o slabé opioidy nebo jejich kombinace. Výsledky asociační analýzy poukázaly na vysokou korelaci mezi užitím anticholinergních léků /anticholinergní aktivitou lékového režimu a výskytem potenciálních anticholinergních nežádoucích účinků. Účinná a bezpečná léčba bolesti ve stáří vyžaduje kontinuální monitorování účinnosti a bezpečnosti předepisovaných lékových režimů.

Klíčová slova: potencionálně nevhodná léčiva, senioři, racionální farmakoterapie, akutní a ambulantní péče, bolest, analgetika, opioidy, Česká republika

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1. INTRODUCTION

The world population has been experiencing a rise in the number of seniors in almost all countries since 1950. The fastest pace of ageing can be noticed in Eastern and South-Eastern Asia and in Latin America and the Caribbean, where the percentage of older population has almost doubled from 1990 to 2019 [1].

From the demographic point of view, fertility, mortality and migration determine the size and age composition of the population. Declining fertility which led to a continuously higher share of older people in the global population and extension of human longevity, associated with the global population growth, contribute dramatically to an inevitable shift in the population age and an increase in prevalence of older individuals in the population. Moreover, age structure in some countries changed significantly due to a massive international migration and, on the other hand, migrants are usually in the younger working age categories [1, 2]. However, migrants who stay in the country for long term will definitely also age and thus will belong to the older population in the next decades. Needless to say, ageing of the world population is one of the most notable trends playing an important role in transforming society including family structures, labour, financial markets, demands for goods and services. Population growth, ageing, urbanization and international migration will have a significant impact on sustainable development in upcoming decades. For this reason, all United Nations Member States in 2015 adopted The 2030 Agenda for Sustainable Development which tackles and recognizes these changes faced by the world [1].

Demographic development of the Czech Republic was largely influenced by the post-war period which came after the Second World War since the government measures targeted newly married couples and families with children whom they provided with financial benefits. Between 1990-1996 the total fertility rate slightly decreased (from 1.89 to 1.2), however from 2004 there was an increase in fertility and natality as the majority of cohort reached reproductive age [3, 4].

The Czech Republic, like other countries, is currently experiencing population ageing. This phenomenon is reflected in the increasing median age of the population which was 39 years in 2001, in 2017 it was 42.4 years and it is predicted to be 46.3 years until 2050 [3]. According to the Czech Statistical Office, population age categories 15-64 should include 6 million people in 2050, which is about 9 % less than in 2018 [3, 4, 5].

The biggest organization in the Czech Republic advocating for improvement of the quality of healthcare delivered to seniors is Czech Society for Gerontology and Geriatrics (CGGS). It

was also supportive organisation when establishing the Department of Gerontology and Geriatrics at the 1st Faculty of Medicine of the Charles University in Prague in 1974 which helped to give a rise to geriatric medicine as an independent medical subspeciality [5].

Even though longevity is a huge achievement of modern society, there are various questions aiming how different countries are prepared for the advanced population ageing and associated economic changes, changes in the labour market, well-being of seniors and availability of health care facilities infrastructure [6].

With the increasing age, polypharmacy and polymorbidity are very frequent phenomena significantly influencing quality of life and mortality in older groups. Many European and non-European countries face the challenges; costs of treatments increase as the use of polypharmacy increases with the population ageing.

The definition of polypharmacy or polypragmasia is the usage of multiple drugs, usually more than four. Some scientists also use term excessive polypharmacy when the patient takes more than nine drugs and minor polypharmacy in case the patients are exposed to two to four medications. When patients' health status changes, drug-related problems (DRP) can be suspected, especially when polypharmacy or inappropriate drugs are prescribed. Nonetheless, polypharmacy does not need to have always negative connotations if a polymorbid individual is treated by multiple medications and it´s proven at the individual level that the whole larger list of drugs is beneficial. Myocardial infection is a concrete example of a disease where four drug groups (antiplatelet agents (or anticoagulants in patients with atrial fibrilations)), statins, beta-blockers and inhibitors of angiotensin-converting enzyme (or sartanes)) are commonly prescribed according to current guidelines for secondary prevention. However, polypharmacy frequently represents a significant risk of harm for the patient [7, 8].

There are different explicit criteria which help prescribers to identify high-risk medications and at the same time to prevent prescription of unnecessary medications in older patients. Among these criteria can be stated Beers criteria 2019 [9], STOPP/START criteria [10], Australian medication use and prescribing indicators [11], NORGEP criteria [12], PRISCUS and FORTA (Fit for the age) criteria [13] and the others. Despite the fact that the first explicit criteria of potentially inappropriate medications in the aged (PIMs) have been published in 1991, it was found by current systematic literature reviews that the prevalence of using PIMs is still very high-pooled prevalence of 22.6 % was documented in European community-dwelling older adults and 49.0% in institutionalized older people in nursing homes in the systematic literature reviews from 2019 with high variations across countries [14].

This thesis focuses on pain management, use of opioids and their negative side effects, particularly anticholinergic and sedative side effects when these medications are prescribed to older persons. Negative outcomes of anticholinergic and sedative medications can be more pronounced in older adults in comparison with younger individuals due to the significant physiological and pharmacological changes accompanying ageing. Also, other prescribing-related factors such as polypharmacy, multimorbidity and geriatric syndromes can potentially further increase the clinical significance of anticholinergic and sedative complications or adverse drug effects.

An Australian cohort study reckoned that 22.3 % of adults over 60 years were prescribed one or more anticholinergic medications. In other countries prevalence was 21-50 % depending on the method of measuring anticholinergic burden [15]. In a meta-analysis conducted by Ruxton et al. [16] it was clearly proven that there is an increased risk of falls, cognitive impairment and higher all-cause mortality in seniors when anticholinergic medications were prescribed. Higher risks of dementia and mortality have been associated with greater cumulative burden caused by cumulative use of anticholinergics. Adverse reactions in the peripheral nervous systems included mainly dry mouth, urinary retention, constipation and paralytic ileus, increased heart rate, blurred vision and others [16, 17, 134]. Despite recommendations to avoid using anticholinergic medications in older people since there are possible associations with long-term negative outcomes as well as known immediate anticholinergic side effects, anticholinergic drugs remain widely prescribed in higher age groups [18].

The aim of some research teams is to develop a risk scale which could enable medication review thus concrete drugs can be either stopped or altered in order to reduce the burden. Unfortunately, there is not any best single anticholinergic burden scale helping to evaluate medication appropriateness in older or frail patients who take multiple medications. Varying scales have been compared, but limitations include differences in exposure to medicines, dosing, route of administration and false positive outputs. Furthermore, a single drug with high-level of anticholinergic burden can cause the same anticholinergic burden as an increased dose or combination of multiple low-level anticholinergic drugs. The dosage information and sedative drugs are tackled in The Drug Burden Index (DBI). Moreover, there are polypharmacy guidance lists such as Cognitive Burden Scale, Anticholinergic Drug Scale and the Anticholinergic Risk Scale (ARS), which rank anticholinergic effects from 1 till 3 [19, 20, 21].

Drugs with anticholinergic activity are used for multiple conditions, such as urinary dysfunction, peptic ulcer disease, irritable bowel syndrome as well as treatment of neurologic or psychiatric conditions [17]. They are often used in combination resulting in cumulative anticholinergic burden. It can be clearly seen that evidence of anticholinergic adverse events in older adults has been growing and pharmacists were often involved in reviews and prevention of anticholinergic burden in older adults [15].

The content of this thesis focuses on pain management in older people, because older people suffering from pain and particularly inappropriately resolved pain are often users of multiple combinations and often suffer from various negative symptoms. The incidence and prevalence of certain pain syndromes increase with patients' age. Moreover, some older patients incorrectly reckon that pain is a normal process of aging and then pain syndrome can be underreported, undertreated and various complications may occur. With regards to the pain management, comprehensive pain assessment including thorough medical history, physical examination, relevant laboratory results, imaging studies and diagnostic tests are essential [22].

In the study of Zimmer et al. published in 2020 [23], pain prevalence ranged from 30 % to about 60 % in adults aged 50 and older across Europe. The similar prevalence has been shown in other studies, e.g., in the study of Breivik et al. published in 2006 which stated that more than a half (66%) of patients experienced moderate pain (5-7) on a 1-10-point numeric rating scale (NRS) scale and 34% were suffering from severe pain (8-10) [24]. Zimmer et al. found out that prevalence ranged form a low prevalence in Netherlands (40.7 %) to a high in Italy (56.2 %). The study concluded that despite differences across countries, in the most of them (but not all) the number of individuals suffering from pain increased during the studied timeline. 9 of 15 countries showed a statistically significant rise in either the earlier or later period. These countries included Germany (54.4 – 65.7 %), France (54.7 – 62.0 %), Spain (52.4 – 56.3 %), Switzerland (42.3 – 45.9 %) and Netherlands (40.7 – 42.6 %) [23, 24].

VAS (Visual Analogue Scale) and NRS are equally sensitive in assessing pain after surgery and for description of subjective feeling of the intensity of pain [25]. There are other assessment tools such as Abbey Pain Scale, Behavior checklist, CNPI (Checklist of Nonverbal Pain Indicators), CPAT (Certified Nursing Assistant Pain Assessment Tool), Mahoney Pain Scale and NOPPAIN (The Non-Communicative Patient's Pain Assessment Instrument). However, it was suggested to review these tools as evidence showed that validation and clinical utility is insufficient [26, 136].

In practice, weak opioids are used for mild to moderate pain alone or in combination with adjuvant analgesics (coanalgesics). After consideration of recommendations by European Association for Palliative Care, WHO analgesic ladder compromising of addition of opioids is put into practice. Supportive drugs (laxatives and antiemetics) are used for the prevention and treatment of opioids´ adverse effects. Often, NSAIDs, glucocorticoids and bisphosphonates are combined with opioids, along or with local or systematic radiotherapy or chemotherapy. Also, N-methyl-D-aspartate (NMDA)- receptor antagonists are recommended for use in combination with opioids in patients who suffer from severe neuropathic pain and spasmolytics in patients with bowel obstruction [27].

Needless to say, opioids play a controversial role in chronic pain management as it triggers a great level of debate that opioid treatment places patients at risk of various adverse outcomes such as gastrointestinal symptoms of nausea, vomiting and constipation; dependency and dosage tolerance; endocrine disorders; opioid-induced hyperalgesia and overdose or death. Overall profile of polypharmacy cannot be overlooked as it increases the potential for adverse interactions and side effects [28].

Harden el al. established The Medication Quantification Scale (MQS) [29], which is an instrument used for quantifying the cumulative detriment of medication regimen in chronic pain populations. The detriment is defined as “the potential to produce acute or chronic adverse effects in patients with chronic non-malignant pain”. Therefore, this scale has the ability to capture the potential for toxicity, dysfunction, drug-drug interactions, addiction potential, abuse potential, insomnia and tolerance. It was found out that higher level of medication detriment correlates with pain intensity, pain-related disability and mood disturbance and reduced quality of life [29].

Consumption of opioids has been increasing since the 1990s especially for the treatment of non-cancer pain. Several barriers such as restrictive laws and governmental regulations, fears of possible addiction, lack of adequate training, awareness among healthcare professionals, limited economic resources and restricted formulary availability of opioids attributed previously to the lower availability of opioids. Inadequate treatment of pain in some countries was also due to social, cultural and educational factors. Even though, there were large disparities in availability and usage of opioid analgesics across Europe. WHO and other organizations took as one of the priorities to guarantee the availability and best treatment for the relief of pain in all patients at need [28, 30]. However, nowadays, opioid consumption has levelled off in many Western and Northern European countries and in many cases their consumption is rather high. Another

debate arises whether the current consumption in not rather associated with unnecessary overuse of opioids and whether opioid treatment is appropriately followed in users of these medications regarding the risk of substantial side effects.

Because there are only few studies dealing with the current situation in analgetic use and use of opioids in the population of seniors in the Czech Republic, I dedicated my research to characteristics of pain and used of opioids and their anticholinergic and sedative side effects in Czech senior population. The theoretical part of rigorous thesis consists of information about pain, its assessment in older patients, use of opioids and their side effects. The practical part comprises results of analyses conducted on data collected in seniors in the Czech Republic in acute and ambulatory care as the part of EUROAGEISM H2020 ESR7 project (2017-2022) which evaluated the rationality of geriatric pharmacotherapy in more than 8 European countries. This project followed initiatives of the EU COST Action IS1402 devoted to the concept of ageism in various fields and sectors in Europe, including medication use. Aspects of ageism were further worked out in the EUROAGEISM H2020 project.

2. OBJECTIVES OF THE THESIS

This thesis is part of the EUROAGEISM H2020 project (programme ESR7) and our cohort consisted of patients who were 65 years old or more and were selected for the study in 4 regionally different parts of the Czech Republic in healthcare facilities of acute and ambulatory care.

Objectives are presented in two parts of the thesis: Theoretical part and Practical part of the thesis.

2.1. Theoretical part

The aims of the theoretical part of the thesis were to:

1. Describe issues associated with ageing in older population and current prevalence of pain in older adults using information from available websites of the Czech Statistical Office, European Commission and United Nations.

2. Present overview of options for pharmacological treatment of pain and its management including non-opioid and opioid medication in older patients and to emphasize for opioid drugs their various potential for adverse drug effects, particularly in long-term therapy including epidemiological data.

3. Present overview of options for pharmacological treatment of pain and its management including non-opioid and opioid medication in older patients and to emphasize for opioid drugs their various potential for adverse drug effects, particularly in long-term therapy including epidemiological data.

4. Prepare the design of analyses using comprehensive lists of drugs having sedative and anticholinergic activity (including opioids) and study literature sources for discussion on anticholinergic and sedative negative effects of opioids.

2.2. Practical part

The aims of the practical part of the theses were to:

1. Evaluate and compare major characteristics (sociodemographic, functional, medication-related, healthcare service utilization- related characteristics) in seniors assessed in the acute and ambulatory care in the Czech Republic during the EuroAgeism ESR7 project. The analyses were focused on patients suffering from pain and using opioids.

2. Another objective was to describe and analyse various characteristics of pain in seniors assessed during the EuroAgeism H2020 ESR7 project (duration, frequency, localization, causes of pain) and evaluate subjective efficacy of the treatment using results of VAS (visual analogue scale) before and after taking the pain medications.

3. The aim was also to analyse the prevalence of anticholinergic side effects in seniors assessed in the EuroAgeism H2020 project and to test associations between anticholinergic drugs/anticholinergic activity of drug regimens and anticholinergic side effects, as well as to test whether the occurrence of these negative symptoms increases in older adults taking opioids.

   Rigorous thesis summarizes from the theoretical and practical points of view current situation in the treatment of pain in seniors in the Czech Republic in acute and ambulatory care, as well as information on the use of opioids alone or in various drug combinations and on expected effects of these drugs. This thesis presents partial descriptive results of the EUROAGEISM H2020 ESR7 project.

3. THEORETICAL PART

Theoretical part of the thesis focuses on description of aspects of pain experienced by seniors, its management and treatment in older people. Primarily, this part is dedicated to opioids and rationality of their use in clinical practice with an emphasis on weak opioids that are more often prescribed in patients suffering from chronic pain. Side effects of opioids and opioid abuse is also described in this Theoretical part.

3.1. Pain in older adults

Pain is often falsely considered as a consequence of aging, but in fact this phenomenon always occurs due to pathology. Persistent pain is prevalent in older population and is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage for persons who are either aged 65 to 79 years old or very aged 80 and over and who have had pain greater than 3 months" [22, 31].

There are many factors contributing to the occurrence of pain such as complex cellular, molecular, and genetic factors along with their relationship to physical, psychological and environmental factors. Undoubtedly, persistent pain interferes with enjoyment of life and has detrimental impact on mood, social life, mobility and independence [31, 32].

Needless to say, an accurate pain assessment is essential for efficient strategy of pain treatment. Obstacles challenging a pain assessment, particularly in higher age groups of patients, include: underreporting of pain by patients, atypical manifestation of pain in older patients, age-associated pharmacodynamic and pharmacokinetic changes of specific drugs, other general age-related changes and misconceptions about higher tolerance or addiction to opioids. Multidisciplinary approach and the appropriate use of various treatment modalities enable physicians to provide geriatric population with suitable analgesia [31].

When treating older individuals, improving quality of life, optimizing functional independence and managing disability should be prioritized. Moreover, it is recommended to start firstly with nonpharmacological strategies (e.g.: exercise, physical therapy), but also on to underestimate or overestimate the need for drug treatment. The intension is to minimize by reducing polypharmacy drug-related complications. The important step is therefore to combine nonpharmacological and pharmacological treatment strategies [32, 33].

3.1.1. Epidemiology of pain in geriatric population

The population has been ageing and it is estimated that the age distribution over 65 years will increase to 36 % by 2050. It is also suggested that group of seniors aged 80 years and older will triple in number of individuals by 2050 as there is a huge potential to live longer. This notable rise in longevity is only a blessing if one stay healthy, active and engaged [34, 35, 36]. However, it may mean also substantial burden with increasing polymorbidity and polypharmacy in older age, or untreated pain and its´ associated burden with polymorbidity and polypharmacy. [37, 38]

Epidemiological studies on relieving pain across the lifespan mark age-related increase in the prevalence of persistent pain which is defined as pain on most days persisting beyond 3 months up until the seventh decade of life. Almost all studies show a continuous increase in pain prevalence during early adulthood (7-20%) peaking throughout late middle age (50-65; 20-80 %), followed by a plateau or decline in old ages (85+ years) (25-60 %). Pain, which peak during later middle age (55 years) includes mainly headache, abdominal pain, back pain and chest pain and then these types of pain decline. On the other hand, articular joint pain and pain in foot or legs have been registered to rise with advancing age. The frequency of pain was reported to be as high as 73 % in the community-dwelling seniors, rising up to 80 % in seniors living in care homes. Those with severe cognitive impairment or dementia experience reduction of frequency and severity of pain by 50 %. It was found out at 83 % of older veterans with chronic pain that one or more high-order physical activities were affected. Moreover, chronic pain can negatively influence mood, sleep, functions and quality of life. About 4 % more individuals with daily pain developed disability in the following year compared of those without daily pain. Moderate to severe pain-related interference with activities was reported by 19.3 % of men and 25.3 % of women in cross-sectional analysis and this interference was also directly related to advancing age (33 % in seniors 80 years and older). Older individuals suffering from pain are also at higher risk factor of falls and depression. Another group which is defined as seniors in the risk of “high negative impact” are seniors characterized by low levels of pain but high levels of functional impairment and high levels of depression as a result of higher prevalence of multiple co-morbidities [34, 35, 39].

Unfortunately, the limits of most studies include inability to incorporate the large number of questions describing pain in more details (e.g., duration of pain, severity at different times, treatment) [40]. Also, biological, psychological, socio-demographic and lifestyle determinants need to be taken into account to determine the targeted and appropriate prevention [41].

Diagram 3.1: Major localization of pain in adults aged 65 years and older (adjusted according to citation No. 39)

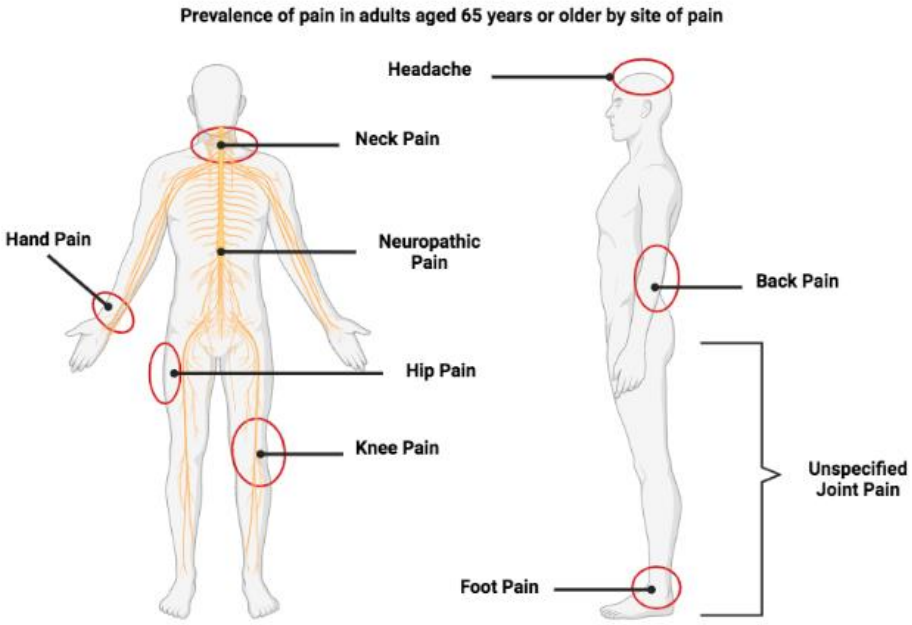


Table 3.1.: Prevalence of types of chronic and acute pain in adults aged 65 years and older (adjusted according to citation No. 39)

Prevalence of pain in adults aged 65+ years		
Site of Pain	**Acute pain**	**Chronic pain**
Headache	7-51 %	3-4.4 %
Neck Pain	16-40 %	20%
Hand pain	9-22 %	15%
Back Pain	22-33 %	5-45 %
Hip Pain	11-21 %	20%
Knee Pain	16-27 %	18%
Foot Pain	9-24 %	14%
Unspecified Joint Pain	NA	40%
Neuropathic Pain	NA	10-52 %

Note: NA: data were not available

3.1.2. Assessment of pain in older patients

The aim of pain assessment in older adults is to accurately measure an individual's pain and its impact on vital life domains. A standardized protocol comprising measurement tool is the best way how to achieve the best outcomes. Additionally, comprehensive assessment needs to take into

consideration the varying, interacting biopsychosocial factors that may contribute to the experience of pain. The biological age of the individual being evaluated is an important factor as it may impact not only the selection of tools and constructs to assess but also the goals of treatment [32].

Geriatric pain assessment is a complex clinical procedure which is influenced by several complicating factors. First of all, person's ability, willingness to engage in the assessment and visual and auditory impairment may interfere with the practical side of the evaluation. As mild cognitive impairment and age-related changes in cognitive processing also might interfere with comprehension of instructions, adding breaks and other modifications may be necessary to improve adherence. Moreover, reluctance of older patients and their various beliefs to report symptoms may be another obstacle to effective assessment. Many of older adults still believe that pain is a normal part of aging and not worthy to be treated. Another point which needs to be considered is heterogeneity which includes differentiation of the effects of normal ageing from those of age-related illnesses. Related to this, many assessors challenge how to answer basic question of how to define an "older" person because there is a wide variability in the definition of "older person" among people which age range from middle 50s to over 90 years old. It is essential to adopt a standardized biopsychosocial approach by clinicians in order to correctly assess pain in seniors. Comprehensive Geriatric Assessment (CGA) is one of such approaches used in geriatric research and clinical practice because it also includes evaluations of functional status, comorbidity, socioeconomic conditions, nutritional status, polypharmacy and geriatric syndromes in older adults such as depression, delirium, falls and others [32, 34, 42].

UK National Guidelines for The Assessment of Pain in Older People [43] were published in order to help healthcare professional to determine the appropriate assessment of pain. Other guidelines designed by National Institute for Health and Clinical Excellence (NICE) includes e.g.: Guideline scope: Chronic pain: assessment and management [44]. A multidisciplinary team tends to be the best strategy to manage pain, especially among older patients, because the biological changes and perception of pain may change and be affected by many factors [45].

Table 3.1: Attitudes of staff to pain in older people and effects upon management (adjusted according to citation No. 34)

Attitudes of staff	Effects upon pain management
Assumption that seniors are unlikely to tolerate opioids	Prescribing and administering analgesics less frequently
Lack of pain expression	Postponing and withholding of analgesia
Pain perception decreases with increasing age	Inability to think beyond the traditional regimens

3.1.3. Management of pain in older patients

When administering pharmacological treatment, one must consider that as adults grow older, changes occur in the body composition and the ability to handle drugs changes, especially in terms of drugs pharmacokinetics and pharmacodynamics. Thus, higher likelihood of drug-drug and drug-disease interactions must be considered by physicians who initiate even only one drug for the treatment of pain (usually into combined drug regimen) and the dosing must be carefully titrated when controlling pain. The biggest difference between younger patient and older one can be seen in sensitivity to analgesic medication, lesser dosage may be effective in seniors. This phenomenon is applied when using opioid analgesics. General approach is to start with lower initial dose and titrate it slowly in older adults starting with nonopioid medications for mild pain and advancing opioid treatment for those with moderate to severe pain. The exact agent should be selected in terms of underlying pathophysiology and preferred should be the one causing the fewest side effects [34, 37].

Among other principles of managing the pain in older patients is the route of administration which should be the least invasive one (oral route). Other factor is timing of medication administration. Episodic and severe pain requires treatment with drugs with rapid onset of action and short duration. On the other hand, regular analgesia (preferably modified release formulations) is the most effective in patients experiencing continuous pain. Non-pharmacological strategies such as physiotherapy, cognitive behavioural approaches and acupuncture should be put into practice in combination with medication [37, 46].

Table 3.2: Physiological changes in older people that affect drug handling (adjusted according to citation No. 46)

Physiological	Change with normal ageing	Clinical consequence of change
Absorption and functioning of GI	Gastric emptying is delayed and peristalsis reduced	Changing drug absorption has little clinical effect
	Reduced blood flow to the GI tract	Increased risk of GI-related side effects (opioid-related gut mobility disturbance)
Distribution	Volume of body water is decreased	Reduced distribution of water-soluble drugs
	Body fat elevated; lipid soluble drugs to accumulate in reservoirs	Lipid soluble drugs have longer effective half-life
	Concentration of plasma proteins lowered and free fraction of drugs that are highly bound to proteins increased	Increased potential for drug–drug interactions

Hepatic metabolism	Decreased hepatic blood flow	Reduced first pass metabolism
	Reduction of liver mass and reduced functioning of liver cells	Oxidative reactions (phase I) may be reduced, leading to prolonged half-life
		Conjugation (phase II metabolism) usually preserved
		Exact effects in an individual are difficult to expect
Renal excretion	Diminished renal blood flow, glomerular filtration, tubular secretion	Lowering the rate of excretion of medications and metabolites eliminated by kidney leads to accumulation and prolonged effects
Pharmacodynamic changes	Decreased receptor density and increased receptor affinity	Increased sensitivity to the therapeutic and side effects

3.2. WHO Three-step analgetic ladder

In 1996, The World Health Organization (WHO) revised a Three-step analgetic ladder as the guideline for treatment of cancer pain depending on intensity. These three steps are: Step 1 Non-opioid treatment of pain plus adjuvant analgesics for mild pain; Step 2 Indication of weak opioid plus non-opioid and adjuvant analgesics for mild to moderate pain; Step 3 Indication of strong opioid plus non-opioid and adjuvant analgesics for moderate to severe pain. When there is a persistent pain it is advised to move up. In case of toxicity or severe adverse reactions physicians are recommended to either reduce doses of drugs or move down one step. This method has a tremendous benefit as it can be used worldwide even in countries with fewer pain management specialists [47, 48].

During the time, notions about pain physiology and management have changed considerably as well as new opioid analgesics and other novel pharmaceuticals emerged. Many commentators appraised that it is necessary to incorporate multimodal and multidisciplinary approached into WHO Three-step ladder as it has some limitations and controversies. The major deficiency of this ladder is that it emphasizes only pharmacological treatment for pain but does not address the importance of nonpharmacological strategies and other various combinations of opioids with non-opioid therapies. These two therapeutic strategies were recommended by Centers for Disease Control and Prevention Guideline in 2016 for Prescribing Opioids for Chronic Pain [49, 50].

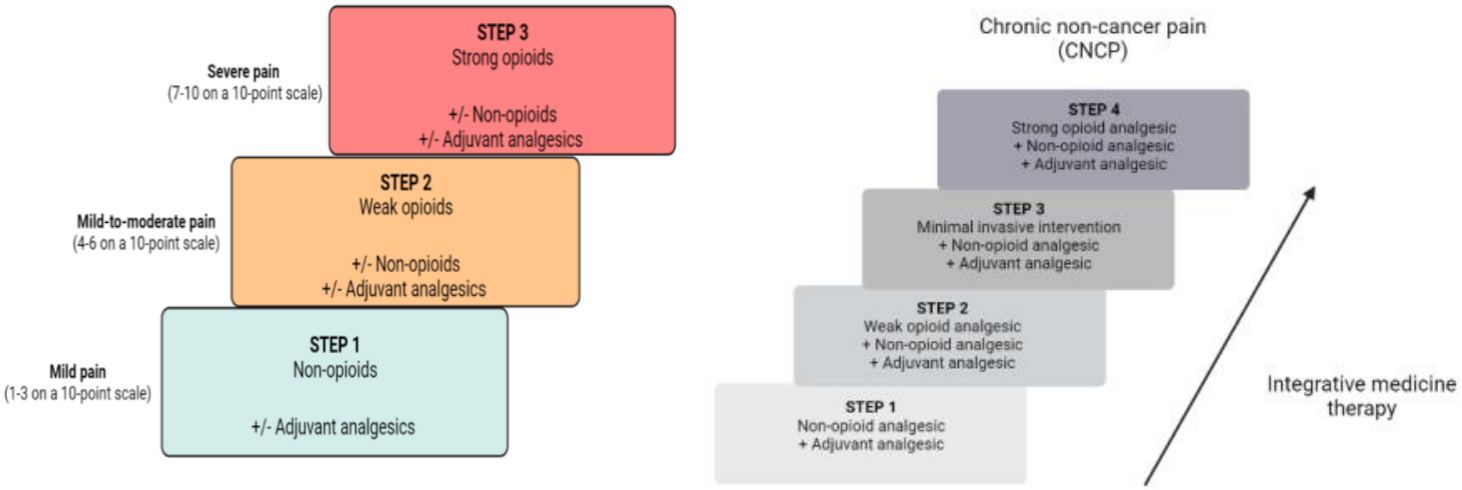
Even though integrative therapies are not shown on the original Three-step analgesic ladder diagram, they can be certainly considered at each step of the revised ladder. Minimally invasive interaction (e.g. radiofrequency, local anaesthetics, surgical intervention, disc decompression)

should be considered in step 3 when the non-opioids and weak opioids failed to control the pain. Furthermore, various factors such as economic, social and cultural determinants play an important role in consumption of opioid analgesics as opioids are used less than in Europe and the USA, especially in some Asian countries. There are studies which suggest adopting revised four-step analgetic ladder into clinical practice [47, 48].

Other issues of concern suggest that analgesic ladder was designed to be easily used even by non-pain medical experts. However, the substantial number of patients suffering particularly from unresolved chronic pain still continue to see pain specialists [48, 51].

Moreover, there is limitation to implement complicated treatment strategies because of lack of proper knowledge of drugs, risk of underdosing or overdosing, wrong timings of drugs, problems with adherence to therapy, fear of addiction in patients and lack of public awareness [52].

Diagram 3.2: Comparison of the WHO Three-step ladder designed for cancer pain and four-step analgesics ladders for chronic non-cancer pain - CNCP (adjusted according to citation No. 47, 48)



3.3. Non-opioids Analgesics

These analgesics are recommended for mild or moderate pain of musculoskeletal origin including osteoarthritis and low back pain. Paracetamol is well tolerated in older patients if both renal and hepatic functions are normal. NICE recommends acetaminophen (paracetamol) as the first-choice analgesic for low back pain and osteoarthritis. Adverse effects are rare on the renal and central nervous system or cardiovascular toxicity but prolonged use of the maximum recommended dose raise concern regarding the hepatic side effects. It is important that the recommended maximum daily dose is not exceeded [44, 46].

NSAIDs are one of the most widely prescribed classes of drugs for pain and inflammation and are more effective for persistent inflammatory pain than paracetamol. NICE recommends oral NSAIDs/selective COX-2 inhibitors in case paracetamol or topical NSAIDs are ineffective for pain relief or provide usually insufficient pain relief for people with higher stages of osteoarthritis and low back pain. NSAIDs must be used with extreme caution in older people due to a high risk of potentially serious and life-threatening side-effects such as gastrointestinal bleeding, ulceration and renal dysfunction. These side effects need to be considered especially when these nonopioid analgesics are part of palliative treatment plan. Although the likelihood of gastrointestinal symptoms can be lowered with the concomitant use of misoprostol or proton pump inhibitors (PPIs), misoprostol is not well tolerated by older people and also long-term use of PPIs may lead to significant side effects. Evidence-based assessments are fundamental to carefully weight the benefits and risks in older patients. The alternative option to NSAIDs are selective cyclooxygenase-2 (COX-2) inhibitors. However, there are concerns about their associations with heart disease and stroke. Medicines and Healthcare products Regulatory Agency (MHRA) guidance on NSAID use suggests that the lowest effective dose of NSAID or COX-2 selective inhibitors should be prescribed for the shortest necessary time [37, 46, 53].

3.4. Opioids

Oral opioids are the most potent analgesics mostly prescribed in palliative care and well established for the treatment of severe acute, surgical and cancer pain. However, their use to ameliorate CNCP (chronic non-cancer pain) is controversial as the side effects of opioids and physical tolerance create a substantial risk and build up anxiety over disapproval of opioids by regulatory bodies in many countries [47]. Opioid use might be associated with less risk than that of NSAIDs, especially in those patients who are at particular risk of NSAID- related side effects.

At WHO ladder Step 2 opioids consist generally of hydrocodone, oxycodone with the combination of paracetamol or NSAIDs. Short-acting agents like oral morphine, hydromorphone, oxycodone and codeine are used alone or in combination with ibuprofen or paracetamol in the treatment of patients with intermittent pain. While, sustained-release opioids should be given for continuous pain, possibly with short-acting preparations available for breakthrough pain. Based on the frequency of use of the short-acting preparation, the dosage of sustained-release opioids can be titrated. The peak of analgesic effect occurs within 60 min and lasts for 2-4 hours in patients with unimpaired renal functions [46, 48, 54].

Previously, opioids were considered as an appropriate medication to manage chronic noncancerous pain. However, potential harms associated with prescription of opioids analgesics are still greatly highlighted, eg. Guidelines such as Centres for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain discourage the very frequent use of opioids [49, 55]. NICE in England has been aiming to publish updated guideline on the management of chronic non-malignant pain (CNMP) including rational prescribing of opioids as there is an increasing trend in deaths associated with more potent opioids. To illustrate, fentanyl-related deaths in England increased from eight in 2008 to 135 in 2017. These guidelines were not updated optimally because they do not clearly state care and support for practical daily decisions in management [56, 57].

3.4.1. Weak opioids

These opioids are usually prescribed for mild-to-moderate pain. Their usage is limited due to adverse effects and as an alternative a low dose of a more potent opioid such as morphine may be better tolerated.

3.4.1.1. Tramadol

Tramadol is a synthetic codeine analogue that is a weak agonist of MOR (μ-opioid receptors) which inhibit uptake of norepinephrine and serotonin which cause analgesic effect. In the treatment of mild and moderate pain, tramadol is as effective as morphine or meperidine but for the severe and chronic pain is less effective [46, 58].

In terms of side effects, tramadol may have less effect on respiratory and GI function than other opioids but confusion might be a problem for seniors. In patients with the history of seizure is tramadol contraindicated and also needs to be use with caution in patients taking serotoninergic drugs since serotonin syndrome has been reported in these patients. Older people require 20 % less doses of tramadol than younger generation despite the fact that the pharmacokinetics remained unaffected by age [46, 58, 59].

3.4.1.2. Dihydrocodeine

Dihydrocodeine is a semisynthetic analogue of codeine with 10 % of the potency of oral morphine and is slightly more effective analgesic than codeine but less effective than tramadol. DHC exerts analgesic action through affinity to μ, kappa and delta opioid receptors [58].

As a result of central actions, dihydrocodeine is used for suppression of cough where lower doses are needed than for analgesia. Higher doses then produce even more antitussive effect [58, 60, 61].

3.4.1.3. Codeine

Codeine is found naturally in poppy seed and it is a methylated morphine derivate displaying analgesic and antitussive activity. It has exceptionally low affinity for opioid receptors and the analgesic effect is because of conversion to morphine. Despite the fact that some preparations may be prescription controlled, many of preparations are readily available and easily accessible in combination therapies with antihistamines, antipyretics, decongestants or expectorants as over-the-counter, non-prescription cough syrups or lozenges in some countries. The ease of availability of such treatments has likely contributed to a perception of their safety and efficacy in society thus this phenomenon has contributed to a widespread use of codeine and its combinations in countries where non-prescription preparations are available [59, 62].

3.4.1.4. Other weak opioids

Pentazocine is a benzomorphan derivate which has mixed agonist and antagonist actions which can precipitate withdrawal in opioid-tolerant patients in combination with naloxone. Another weak opioid is nalbuphine which is competitive MOR antagonist exerting analgesic activity by acting as agonist at KOR receptors (κ-opioid receptor). Additionally, meptazinol is an opioid with mixed agonist/antagonist properties which is usually used in obstetrics or following surgery [58, 63].

3.4.2. Strong opioids

The World Health Organization (WHO) guidelines recommend using strong opioids only as third-line therapy and data also suggest the utility of strong opioids for the first-line treatment of pain in patients with terminal cancer. All incurable oncologic patients demonstrated safety of opioid analgesics and a strong opioid should be administered independently of the intensity of pain especially due to quick progression of disease and reduced life-expectancy. Also, literature well establish the necessity of strong opioid in the treatment for severe pain (VAS > 7). Due to a wide therapeutic efficacy and tolerability, strong opioids should be considered as a very important instrument in the care of the intractable patient [64, 65].

Apart from WHO Three-step ladder which was initially targeted at the treatment of cancer pain, there are numerous societies and agencies which published guidelines for the use of strong opioids in treating pain such as the American Academy of Pain Medicine, the American Pain Society, Federation of State Medical Boards and the Drug Enforcement Agency. Strong opioid group includes drugs such as morphine, pethidine, hydromorphone, methadone, oxycodone, fentanyl, tapentadol, buprenorphine, piritramide and diamorphine [58, 66]

3.5. Characteristics associated with opioid prescribing

3.5.1. Risk-benefit of prescribing opioids

Despite numerous recommendations of opioid therapy in patients with chronic pain, many physicians remain uncertain about prescribing these drugs. Minority of physicians argue that opioids have a minimal effect on the pain and may even worsen the outcome. Some of them are "scared" of prescribing opioids because of the affair of opioid addiction and overprescribing opioids in early to mid-1990s in the USA. A question about opioid addiction arose about developing countries, however, there is no updated statistics available which could give us reliable data [28, 67].

In terms of prescription drug abuse, many research papers indicated that this trend seems to be heavily localized in rural, suburban and small urban areas. An important moment is to identify the problems and consequences associated with the initiation of opioid misuse (e.g., pain relief, management of stress, depression or anxiety) as we could understand the motive behind these issues. Patients' initiation opioid treatment should be monitored for development of adverse reactions so that adequate measures can be taken. The key is not to return to the middle ground where opioids can be used for treatment of certain types of pain. The challenging part is to define the middle ground and achieve the appropriate risk-benefit ratio [28, 30, 67, 68, 69,70].

3.5.2. Clinical studies

Generally, patients with chronic pain not associated with terminal disease can achieve satisfactory analgesia by using stable dose of opioids with a minimal risk of addiction if the length of treatment is up to six years. Studies have shown that cognitive function including ability to drive and operate machinery is preserved in these patients. However, cognitive functions may be negatively influenced up to seven days after an increase of dose [67].

Short intravenous infusions of opioids confirm responsiveness of various pain syndromes. Treatment of neuropathic pain was shown to be effective if an adequate dose can be reached providing analgesia without side effects. Some studies indicated that the neuropathic pain is opioid-resistant; resistance of neuropathic pain to opioids is relative. Guidelines on chronic pain agree on few strategies which could help to mitigate the risks associated with taking opioids (e.g.: attention to drug-drug and drug-disease interactions, using assessment tools, treatment agreements and urine drug testing [28, 67, 71, 72].

3.5.3. Adverse outcomes

3.5.3.1. Opioid tolerance and physical dependence

Opioid tolerance is a pharmacological phenomenon which arise form repeated use of opioids and cause the need to increase the dose to maintain equipotent analgesic effects. Physical dependence is the process which alters physiological state that is revealed by an opioid withdrawal syndrome involving autonomic and somatic hyperactivity. Tolerance can be distinguished between associative (learned) and nonassociative (adaptive) tolerance depending which neurotransmitter mechanism is involved. Associative tolerance is linked to environmental clues and involves also psychological factors which can be noted when there is a marked reduction in opioid tolerance. Also, learned tolerance results in a decrease in efficacy as compensatory mechanisms are incorporated or learned. Non-associative tolerance is an adaptive process involving down-regulation or desensitization of opioid receptor or both. In patients receiving prolonged opioid therapy, increased expression of the endogenous opioid dynorphin has been noted. However, the precise mechanism of this effect is unclear. Evidence and research suggest that NMDA receptors are involved [67, 73].

3.5.3.2. Opioid-induced abnormal pain sensitivity

Apart from a diverse array of side effects related to activation by peripheral and central mechanism there are also changes induced by central mechanism associated with hyperalgesia [28].

During the inflammatory phase of the nerve injury, abnormal pain sensitivity occurs caused by long-term use of opioids. This is manifested as increased pain from noxious stimuli (hyperalgesia) and as pain previously innocuous stimuli (allodynia). Studies have shown that NMDA-receptor-mediated changes that trigger abnormal pain sensitivity occurring in spinal cord dorsal-horn cells

after repeated exposure of opioids. Analgesic tolerance and opioid-induced hyperalgesia are related phenomena and both may have important clinical implications [28, 67].

Continuous administration of opioids not only results in the development of tolerance (desensitization) but also leads to a pro-nociceptive (sensitization) process. Both of these occurrences are results from prolonged opioid therapy which may contribute to a significant decrease in analgesic efficacy. Hence, the necessity to escalate the dose of opioids may be the result of pharmacologic opioid tolerance, opioid-induced abnormal pain sensitivity or disease progression [28, 54, 67].

3.5.3.3. Opioid-induced hormonal changes

Opioids influence two levels in the endocrine system: hypothalamic-pituitary-adrenal axis and also on the hypothalamic-pituitary-gonadal axis which result in reduced serum of luteinizing hormone, follicle-stimulating hormone, testosterone, oestrogen, cortisol level and increased prolactin level. Accumulated effect of the hormonal changes at chronic opiate users may lead to diminishing bone density, decreasing libido, aggression, irregular menses, galactorrhoea and impaired sexual performance [54, 67, 74].

3.5.3.4. Opioid-induced immune modulation

Opioids can have various impact on the immune system and differential interaction within immunocytes, some might be immunosuppressive whereas others tend to have immunostimulatory effect. There are many studies showing that individual opioids can affect the immune system in different ways. Short term/low dose administration of opioids may seem to have positive impact on the immune system, but long term/high dose has a negative impact. Bone marrow progenitor cells, macrophages, natural killer cells, immature thymocytes and T-cells, and B-cells are all involved. Opioids play also various roles in inflammation, cancer process and addiction because of their different effect on the immune system. On one hand, they could prevent inflammation, inhibit tumor growth and ameliorate addiction, but they could additionally aggravate inflammatory reaction, help the tumor escape from the immune immunosurveillance, induce addiction and increase the rate of infection [67, 75].

3.5.3.5. Opioid-induced sedation

The sedating effects of opioids are believed to be caused by the anticholinergic activity. Dose initiation and rapid dose escalation may result in drowsiness and consequently lead to nonadherence and/or reduced quality of life [73]. Also, interactions of opioids with other central nervous system sedative drugs such as barbiturates, benzodiazepines, antidepressants and antipsychotics may have additive effects on sedation [54, 76].

3.5.3.6. Opioid-induced constipation

Constipation is a common problem which occurs in 40% to 45% (up to 90%) of patients treated with opioids which can lead to significant morbidity and mortality. Thus, prophylactic treatments are vital to minimize complications such as haemorrhoids formation, rectal pain and burning, bowel obstruction and potential bowel rupture. It is not clear whether constipation is predominantly centrally or peripherally mediated. The constipating effects of opioids seem to be dose-related and tolerance to this symptom rarely develops [73, 77, 78].

3.5.3.7. Opioid-induced bladder dysfunction

Bladder dysfunction caused by opioids (difficulty voiding, urinary retention) occurs due to anticholinergic effect of opioids and it is a significant problem in postoperative patients. However, it is difficult to estimate as many other factors can play a role. About 10 % of this phenomenon is assigned to various medications such as anticholinergic respiratory inhalants, antidepressants, antipsychotics, opioids, alpha agonist and calcium channel blockers [73, 79].

3.5.3.8. Cardiac effects of opioids

Side effects on cardiovascular system caused solely by opioids are not very common but when combined with other medications there can be significant changes in cardiac function. The administration of several opioids can lead to vagus nerve-mediated bradycardia. Moreover, acute administration of opioids can lead to vasodilatation and decreased sympathetic tone. Cardiac output can be significantly decreased when opioids are administered with benzodiazepines. Potentially, major cardiovascular effects can be observed when opioids are administered with inhaled anaesthetics [73, 80].

3.5.4. Epidemiology of potential adverse effects of long-term opioid therapy

The outcomes of clinical studies related to long-term opioid therapy varies but approximately 20-45 % of patients will tolerate and benefit from chronic usage of opioids without significant side effects [81].

Constipation is a prevalent side effects reported by 40-45 % of patients on opiate therapy, while 25 % experience nausea. Some studies suggest that up to 90 % of patients who take opioids suffer from constipation which can occur with a single dose [82, 83].

In terms of respiratory system effects, sleep-related breathing disorders are observed in 3 %-20 % of population however opioid therapy lasting at least 6 months increases the likelihood of developing sleep-related breathing disorder (ranging from mild to severe central and/or obstructive apnoea) up to 75 % of patients. About 10 % of patients on chronic opiate therapy experience some degree of hypoxemia. Ataxic breathing has been observed at patients taking morphine; it has occurred in up to 92 % of individuals taking a morphine-equivalent dose of 200 mg, 61 % of individuals taking under 200 mg and 5 % of individuals not taking opioids. Respiratory depression, bradycardia and hypotension can be potentially life-threatening side effects of opioid therapy, which occur in opioid overdose. There was a substantially increased risk of overdose at patients who had prescribed larger opioid doses. Literature has demonstrated 8.9-fold increase among patients prescribed > 100 mg/day (relative to patients on opioid regimens of less than 20 mg) and 3.7-fold increase among patients prescribed > 50 mg/day. Additionally, 12 % of identified overdoses were fatal, suggesting an annual fatal overdose risk of about 2 per 1000 per year among patients on higher-dose opioid regimens. Opioid misuse in the United States and Canada involve about one-quarter of prescribed patients thus the phenomenon is considered quite common in these countries [83].

Opioid therapy was also associated with an increased risk (77 %) of myocardial infection and cardiovascular revascularization among individuals on long-term opioid therapy relative to general population. During the first 30 days, the risk of cardiovascular events was similar across different opioid medications. However, after 180 days of therapy, codeine was associated with a 62 % increase in these adverse events compared to hydrocodone [83].

Endocrine system is affected as soon as the opioid therapy starts. There are many studies in this area but the majority of them are small. Therefore, it is difficult to precisely estimate the percentage of influenced individuals. Some evidence indicates that the prevalence of opioid-induced hypogonadism in patients taking chronic opioid therapy is as high as 90 %. Potential consequences

of hypogonadism include depression, anxiety or apathy. Patients aged over 60 years taking opioids equivalent to ≥ 50mg/day morphine for pain have 10 % rate of fracture per year. These patients have a 2-fold higher risk of fracture than if they did not take opioids [74, 83, 84].

Table 3.3: Frequency of potential adverse effects of opioids (adjusted according to citation No. 83)

Medical Risk	Frequency	Description and information
Respiratory depression / Opioid overdose	< 1 % per year	Caused by severely slowed breathing
		Managed in the hospital
		Likely to cause death
Breathing problems during sleep	25%	Can cause or worsen apnea
		Not always noticeable
Falls causing hips and pelvis fractures	1 - 2 % per year	NA (most probably due to sedative side effects)
Constipation	30 - 40 %	Using stool softeners or medicines stimulation bowel movements
Serious intestinal blockage	< 1 % per year	Caused by severe constipation (treated in the hospital)
Hypogonadism, impotence, infertility	25 % - 75 %	Lowered sex hormones - worsening sexual function
Osteoporosis	25 % - 75 %	Increasing risk of fractures
Sedation	15%	Driving and thinking may be worsened
Disruption of sleep	25%	NA (see above)
Depression, anxiety, deactivation, apathy	30 % - 40 %	Loss of interest in usual activities leading to depression which can worsen pain and vice versa
Addiction, misuse, and diversion	5 % - 30 %	Misuse can occur if children or teens gain access to the medicine
Dry mouth that may cause tooth decay	25%	Important is to brush the teeth and rinse the mouth often
		Avoiding carbonated drinks and sugar
Hyperalgesia	not known	Being more sensitive to pain

3.5.5. Opioid use disorder (OUD)

OUD is a chronic, relapsing disease which has significant economic, personal and public health consequences. From 1999 to 2017, almost 400.000 people died in the USA from overdose involving any opioid which also involves prescription of illicit opioids. It was 26.8 million people who were estimated to be living with OUD in 2016, with >100.000 opioid overdose deaths annually, including >47.000 in the USA in 2017. There are other substances associated with OUD

such as tobacco, alcohol, cannabis, stimulants and BZD which are often taken to reduce symptoms of opioid withdrawal or craving for opioids. Undoubtedly, additional consequences arise such as neonatal abstinence syndrome as their mothers used these substances during pregnancy and increased spread of infectious diseases (HIV, Hepatitis C). Diagnosis of OUD is mainly founded on these criteria: loss of control, risky use, social problems, physical dependence within the same 12-month period [85, 86].

When assessing an individual, we also need to take into consideration physical evaluation and toxicology in order to diagnose OUD. Opioid agonists (methadone and buprenorphine) have great efficacy for OUD treatment but other commonly practices such as detoxification alone lack scientific evidence [85, 86, 87].

4. PRACTICAL PART

4.1. METHODS

Data for this thesis were collected as part of the EUROAGEISM H2020 project conducted between 2017-2022 and financed by Marie Skłodowska-Curie Framework for Research and Innovation of Horizon 2020 research programme, coordinated by an international consortium and the Research Executive Agency of the European Commission.

Project EUROAGEISM H2020 comprised of 15 research programs focusing on improvement of ageism in various sectors of society such as increase of active participation of seniors in labour market, better availability of goods and services to older adults, reducing aspects of age-related discrimination and promoting an age-friendly society, which should enable older adults to realize their full potential. One of the research projects under the umbrella of the EUROAGEISM H2020 project was ESR7 programme on "Inappropriate Prescribing and Availability of Medication Safety an Medication Management Services in Older Patients in Europe", chaired by Assoc. Prof. Daniela Fialová, PharmD, Ph.D. and ESR7 researcher J. Brkič, MSc. from the Charles University, Faculty of Pharmacy, Department of Social and Clinical Pharmacy. The aim of this project was to analyse current policies and prescribing practices in the area of inappropriate medication use and management of medication safety in different European countries and also in some developing countries (e.g., India and Ethiopia).

With the use of the EuroAgeism H2020 study protocol based on CGA (Comprehensive Geriatrics Assessment), extensive information was collected about 589 patients in acute care and 563 patients in ambulatory care in the Czech Republic, specifically in Prague, Brno, Hradec Králové and Opava. This thesis analysed data from both settings of care that were collected between August 2018 and January 2019 at the Department of Geriatrics of the First Faculty of Medicine of the Charles University and General University Hospital in Prague, at the Internal, Geriatric and General medicine ward of the University Hospital Brno, at the Department of Metabolic Disorders and Gerontology at the University Hospital in Hradec Králové and at the Department of Geriatrics and Internal Medicine at the Silesian Hospital in Opava, Czech Republic. Ethical committee of the Faculty of Pharmacy, Charles University approved this project, as well as Executive boards and Ethical Committees of participating healthcare facilities. The project fully followed rules of GDPR (General Data Protection Regulation), national laws regarding research and international ethical guidelines.

All patients older 65 years and older who fulfilled certain criteria and signed informed consents were included in cross-sectional observational study. Patients taking part in the study were able to answer questions alone or with the help from the healthcare staff. Seniors who were not able to communicate, were in critical health conditions, terminally ill or at ICU (intensive care unit), had serious hearing impairment or speech disorder or/and suffered from severe cognitive deficit (scored in cognitive test MMSE under 10 points) were not included in the study.

The whole sample used in analyses finally included data collected from 1152 older patients 65+ in acute or ambulatory care. Data were assessed and recoded anonymously so that the identity of individuals remain unrecognized. Information about patients was inserted under specific codes in electronic and paper forms.

Information about the patients were acquired from the interviews and additionally also from health care documentation and questions answered by healthcare professionals. All answers were recorded to standardized questionnaire of the project EUROAGEISM H2020 ESR7 which was translated by two independent researches into local languages. The questionnaire was protected research form of the project and includes 350 items related to clinical and functional status of geriatric patients, their diagnoses, symptoms, pharmacotherapy, provided healthcare services and known laboratory results from the past 7 days.

The first part of the questionnaire evaluated sociodemographic parameters (age, gender, education, marital status), functional status of older patient (ADL – Activities of Daily Living), frailty syndrome, mobility, cognitive functions (MMSE)), assessment of mood and behaviour, nutritional status (BMI, type of nutrition), lifestyle (smoking, alcohol), utilization of healthcare services (number of hospitalizations in the last year, number of visits at general practitioner or at a specialist per year, utilization of rehabilitation or other services). Another part of the protocol was dedicated to clinical characteristics, diagnosis, symptoms, characteristic of pain and history of falls followed by information about laboratory results. The last part included detailed information about medication use, including anatomical therapeutic chemical codes (ATC codes) of medications, their dosages, strengths, frequency of use and subjectively reported adherence of the individuals. Possible side effects and rationality of pharmacotherapy use at the individual level was also assessed and recorded by study researchers.

The main goal of this thesis was to determine rational treatment of pain, use of opioids and assessment whether opioid treatment increased the risk of anticholinergic side effects and complications in seniors assessed in acute and ambulatory care. All parameters were assessed for patients without pain, with pain and using opioids or their combinations.

In first descriptive tables related to pain assessment, main characteristics of pain for seniors in the sample were described- localization, frequency, cause and intensity of pain before and after medication use by evaluating with Visual Analogue Scale [25]. These characteristics were analysed by descriptive statistical methods. Numerous analgetic drugs and their combinations were also evaluated and analysed with regards to pain treatment. We described by descriptive statistics particularly prevalence of use of all analgesics used including their combinations, namely:

- Coanalgesics
- Opioids
    - Any weak opioid or their fixed combinations (no other analgesics used)
    - Any weak opioid or their fixed combinations and other analgesics
    - Strong opioids
- Anticholinergic drugs

ATC codes of analgesics and opioids were found in the database from WHO Collaboration Centre for Drug Statistics Methodology [88] because it was considered the most reliable resource. The list of analgesic drugs used for analysis was compared across numerous studies and literature sources focusing on pharmacology and pain medication use (Pain Physician Journal [89], Clinical Journal of the American Society of Nephrology [90], British Journal of Pharmacology [91]). Frequency of use of these drugs and their efficiency in pain management was also analysed.

Table 3.4 ATC codes of weak opioids and their combinations used in analyses in the practical part of the thesis

Weak opioids			
Active substances		**Combinations**	
	ATC code		**ATC code**
codeine	R05DA04	codeine without psycholeptics	N02AA59
dihydrocodeine	N02AA08	codeine with psycholeptics	N02AA79
pentazocine	N02AD01	dihydrocodeine + paracetamol	N02AJ01
nalbuphine	N02AF02	dihydrocodeine combinations	N02AA58
meptazinol	N02AX05	dihydrocodeine + ASA	N02AJ02
		dihydrocodeine + non-opioid analgesics	N02AJ03
		codeine + paracetamol	N02AJ06
		codeine + ASA	N02AJ07

		codeine + ibuprophen	N02AJ08
		codeine + non-opioid analgesics	N02AJ09
		tramadol	N02AX02
		tramadol + paracetamol	N02AJ13
		tramadol + dexketoprofen	N02AJ14
		tramadol + non-opioid analgesics	N02AJ15
		tramadol + non-opioid analgesics	N02AJ15

Table 3.5: ATC codes of strong opioids and their combinations analyzed in the practical part of the thesis

Strong opioids			
Active substances		**Combinations**	
	ATC code		**ATC code**
morphine	N02AA01	morphine + combinations	N02AA51
pethidine	N02AB02	hydromorphone + naloxone	N02AA53
hydromorphone	N02AA03	oxycodone + naloxone	N02AA55
oxycodone	N02AA05	oxycodone + naltrexone	N02AA56
buprenorphine	N02AE01	pethidine combinations without psycholeptics	N02AB52
piritramide	N02AC03	fentanyl combinations without psycholeptics	N02AB53
methadone	N02AC90	pethidine + psycholeptics	N02AB72
fentanyl	N02AB03	fentanyl + psycholeptics	N02AB73
tapentadol	N02AX06	methadone combinations without psycholeptics	N02AC52
diamorphine	N02AA09	morfin + spasmolytics	N02AG01
		pethidine + spasmolytics	N02AG03
		hydromorphone + spasmolytics	N02AG04
		oxycodone + paracetamol	N02AJ17
		oxycodone + ASA	N02AJ18
		oxycodone + ibuprophen	N02AJ19

Table 3.6: ATC codes of analgesics analyzed in the practical part of the thesis

Analgesics	
	ATC Code
pyrazolones (eg. metamizole, prohyphenazone)	N02BB*
anilides (eg. paracetamole, phenacetine)	N02BE*
acetic acid derivates (eg. diclofenac, indometacin, sulindac)	M01AB*
oxicams (eg. meloxicam, tenoxicam, lormoxicam, piroxicam)	M01AC*
propionic acid derivates (eg. ibuprofen, ketoprofen, tiaprofen, naproxen etc.)	M01AE*
coxibs (eg. celecoxib etc.)	M01AH*
other anti-inflammatory and antirheumatic agents, non-steroids (eg. nabumeton, nimesulid)	M0A1X*
other analgesics and antipyretics (eg. methoxyflurane)	N03BG*
acetylsalicylic acid and derivates (eg. acetylsalicylic acids, sodium salicylate)	N02BA*

Table 3.7: ATC codes of coanalgesics analyzed in the practical part of the thesis

Coanalgesic	
	ATC Code
Antipsychotics (promazine, haloperidol, flupentixol etc.)	N05A*
Antidepressants (desipramine, fluoxetine, sertraline etc.)	N06A*
Anticonvulsant (phenobarbital, phenytoin, clonazepam etc.)	N03*
Anxiolytics (BZDs, mephenaxolone etc.)	N05B*
Benzodiazepine derivates (diazepam, alprazolam etc.)	N05BA*
Glucocorticoids (hydrocortisone, cortison, prednison)	H02AB*
Bisphosponates (alendronic acid, ibandronic acid etc.)	M05BB*
Spasmolytics (mebeverine drotaverine, alverine etc.)	A03A*
Myorelaxans (dantrolen, baclofen etc.)	M03*
Anaesthetics local (nitrous oxid, sevoflurane etc.)	N01A*
Anaesthetics central (lidocaine, mesocaine etc.)	N01B*
Selective serotonine agonists (sumatriptan etc.)	N02CC*
Other antimigrenics	N02CX*
Antagonists of calcitonin-gene related peptide (erenumab, galkanezumab etc.)	N02CD*

As an additional goal of this thesis, we evaluated the influence of opioids on anticholinergic burden (prevalence of anticholinergic side effects), considering also burden caused by other ACH medications. For this purpose, we used the same methodology applied in diploma thesis of A.

Havrošová (supervisor Assoc. Prof. Daniela Fialová, PharmD, Ph.D.) defended in September 2020 at the Faculty of Pharmacy, Charles University, Department of Social and Clinical Pharmacy [92]. Moreover, by comparing various guidelines, literature sources and clinical research studies, the sum of anticholinergic side effects appearing in the majority of articles were selected for this thesis (see table 3.8: Anticholinergic side effect used in analyses). Study "An anticholinergic burden score for German prescribers: score development published by Kiesel et al. in 2018 was finally chose as the most adequate sources describing all different types of anticholinergic side effects [93]. Unfortunately, we were not able to analyse all relevant ACH side effects as not all of them were assessed by our researchers. Blurred vision, hallucination, delirium and confusion were considered as ACH side effects but were only assessed in acute care, These side effects were not included in our analysis as they were not evaluated in both types of care.

Table 3.8: Anticholinergic side effects used in analyses

Anticholinergic side effects	
Systemic	**Central**
Dry mouth	Hallucinations
Constipation	Cognitive impairment
Blurred vision	Confusion
Irregular heartbeat	
Urinary retention	

The list of all anticholinergic medications created by other diploma thesis students that was used in this rigorous thesis classified ACH drugs according to severity of ACH effects into 3 groups from 1 till 3 (1 = weak anticholinergic effect, 3 = severe anticholinergic effect). The final anticholinergic effect of drug regimen in our study was calculated as cumulative anticholinergic activity of all drugs in the drug regimen and these regimens were divided in our study into 4 categories: no ACH activity (around 0, (0-0.49)), mild ACH activity (around 1 (0.5-1.49)), moderate (around 2 (1.5-2.49) and strong ACH activity (around 3 and more (2.5 and more)), which can be seen in Table 4.17. If there was a discrepancy in anticholinergic activity across literature sources (SmPC, original studies – see diploma thesis of A. Havrošová), average value was applied.

Data were statistically analysed using R-software version 4.0.5. All data were repeatedly checked by several researchers after inserting data from paper forms into e-database. Descriptive statistical analysis was used for data analyses. Average age of the patients in acute and ambulatory care was compared by t-test. Chi-square test was used for comparison of the prevalences between

selected categories if all expected frequencies were at least 5, otherwise Fisher's exact test was applied.

Kendall rank correlation coefficient was used to assessed association of number of anticholinergic drugs and their activity. Ordinal regression was applied when evaluating association between the number of anticholinergics (and their activity) and the number of anticholinergic symptoms. All results were interpreted as statistically significant if the p-value (attained significance level) was less than 0.05.

4.2. RESULTS

4.2.1. Sociodemographic characteristics of the studied sample

The whole sample includes information from 1152 patients - 589 (51.1 %) assessed in acute care and 563 (48.9 %) in ambulatory care. The majority of seniors were 75-84 years old (38.5%) in acute care which was also the biggest group suffering from pain and using opioids. While in ambulatory care the biggest number of seniors using opioids fell into age category of 85-94 years (42.8 %) old patients.

In the whole dataset, there were 67.4 % (N=777) of women and 32.5 % (N= 375) of men and the proportion of women prevailed in both types of health care. Almost the same absolute number of seniors suffered from pain in acute and ambulatory care (56.7 %, 59.3 %), however, opioids (both week-15.8 %, 9.4 % and strong opioids- 5.3 %, 1.1 %) were used with higher prevalence in acute care (22.4 % users of opioids in acute care compared to 10.4 % in ambulatory care) (see also Table 4.1.1).

As for marital status, the majority of seniors were widowed (49.3 %) followed by married older patients (37.9 %). While the smallest percentage declared they are separated (1.5 %). The majority of study subjects in acute care absolved secondary schools (58.6 %), while in ambulatory patients was documented that they completed tertiary education in the most of cases (9.2 %).

The majority of older persons in the sample were able to go outside and did not need to use the device or wheelchair. The table illustrates cognitive functions of seniors included in our sample which were evaluated in some facilities (only in patients expected to suffer from cognitive impairment) using MMSE (Mini-Mental State Examination). This test was carried out at the slight majority of hospitalized individuals (53.3 %), on the other hand, outpatients' documentation did not include results from this assessment at 75.3 %. MMSE testing was not conducted in cognitively unimpaired patients, only in those with the risk of cognitive impairment.

Still, intact category also among assessed patients (in some facilities this assessment was a standard procedure during admission process of geriatric patients) presents the biggest group of patients followed by patients with moderate impairment. Interestingly, at 61.3 % patients taking opioids, MMSE was carried out.

Table 4.1: Major sociodemographic and functional characteristics of the studied sample of patients

Major characteristics	Overall cohort				Patients with pain				Patients using any type of opioid				Patients with pain using weak opioids and their combinations				Patients with pain using strong opioids and their combinations			
	Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
	589	100	563	100	335	100	334	100	132	100	59	100	93	100	53	100	31	100	6	100
Age																				
65-74	193	32.8	117	20.8	102	30.4	43	12.9	36	27.3	7	11.9	23	24.7	7	13.2	14	45.2	0	0.0
75-84	227	38.5	169	30.0	125	37.3	84	25.1	53	40.2	11	18.6	37	39.8	9	17.0	9	29.0	1	16.7
85-94	153	26.0	241	42.8	95	28.4	174	52.1	39	29.5	37	62.7	29	31.2	33	62.3	7	22.6	5	83.3
95+	16	2.7	36	6.4	13	3.9	33	9.9	4	3.0	4	6.8	4	4.3	4	7.5	1	3.2	0	0.0
Gender																				
men	256	43.5	119	21.1	128	38.2	56	16.8	51	38.6	12	20.3	39	41.9	11	20.8	9	29.0	1	16.7
women	333	56.5	444	78.9	207	61.8	278	83.2	81	61.4	47	79.7	54	58.1	42	79.2	22	71.0	5	83.3
Marital Status																				
single	20	3.4	27	4.8	14	4.2	22	6.6	2	1.5	5	8.5	1	1.1	5	9.4	1	3.2	0	0.0
married	254	43.1	183	32.5	130	38.8	77	23.1	53	40.2	13	22.0	38	40.9	12	22.6	14	45.2	1	16.7
widowed	265	45.0	303	53.8	160	47.8	200	59.9	65	49.2	36	61.0	45	48.4	31	58.5	14	45.2	5	83.3
separated	3	0.5	14	2.5	2	0.6	12	3.6	0	0.0	2	3.4	0	0.0	2	3.8	0	0.0	0	0.0
divorced	47	8.0	36	6.4	29	8.7	23	6.9	12	9.1	3	5.1	9	9.7	3	5.7	2	6.5	0	0.0
Education																				
primary	126	21.4	162	28.8	74	22.1	118	35.3	30	22.7	27	45.8	24	25.8	27	50.9	4	12.9	1	16.7
secondary	345	58.6	348	61.8	195	58.2	191	57.2	70	53.0	29	49.2	50	53.8	25	47.2	19	61.3	3	50.0
tertiary	117	19.9	52	9.2	66	19.7	24	7.2	32	24.2	3	5.1	19	20.4	1	1.9	8	25.8	2	33.3
NA	1	0.2	1	0.2	0	0.0	1	0.3	0	0.0	0	0.0	0	0.0	0	0	0	0.0	0	0.0

Mobility																				
Bound to a wheelchair	73	12.4	60	10.7	43	12.9	43	12.9	25	18.9	13	22.0	16	17.2	11	20.8	6	19.4	2	33.3
Able to get up from the wheelchair but usually do not	142	24.1	65	11.5	100	29.9	46	13.8	50	37.9	11	18.6	37	39.8	9	17.0	10	32.3	3	50.0
Going outside	374	63.5	438	77.8	192	57.3	245	73.4	57	43.2	35	59.3	40	43.0	33	62.3	15	48.4	1	16.7
Cognition																				
MMSE was not carried out	275	46.7	424	75.3	162	48.4	247	74.0	47	35.6	43	72.9	36	38.7	40	75.5	8	25.8	3	50.0
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
MMSE during hospitalization	314	100	139	100	173	100	87	100	85	100	16	100	57	100	13	100	23	100	3	100.0
Intact	186	59.2	65	46.8	97	56.1	45	51.7	50	58.8	7	43.8	33	57.9	2	15.4	14	60.9	2	66.7
Mild impairment	42	13.4	18	12.9	25	14.5	10	11.5	13	15.3	3	18.8	11	19.3	4	30.8	0	0.0	1	33.3
Moderate impairment	84	26.8	53	38.1	49	28.3	29	33.3	22	25.9	6	37.5	12	21.1	2	15.4	9	39.1	0	0.0
Severe impairment	2	0.6	3	2.2	2	1.2	3	3.4	0	0.0	0	0.0	1	1.8	5	38.5	0	0.0	0	0.0

For every value in “N” column the denominator is the number expressing 100 % in acute and ambulatory care (overall cohort: N=589, N=563 respectively; patients with pain N=335, N=334; patients using any type of opioid 1 N=32, N=59; patients with pain using weak opioids and their combinations N=93, 53; patients with pain using strong opioids and their combinations N=31, N=6)

NA = Not Available (i.e., missing values)

There were 191 (16.6 %) patients using opioids in the cohort – 176 suffered from pain and 15 did not indicate pain in the section "PAIN", but were treated by pain medications (probably because the pain was for long-term under full control or medications could have been taken for other reasons). From those who indicated pain, 139 (79.0 %) were using only weak opioids or their interactions, 30 (17.0 %) were using only strong opioids or their combinations and 7 (4.0 %) were using weak opioids and strong opioids in combination. This means that 7 patients are involved in both groups of patients using weak opioids or their combinations with strong opioids.

When looking at the other 15 patients that did not refer having pain (14 in acute care, 1 in ambulatory care) – 11 (73.3 %) used weak opioids and 4 (26.7 %) used strong opioids. It is most likely that opioids were taken to relief pain, but it was not indicated in the questionnaire by assessors. All indications were assessed individually during the interviews with the patients.

Table 4.2: Patients taking opioids but not indicating having pain in the questionnaire

Identification of the patient in the database	Expected indication	Opioid drug
acu107H	chest pain	tramadol/paracetamol
acu110Praha	cancer – mammary	tramadol, paracetamol
acu112Praha	metastases – ileum	tramadol/paracetamol
acu115Praha	bronchogenic carcinoma, fracture of left femoral bone neck	hydromorphone
acu11Praha	osteoporosis, breast cancer in the past, varices of the lower limbs, fall	tramadol/paracetamol
acu121Praha	pertrochanteric left femoral fracture, nephrolithiasis	tramadol/paracetamol
acu128Praha	bunion operation	oxycodone
acu134Praha	Bechterew's disease	fentanyl
acu135Praha	painful syndrome	tramadol/paracetamol
acu146Opava	adenoma in the past, cystis renis	tramadol
acu56HK	cancer - bladder, cough	codeine
acu5Opava	fracture – pubis	fentanyl
acu6Praha	spastic paraparesis	tramadol/paracetamol
acu95Praha	osteonecrosis of the femoral head bilaterally	tramadol/paracetamol
amb57Brno	diabetic neuropathy	paracetamol/codeine

4.2.2. Patients' subjective opinion on their health status

41.9 % of patients in acute care reported that their health status is bad, which was almost double prevalence compared to reports of „average" or „very bad health status" by other seniors in acute care (by 22.1 % and 19.0 %, respectively). However, ambulatory care patients reported that their health status is rather good (33.2 %) or average (37.7 %). In terms of patients suffering from pain, in acute care there was 40.6 % of individuals stating that they health status is "bad" and the majority of acute care older patients (47.6 %) thought their health status is "average".

Table 4.3: Older patients' subjective opinion on their health status

Subjectively assessed health statius	Overall cohort				Patients with pain				Patients using any type of opioid				Patients with pain using weak opioids and their combinations				Patients with pain using strong opioids and their combinations			
	Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
	589	100	563	100	335	100	334	100	132	100	59	100	93	100	53	100	31	100	6	100
Excellent	1	0.2	37	6.6	0	0.0	11	3.3	16	18.9	12	3.4	0	0.0	0	0.0	8	25.8	1	16.7
Good	99	16.8	187	33.2	51	15.2	72	21.6	33	43.9	26	32.2	14	15.1	11	20.8	4	12.9	1	16.7
Average	130	22.1	212	37.7	76	22.7	159	47.6	58	25.0	19	44.1	24	25.8	25	47.2	7	22.6	2	33.3
Bad	247	41.9	108	19.2	136	40.6	87	26.0	25	12.1	2	20.3	40	43.0	15	28.3	10	32.3	2	33.3
Very bad	112	19.0	19	3.4	72	21.5	5	1.5	0	0.0	0	0.0	15	16.1	2	3.8	2	6.5	0	0.0

For every value in "N" column the denominator is the number expressing 100 % in acute and ambulatory care (overall cohort: N=589, N=563; patients with pain N=335, N=334; patients using any type of opioid N=132, N=59; patients with pain using weak opioids and their combinations N=93, N=53; patients with pain using strong opioids and their combinations N=31, N=6).

4.2.3. Utilization of health care services by patients in the studied sample

There were five categories that were assessed regarding utilization of various healthcare services by older patients participating in our study, particularly rehabilitation (45.6 %, 10.5 %), home care (36.9 %, 83.1 %), dialysis (2.0 %, 0.6 %) and other healthcare services – oncology clinic, osteology clinic, spa, etc. (15.4 %, 0.3 %) in acute and ambulatory care. In the substantial percentage of acute care patients, the last hospitalization was found to be between 2 weeks and 3 months (28.2 %). The proportion of patients who were admitted to hospital in 3 months to 1 year, in 1 year to 5 years and over 5 years was distributed more or less equally in acute care (19.4 %, 20.9 % and 20.5 %, respectively). Whereas, in ambulatory patients the category "hospitalization" between 1 to 5 years" included 43.5 % patients, which was also the biggest percentage documented across all categories of ambulatory patients.

The biggest difference between acute care and ambulatory care patients was in the number of hospitalizations in the last year. 38.2 % ambulatory care patients were not admitted to a hospital in the last year at all whereas the same could be applied only for 2.9 % acute care individuals. Half of the acute care patients (50.6 %) were admitted at the hospital at least once during the last year.

The percentage of acute care patients who went to their GP 5 to 8 times or even more per year increased substantially in all older patients suffering from pain (6.5 % of patients without pain, 54.6 % with pain). Ambulatory care patients mostly visited their GPs 2 to 4 times per year.

Acute care patients (52.3 %) went to see about 2-4 specialists per year while the bigger majority of ambulatory care individuals had only 0-1 specialist doctors (80.3 %).
Interestingly, about 70.0 % of acute care patients did not use any other additional healthcare services (e.g.: rehabilitation etc.). 80.0 % of ambulatory care patients used home care.

Table 4.4: Utilization of health care services by patients in studied sample

Utilizationof healthcare services	Overall cohort				Patients with pain				Patients using any type of opioid				Patients with pain using weak opioids and their combinations				Patients with pain using strong opioids and their combinations			
	Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
	589	100	563	100	335	100	334	100	132	100	59	100	93	100	53	100	31	100	6	100
The last hospitalization																				
>5years	121	20.5	167	29.7	65	19.4	77	23.1	25	18.9	10	16.9	19	20.4	10	18.9	8	25.8	1	16.7
1-5 year	123	20.9	245	43.5	67	20.0	166	49.7	21	15.9	31	52.5	16	17.2	29	54.7	4	12.9	1	16.7
3 month- 1 year	114	19.4	99	17.6	80	23.9	59	17.7	26	19.7	9	15.3	18	19.4	7	13.2	7	22.6	2	33.3
2 week - 3 month	166	28.2	40	7.1	97	29.0	25	7.5	49	37.1	9	15.3	33	35.5	7	13.2	10	32.3	2	33.3
in the last 14 days	62	10.5	12	2.1	25	7.5	7	2.1	11	8.3	0	0.0	7	7.5	0	0.0	2	6.5	0	0.0
NA	3	0.5	0	0.0	1	0.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Number of hospitalization in the last year																				
none	17	2.9	215	38.2	11	3.3	145	43.4	8	6.1	30	50.8	6	6.5	29	54.7	0	0.0	1	16.7
1	298	50.6	267	47.4	161	48.1	127	38.0	63	47.7	18	30.5	50	53.8	13	24.5	8	25.8	5	83.3
2	163	27.7	59	10.5	91	27.2	47	14.1	33	25.0	8	13.6	18	19.4	8	15.1	15	48.4	0	0.0
3	56	9.5	17	3.0	38	11.3	13	3.9	13	9.8	3	5.1	7	7.5	3	5.7	4	12.9	0	0.0
4 +	40	6.8	5	0.9	28	8.4	2	0.6	13	9.8	0	0.0	10	10.8	0	0.0	4	12.9	0	0.0
NA	15	2.5	0	0.0	6	1.8	0	0.0	2	1.5	0	0.0	2	2.2	0	0.0	0	0.0	0	0.0
Number of visits at GP																				
0-1	178	30.2	147	26.1	100	29.9	56	16.8	42	31.8	14	23.7	30	32.3	13	24.5	9	29.0	2	33.3
2-4	310	52.6	367	65.2	6	1.8	238	71.3	69	0.8	39	66.1	1	1.1	34	64.2	17	54.8	4	66.7
5-8	38	6.5	41	7.3	183	54.6	33	9.9	9	52.3	6	10.2	48	51.6	6	11.3	4	12.9	0	0
9-12	33	5.6	6	1.1	22	6.6	6	1.8	6	6.8	0	0.0	7	7.5	0	0.0	1	3.2	0	0

13+	10	1.7	1	0.2	19	5.7	0	0.0	1	4.5	0	0.0	5	5.4	0	0.0	0	0.0	0	0
NA	20	3.4	1	0.2	5	1.5	1	0.3	5	3.8	0	0.0	2	2.2	0	0.0	0	0.0	0	0
Number of specialists																				
0-1	215	36.5	452	80.3	116	34.6	292	87.4	50	37.9	49	83.1	34	36.6	43	81.1	11	35.5	6	100.0
2-4	308	52.3	104	18.5	179	53.4	40	12.0	64	48.5	9	15.3	47	50.5	9	17.0	15	48.4	0	0.0
5+	36	6.1	5	0.9	26	7.8	1	0.3	13	9.8	0	0.0	8	8.6	0	0.0	5	16.1	0	0.0
NA	30	5.1	2	0.4	14	4.2	1	0.3	5	3.8	1	1.7	4	4.3	1	1.9	0	0.0	0	0.0
Other healtcare services																				
using healthcare services	149	25.3	295	52.4	99	29.6	222	66.5	46	65.2	44	16.9	28	30.1	39	73.6	14	45.2	1	16.7
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
	149	100	295	100	99	100	222	100	46	100	44	100	28	100	39	100	17	100	5	100
Rehabilitation	68	45.6	31	10.5	41	41.4	18	8.1	19	41.3	2	4.5	10	35.7	2	5.1	8	47.1	0	0.0
Home care	55	36.9	245	83.1	43	43.4	188	84.7	17	37.0	25	56.8	12	42.9	36	92.3	6	35.3	5	100.0
Dialysis	3	2.0	2	0.6	2	2.0	2	1.0	2	4.4	0	0.0	2	7.1	0	0.0	0	0.0	0	0.0
Other*	23	15.4	17	0.3	13	13.1	14	6.3	8	17.4	17	38.6	4	14.3	1	2.6	3	17.6	0	0.0
patients not using any healthcare services	433	73.5	162	28.8	235	70.1	81	24.3	86	34.8	10	74.6	65	69.9	9	17.0	17	54.8	5	83.3
NA	7	1.2	106	18.8	1	0.3	31	9.3	0	0.0	5	8.5	0	0.0	5	9.4	0	0.0	0	0.0

For every value in "N" column the denominator is the number expressing 100 % in acute and ambulatory care (overall cohort: N= 589, N=563; patients with pain N=335, N=334; patients using any type of opioid N=132, N=59; patients with pain using weak opioids and their combinations N=93, N=53; patients with pain using strong opioids and their combinations N=31, N=6).

NA = Not Available (i.e., missing values)

*carer, charity home, cytoscopy, daycare, delivery of lunches, visiting nurse, INR testing, oncology clinic, osteology clinic, social workers, spa, transfusion department, urological clinic and others.

4.2.4. Prevalence of pain and pain characteristics in analyzed sample

This part of the thesis focuses on analyses of characteristics of pain in the whole sample of patients suffering from pain and users of opioids (weak and strong opioids) in acute and ambulatory care. From 1152 patients there were 669 (58.1 %) individuals who suffered from pain. Half of these patients (N=335, 29.0 %) was assessed in acute care and another half (N=334, 29.0 %) in ambulatory care.

4.2.4.1. Characteristics of pain (1) - pain duration

The figures for this analysis are expressed with the denominator being either 100% of individuals for the particular category as it is described under Table 4.5 or they are with indices expressing only patients with pain in acute and ambulatory care. Pain was reported by 58.9 % and 59.3 % seniors in acute care and ambulatory care, respectively, and the use of opioids (any) by 22.4 % and 10.4 % of patients in the overall cohort of 1152 seniors. The prevalence of acute and chronic pain in the sample of older adults assessed in acute care was similar (29.0 % and 29.2 %, [1]51.0 %, [1]51.3 %-for denominators see Table 4.5), with little higher prevalence of opioid drugs users in cohort of patients suffering from acute pain (50.8 %, [1]20.0 %) compared to chronic pain (41.7 %, [1]16.4 %) (see Table 4.5). In the ambulatory care, the majority of older individuals were treated with chronic pain (55.4 %, [2]93.4 % of older individuals with chronic pain compared to 8.5 %, [2]14.4 % reporting acute pain).

The majority of opioid users (over 2/3) in both settings of care were prescribed weak opioid (alone or in combined therapy) and strong opioids were prescribed only to 31 patients ([1]9.3 %) in acute care and 6 ([2]1.8 %) patients in ambulatory care in the cohort of patients suffering from pain. When looking at opioid usage at these patients, there is a higher percentage of individuals with acute pain 52 %, [1]4.7 % and 83.3 %, [2]1.5 % in acute and ambulatory care if we consider the total number of strong opioid users in these settings of care.

It can be clearly seen that patients were mostly taking weak opioids or their combinations while strong opioids were used minimally.

Table 4.5: Duration of pain (acute, chronic, breakthrough pain) in the studied sample

Characteristics of pain*	Acute care								Ambulatory care							
	Total sample		Patients using any type of opioid		Patients with pain using weak opioids and their combinations		Patients with pain using strong opioids and their combinations		Total sample		Patients using any type of opioid		Patients with pain using weak opioids and their combinations		Patients with pain using strong opioids and their combinations	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
	589	100	132	100	93	100	31	100	563	100	59	100	53	100	6	100
Chronic	171	29.0	55	41.7	40	43.0	18	58	312	55.4	55	93.2	50	94.3	6	100
Acute	172	29.2	67	50.8	54	58.1	16	52	48	8.5	17	28.8	13	24.5	5	83.3
Breakthrough	44	7.5	11	8.3	8	8.6	3	9.7	11	2.0	7	11.9	4	7.5	4	66.7
NA	8	1.4	0	0.0	0	0	0	0	0	0	0	0.0	0	0	0	0

Note: Some patients are included in more categories listed in the table if they were suffering from more types of pain.

For every value in "N" column the denominator is the number expressing 100 % in acute and ambulatory care (total sample: N=589, N=563; patients using any type of opioid N=132, N=59; patients with pain using weak opioids and their combinations N=93, N=53; patients with pain using strong opioids and their combinations N=31, N=6).

[1] denominator is 335 which is the number of patients suffering from any pain in acute care

[2] denominator is 334 which is the number of patients suffering from any pain in ambulatory care

NA = Not Available (i.e., missing values)

4.2.4.2. Characteristics of pain (2) - pain frequency

We outlined duration of pain in the previous table (Tab. 4.5) and specified the % of patients with pain. As it can be seen that frequency of pain was classified into four categories. Patients with pain in the acute care experienced pain mostly several times per day (58.8 %) or 2-3 times per week (22.4 %) Among older patients in ambulatory care, 54.8% suffered from pain at least 2-3 times per week but not daily while 24.6 % of patients experiences pain even less often. The similar trends were observed for patients using any type of opioid. In both settings of cares, patients taking strong opioids suffered from pain several times per day (64.5 % of strong opioid users in acute care and 66.7 % in ambulatory care).

A significant difference was documented between acute and ambulatory care in pain frequency in the group of older patients taking weak opioid or their combination – pain at the frequency of several times per day was stated by the majority of acute care patients (62.4 %) while ambulatory care patients reported by majority pain at least 2-3 times per week but not daily (43.4 %).

Table 4.6: Pain frequency in the studied sample

Pain frequency	Acute care								Ambulatory care							
	Patients with pain		Patients using any type of opioid		Patients with pain using weak opioids and their combinations		Patients with pain using strong opioids and their combinations		Patients with pain		Patients using any type of opioid		Patients with pain using weak opioids and their combinations		Patients with pain using strong opioids and their combinations	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
	335	100	132	100	93	100	31	100	334	100	59	100	53	100	6	100
several times per day	197	58.8	75.0	56.8	58	62.4	20	64.5	43	12.9	11	18.6	8	15.1	4	66.7
1x/day	30	9.0	9.0	6.8	6	6.5	3	9.7	26	7.8	7	11.9	6	11.3	1	16.7

at least 2-3x/week but not daily	75	22.4	26.0	19.7	20	21.5	7	22.6	183	54.8	24	40.7	23	43.4	1	16.7
less often	32	9.6	9.0	6.8	9	9.7	1	3.2	82	24.6	16	27.1	16	30.2	0	0
NA	1	0.3	13.0	9.8	0	0.0	0	0	0	0.0	1	1.7	0	0	0	0

For every value in "N" column the denominator is the number expressing 100 % in acute and ambulatory care (patients with pain N=335, N=334; patients using any type of opioid N=132, N=59; patients with pain using weak opioids and their combinations N=93, N=53; patients with pain using strong opioids and their combinations N=31, N=6).

NA = Not Available (i.e., missing values)

4.2.4.3. Characteristics of pain (3) - localization

Pain was reported by 58.9 % and 59.3 % seniors in acute care and ambulatory care, respectively, in the overall cohort of 1152 seniors. We observed frequency of eleven localizations of pain which were mostly mentioned in our questionnaires. Pain was mostly reported by older patients in acute care (15.3 %) as being localized in legs, followed by chest (9.0 %) and back pain (8.1 %). Also, pain was by majority located at one place in 34.8 % of acute care patients. Weak opioids and their combinations were mostly used in acute care patients suffering from pain in legs (26.9 %), chest (11.8 %) and hips and pelvis (10.8 %).

With regards to ambulatory care patients, 19.5 % individuals experienced pain in knees. Other the most frequent categories of pain localization were spine (14.2 %) and back (12.1 %). Weak opioids and their combinations were mostly prescribed in ambulatory care setting for patients suffering from pain in spine (37.7 %), knees (24.5 %) and back (18.9 %).

There were many acute care (53.8 %) and ambulatory care (39.3 %) patients who did not specify the localization of their pain. However, acute care patients were having pain mostly in one place (39.3 %) and interestingly almost the same number of patients described the pain at 1 or 2 places (by proportion 39.3 % and 38.7 % of patients with pain, respectively).

Table 4.7: Localization of pain in the studied sample

Localization of pain	Overall cohort				Patients with pain				Patients using any type of opioid				Patients with pain using weak opioids and their combinations				Patients with pain using strong opioids and their combinations			
	Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
	589	100	563	100	335	100	334	100	132	100	59	100	93	100	53	100	31	100	6	100
bones	11	1.9	26	4.6	11	3.3	26	7.8	8	6.1	3.0	5.1	6	6.5	3	5.7	2	6.5	0	0
muscles	17	2.9	16	2.8	16	4.8	15	4.5	4	3	1	1.7	2	2.2	1	1.9	2	6.5	0	0
joins	27	4.6	25	4.4	27	8.1	25	7.5	10	7.6	2	3.4	7	7.5	2	3.8	4	12.9	0	0
back	48	8.1	68	12.1	48	14.3	67	20.1	19	14.4	10	16.9	13	14	10	18.9	7	22.6	0	0
knees	14	2.4	110	19.5	14	4.2	109	32.6	6	4.5	15	25.4	5	5.4	13	24.5	1	3.2	2	33.3
arms	7	1.2	35	6.2	7	2.1	35	10.5	2	1.5	6	10.2	2	2.2	6	11.3	0	0	0	0
legs	90	15.3	38	6.7	90	26.9	38	11.4	30	22.7	8	13.6	25	26.9	7	13.2	8	25.8	1	16.7
spine	28	4.8	80	14.2	27	8.1	80	24.0	11	8.3	21	35.6	8	8.6	20	37.7	5	16.1	2	33.3
head	34	5.8	19	3.4	29	8.7	15	4.5	8	6.1	3	5.1	6	6.5	3	5.7	3	9.7	0	0
chest	53	9.0	31	5.5	39	11.6	22	6.6	15	11.4	5	8.5	11	11.8	5	9.4	3	9.7	1	16.7
hips and pelvis	29	4.9	50	8.9	29	8.7	49	14.7	12	9.1	10	16.9	10	10.8	7	13.2	2	6.5	3	50.0
No. of localization																				
1 place	205	34.8	218	39.3	184	54.9	205	61.4	63	47.7	37	62.7	54	58.1	34	64.2	13	41.9	3	50.0
2 places	50	8.5	98	38.7	50	14.9	96	28.7	17	12.9	15	25.4	13	14	13	24.5	4	12.9	3	50.0
3 places	15	2.5	21	17.4	15	4.5	21	6.3	8	6.1	4	6.8	5	5.4	4	7.5	4	12.9	0	0.0
4 places	2	0.3	4	3.7	2	0.6	4	1.2	1	0.8	0	0.0	0	0.0	0	0	1	3.2	0	0.0
5 places	0	0.0	1	0.2	0	0	1	0.3	0	0.0	1	1.7	0	0.0	1	1.9	0	0	0	0.0
Not specified	317	53.8	221	39.3	84	25.1	7	2.1	43	32.6	2	3.4	21	22.6	1	1.9	9	29.0	0	0.0

For every value in "N" column the denominator is the number expressing 100 % in acute and ambulatory care (overall cohort N=589, N=563; patients with pain N=335, N=334; patients using any type of opioid N=132, N=59; patients with pain using weak opioids and their combinations N=93, N=53; patients with pain using strong opioids and their combinations N=31, N=6).

4.2.4.4. Characteristics of pain (4) - cause of pain

We evaluated nine specific causes of pain which were repeatedly stated by the researchers when collecting data; category "others" include causes which were stated only once. The most frequent cause of the pain in acute care patients were fractures (8.8 %) which was also the biggest group of patients taking opioids (15.5 %) in the acute care. Even though almost equal proportion of individuals experienced pain as the result of neuropathy (6.5 %) and osteoarthritis (5.4 %), opioids were much more prescribed for patients reporting neuropathic pain (12.9 % compared to 7.6 % respectively).

In ambulatory care patients, osteoarthritis among the causes of pain presented the most prevalent cause (26.6 % of patients suffering from pain) and the second most frequent cause of pain in these patients was vertebral algic syndrome (VERTAS) (18.1 %). Both of these localizations of pain were the most frequent also among older individuals using opioids (around 40.0 %).

Table 4.8: Causes of pain in the studied sample

Cause of pain	Overall cohort				Patients with pain				Patients using any type of opioid				Patients with pain using weak opioids and their combinations				Patients with pain using strong opioids and their combinations			
	Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care		Acute care		Amb. care	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
	589	100	563	100	335	100	334	100	132	100	59	100	93	100	53	100	31	100	6	100
osteoarthritis	32	5.4	150	26.6	32	9.6	149	44.6	10	7.6	22	37.3	7	7.5	19	35.8	4	12.9	3	50.0
neuropathy	38	6.5	16	2.8	38	11.3	16	4.8	17	12.9	5	8.5	13	14.0	4	7.5	5	16.1	1	16.7
VERTAS	29	4.9	102	18.1	28	8.4	102	30.5	12	9.1	23	39.0	9	9.7	22	41.5	4	12.9	2	33.3

fracture	52	8.8	6	1.1	52	15.5	6	1.8	29	22.0	0	0.0	26	28.0	0	0.0	3	9.7	0	0.0
surgery	14	2.4	2	0.4	14	4.2	2	0.6	5	3.8	0	0.0	3	3.2	0	0.0	2	6.5	0	0.0
accident	4	0.7	2	0.4	4	1.2	2	0.6	1	0.8	0	0.0	1	1.1	0	0.0	0	0	0	0.0
cancer	11	1.9	1	0.2	11	3.3	1	0.3	5	3.8	0	0.0	0	0.0	0	0.0	5	16.1	0	0.0
confusion	2	0.3	0	0.0	2	0.6	0	0.0	1	0.8	0	0.0	1	1.1	0	0.0	0	0	0	0.0
nerve block	5	0.8	4	0.7	5	1.5	4	1.2	2	1.5	2	3.4	2	2.2	2	3.8	2	6.5	0	0.0
others	15	2.5	20	3.6	15	4.5	19	5.7	3	2.3	3	5.1	3	3.2	3	5.7	0	0	0	0.0
NA	0	0.0	1	0.2	0	1.0	0	0.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0.0

For every value in “N” column the denominator is the number expressing 100 % in acute and ambulatory care (overall cohort N=589, N=563; patients with pain N=335, N=334; patients using any type of opioid N=132, N=59; patients with pain using weak opioids and their combinations N=93, N=53; patients with pain using strong opioids and their combinations N=31, N=6).

NA = Not Available (i.e., missing values)

4.2.5. Medication used for pain in the studied sample

Table 4.9 outlines the overview of prevalence of analgesics and opioids and their combinations. There were 52.8 % of acute care patients from overall sample suffering from pain who were taking analgesics and 35.2 % took opioids or their combinations. Some of the patients taking analgesics were taking coanalgesics as part of the pain management – categories of coanalgesics will be outlined more in detail in Table 4.13.

In terms of treatment by opioids, 14.9 % of older patients in acute care were taking tramadol or its combinations or weak opioids or their combinations without any other additional analgesics and 13.7 % patients were taking the same opioids with other analgesics.

Opioids in ambulatory treated older individuals were not as frequently used as in acute care patients - only 17.4% of older patients took an opioid drug with the majority taking only tramadol or its combinations or weak opioids or their combinations (11.4 %). 4.8 % were treated by weak opioids in combinations with other analgesics.

Table 4.9: Analgesics used for the treatment of pain in the studied sample

Treatment of patients with pain	Acute care		Ambulatory care	
	N	(%)	N	(%)
	335	100	334	100
analgesics	177	52.8	104	31.1
opioids (or their combinations)	118	35.2	58	17.4
more than one opioid (or their combinations)	13	3.9	2	0.6
strong opioid (or their combinations)	31	9.3	6	1.8
tramadol (without fixed combinations)	24	7.2	16	4.8
tramadol (or fixed combinations) or weak opioids (or their combinations) (not using other analgesics)	50	14.9	38	11.4
tramadol (or fixed combinations) or weak opioids (or their combinations) and other analgesics	46	13.7	16	4.8
tramadol (or fixed combinations) or weak opioids (or their combinations) and paracetamol (no other strong analgesics)	14	4.2	4	1.2

tramadol (or fixed combinations) or weak opioids (or their combinations) and NSAID (no other strong analgesics)	5	1.5	7	2.1
tramadol (or fixed combinations) or weak opioids (or their combinations) and NSAID (no other strong analgesics) and paracetamol	1	0.3	1	0.3

Note: Some patients are included in more categories listed in the table if they were taking combination of analysed categories of medication.

For every value in "N" column the denominator is the number expressing 100% in acute and ambulatory care (patients with pain N=335, N=334).

4.2.5.1. Drug classes of analgesics used in the studied sample

As already described in previous tables and as expected, the use of analgesics was much more prevalent in older adults assessed in acute care than in ambulatory care. Almost a third (29.4 %) of acute care patients were using pyrazolone derivates (which included mostly metamizole) whereas only 12.6 % of ambulatory care patients were taking this drug.

Drug preparations which included paracetamol were used in 11.9 % of acute care older patients and 4.4% of ambulatory care older patients. Acetic acid derivates (e.g. diclofenac) were used in a very small number of patients, in 1.2 % in acute and 2.5 % in ambulatory care. Even lower was the prevalence of use of propionic acid derivates (e.g. ibuprofen).

Table 4.10: Drug classes of analgesics used in the studied sample

Various analgesics in cohort	Acute care		Ambulatory care	
	N	(%)	N	(%)
	589	100	563	100
Pyrazolones (metamizole)	173	29.4	71	12.6
Anilides (paracetamol)	70	11.9	25	4.4
Acetic acid derivates (diclofenac, indometacin)	7	1.2	14	2.5
Oxicams (meloxicam, piroxicam)	5	0.8	10	1.8
Propionic acid derivates (ibuprofen, ketoprofen, naproxen)	1	0.2	7	1.2
Coxibs (celecoxib)	0	0	0	0
Other anti-inflammatory and antirheumatic agents, non-steroids (nimesulid)	0	0	0	0

For every value in "N" column the denominator is the number expressing 100% in acute and ambulatory care (overall cohort N=589, N=563).

4.2.5.2. Coanalgesics used in the studied sample

When comparing use of classes of analgesics medication and coanalgesics in the studied sample, there was a notable difference – coanalgesics were mostly more frequently used, but as expected, prescribed by majority of patients for other primary indications. The most used coanalgesics were antipsychotics and antidepressants; prevalence of use of both these drug classes was comparable in patients in acute care, 21.4 % and 21.2 % respectively. Anticolvulsants, anxiolytics, BZDs were other three classes of drugs which were the most commonly used in patients in acute care in these proportions: 16.6 %, 15.1 % and 14.8 %, respectively. Mephenoxalone was prescribed only to 2 patients in Brno and Prague in acute care.

In ambulatory care antidepressants were also used by 27.4 % as the most frequently prescribed group of coanalgetics. The second largest group (19.4 %) comprised by antipsychotics followed by anxiolytics and benzodiazepines which were almost used with the same prevalence (14.6 % and 14.4 %). Local and central anaesthetics, other antimigrenics and antagonists of calcitonin-gene related peptide were not used in any of the analysed sample.

Table 4.11: Drug classes of coanalgesics used in studied sample

Coanalgesics	Acute care		Ambulatory care	
	N	(%)	N	(%)
	589	100	563	100
Antipsychotics (promazine, haloperidol, flupentixol etc.)	126	21.4	109	19.4
Antidepressants (desipramine, fluoxetine, sertraline etc.)	125	21.2	154	27.4
Anticonvulsants (phenobarbital, phenytoin, clonazepam etc.)	98	16.6	76	13.5
Anxiolytics (BZDs, mephenaxolone)	89	15.1	82	14.6
Benzodiazepine derivates (diazepam, alprazolam etc.)	87	14.8	81	14.4
Glucocorticoids (hydrocortisone, prednisone, prednisolone)	49	8.3	14	2.5
Bisphosponates (alendronic acid, ibandronic acid etc.)	0	0	42	7.5
Spasmolytics (mebeverine, drotaverine, alverine etc.)	9	1.5	2	0.4
Myorelaxants (dantrolen, baclofen,etc.)	6	1	5	0.9

Selective serotonine agonists (sumatriptan etc.)	2	0.3	2	0
Anaesthetics local (nitrous oxid, sevoflurane etc.)	0	0	0	0
Anaesthetics central (lidocaine, mesocaine etc.)	0	0	0	0
Other antimigrenics	0	0	0	0
Antagonisté calcitonin-gene related peptide (erenumab, galkanezumab etc.)	0	0	0	0

For every value in "N" column the denominator is the number expressing 100% in acute and ambulatory care (overall cohort N=589, N=563).

4.2.5.3. Efficacy of analgesics and their combinations assessed by Visual Analogue Scale (VAS)

Intensity of pain was assessed as subjectively reported intensity of pain before and after taking the medication and reported by Visual Analogue Scale (VAS). Drawback of this analysis is that pain intensity could be influenced also by other drugs (coanalgesics), but only analgesics are stated in these analyses

Some of the categories include less than 30 patients meaning that the confidence interval is not 95% as for other categories thus estimation is not so reliable. In acute care, particularly the category 4, 6, and 9 does not include more than 30 individuals and in ambulatory care these were categories 4, 5, 6, 8, and 9.

We also assessed category 11 which included patients with pain taking tramadol (or fixed combination) or weak opioids (or their combination) and NSAIDs and paracetamol. However, in both types of care there was only 1 individual with this combination. Hence, this category is not stated in the graph.

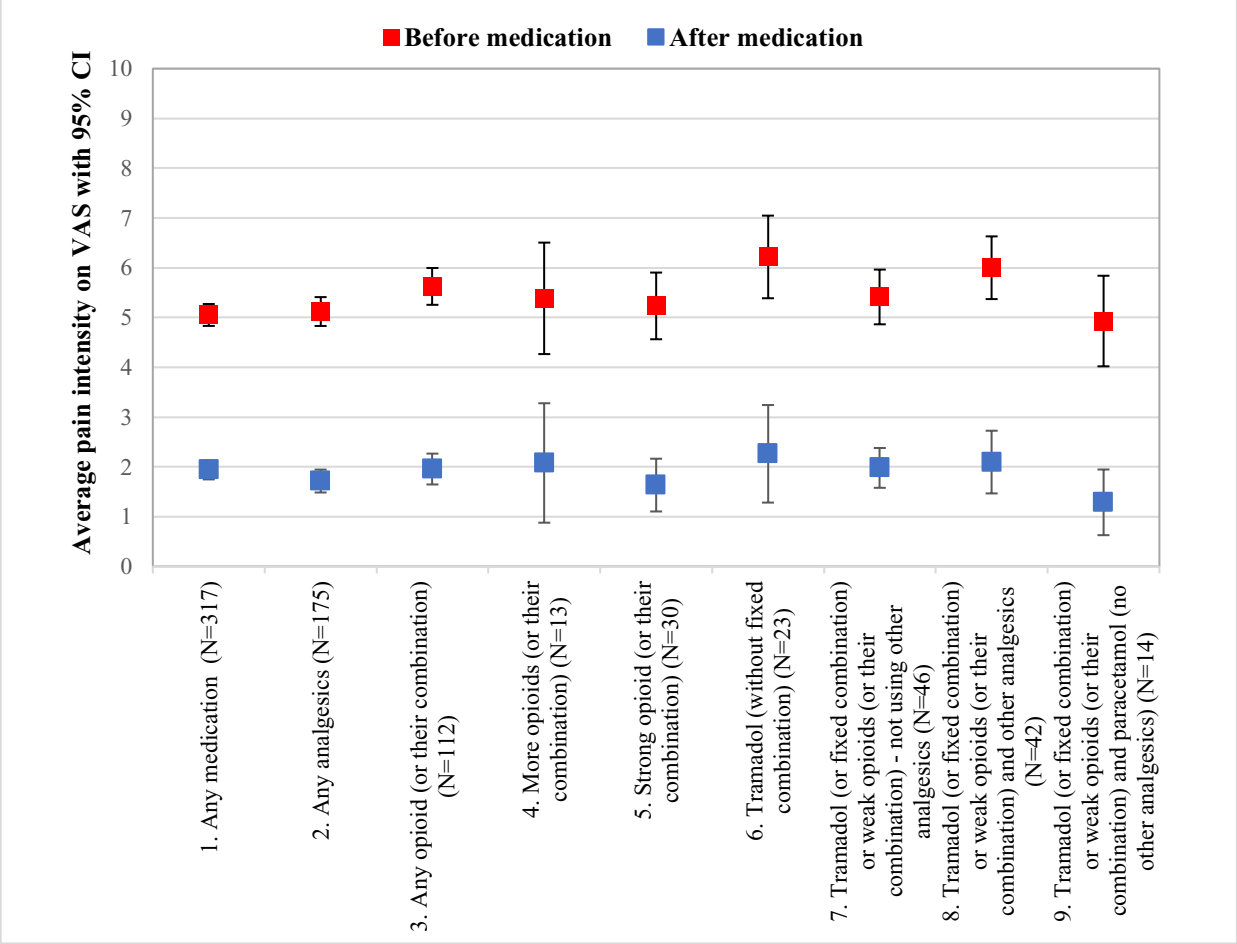
4.2.5.3.1. Efficacy of analgesics and their combinations in acute care

The biggest improvement in pain intensity (4.75 points on VAS) was in the group of patients taking weak opioids (or their fixed combinations) together with NSAID. However, this group only involved 4 patients thus is not included in Graph 4.1. Also, in individuals in other categories in Graph 4.1 pain was diminished significantly (the 95% confidence intervals are not overlapping) by 3-4 points on VAS.

We must keep in mind that pain could have been influenced by other medications and non-pharmacological strategies which were not assessed in our analysis, and other factors not considered (e.g. age). This means that not only listed medication in the graph have helped to decrease the pain at some individuals.

Moreover, only patients who had pain assessed before and after medication are involved in this descriptive statistics (see N in Graph 4.1 and Graph 4.2.). Some data regarding pain before and/or after analesics use were missing thus not all patients with pain were observed for this part of our analysis.

Graph 4.1: Efficacy of analgesics and their combinations in acute care assessed by Visual Analogue Scale (VAS) among patients with pain



Note: 95% Confidence Interval (95 % CI)

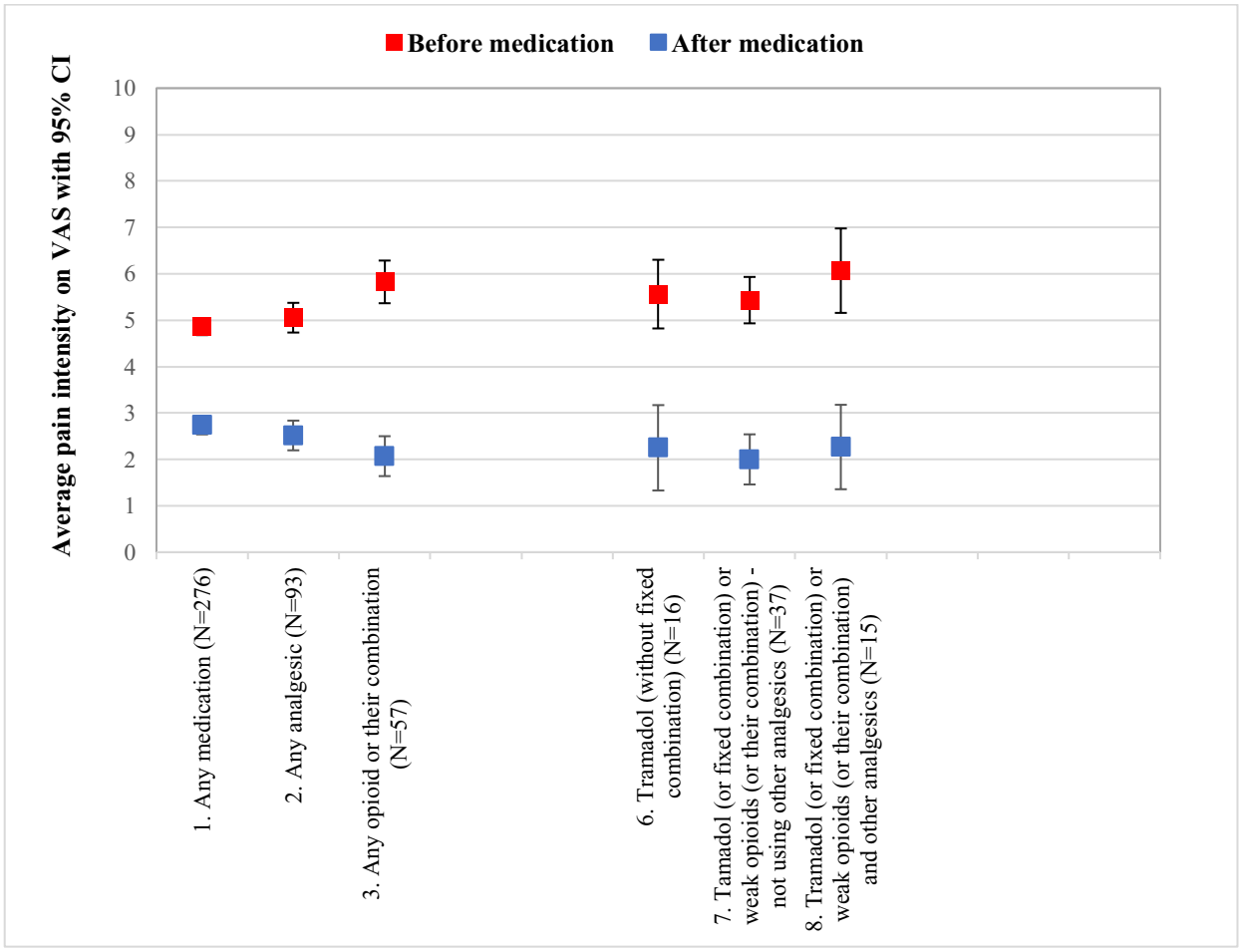
4.2.5.3.2. Efficacy of analgesics and their combinations in ambulatory care

There was a huge decrease in the intensity of pain from 8 to 2 on VAS in patients taking strong opioids or their combinations, which were prescribed for individuals suffering from the most severe pain in the cohort. However, only 6 patients were assessed in this category which means that the

result can be affected by this small number of patients. Almost the same efficacy showed the combination of weak opioids with the combination of paracetamol or NSAID, by average these combinations reduced pain from 6.5 to 1.7 on the VAS scale. Unfortunately, both of these categories included only 4 and 7 patients. None of these categories and also category involving the patients with pain taking more opioids in ambulatory care are not in the Graph 4.2 due to small numbers of individuals (i.e., the estimates of the average pain intensity are unreliable). Similarly, to the acute care, none of the treated patients had pain intensity reduced completely (to 0 on VAS).

Pain was diminished significantly also in other categories (Graph 4.2.) by 2-4 points in VAS (the 95% confidence intervals are not overlapping). This graph has the same limitations as Graph 4.1.

Graph 4.2: Efficacy of analgesics and their combinations in acute care assessed by Visual Analogue Scale (VAS) among patients with pain



Note: 95% Confidence Interval (95 % CI)

4.2.6. Use of combinations of opioids with other sedative and anticholinergic drugs

In this part of the analysis we focused on use of anticholinergic drugs in the older individuals taking any opioids as anticholinergic effects might be enhanced by combinations of these drugs. Also, our intension was to test the negative influence of sedative medications on worsening of sedative symptoms in opioid users, however, a very few patients were prescribed combinations of any opioids with other medications having sedative effect. For this reason, this second analyses could not be conducted.

The extensive lists of sedative and anticholinergic medication were created together with other colleagues (diploma thesis students- see methodology) and these were used in prevalence analyses and analyses of associations with negative symptoms by statistician. For this particular analysis, we chose anticholinergics with ACH burden 1-3. Some anticholinergics can have also sedative potential and vice versa, so one drug can appear in more categories. Opioids can be also classified as anticholinergics, because some of them have ACH potential.

4.2.6.1. Use of weak opioids in combinations with other sedative or/and anticholinergic medications

Almost all patients taking weak opioids (16.8 %, [1]29.5 % acute care, 8.3 %, [2]14.0 % ambulatory care) from the cohort were taking any medications having anticholinergic or sedative activity (predominantly medications having anticholinergic activities). The largest proportion took any anticholinergic and sedative medication together with weak opioid, 10.7 %, [1]18.8 % acute care and 4.6 %, [2]7.8% ambulatory care. Very few patients form acute and ambulatory care (1.4 % and 0.2 %) have been prescribed combination of weak opioids with any other sedatives. Other combinations of opioids with sedative drugs were not documented in the sample.

The trend is that acute care patients might take weak or mild opioids more often as a result of acute pain than ambulatory care patients.

Table 4.12: Use of weak opioids in combinations with other sedative or/and anticholinergic medications

Combination of weak opioids together with anticholinergic and/or sedative medication	Acute care		Ambulatory care	
	N	(%)	N	(%)
	589	100	563	100
Weak opioid without combination with anticholinergic and sedative medication	4	0.7	7	1.2

Anticholinergic or sedative medication without weak opioid	408	69.3	371	65.9
Weak opioid in combination with any anticholinergic or sedative medication	99	16.8	47	8.3
Weak opioid in combination with any anticholinergic and sedative medication	63	10.7	26	4.6
Weak opioid in combination with any anticholinergic drug (nonusers of sedatives)	28	4.8	20	3.6
Weak opioid in combination with any sedative medication (nonusers anticholinergics)	8	1.4	1	0.2

Note: Some drugs are included in more categories listed in the table if they had anticholinergic and sedative characteristics.

For every value in "N" column the denominator is the number expressing 100% in acute and ambulatory care (overall cohort N=589, N=563).

[1] denominator is 335 which is the number of patients suffering from any pain in acute care

[2] denominator is 334 which is the number of patients suffering from any pain in ambulatory care

4.2.6.2. Use of strong opioids in combinations with other sedative or/and anticholinergic medications

Strong opioids had much lower prevalence in the overall cohort than weak opioids. Hence, the percentage of individuals were small across our evaluated categories. The larger majority of patients taking any anticholinergic or sedative medication did not take strong opioids (80.1 % acute care and 73.2 % ambulatory care). Strong opioids in combination with any anticholinergic or sedative drug were present in 5.9 %, [1]10.4 % of acute care patients and 1.1 % and [2]1.8 % of ambulatory care patients.

There were not any acute care patients taking strong opioid in combination with only sedative drug; in ambulatory care there were no patients taking strong opioids together with only anticholinergic or only sedative drug.

Table 4.13: Use of strong opioids in combinations with other sedative or/and anticholinergic medications

Combination of strong opioids together with anticholinergic and/or sedative medication	**Acute care**		**Ambulatory care**	
	N	(%)	N	(%)
	589	100	563	100
Strong opioid without combination with anticholinergic and sedative medication	0	0	0	0

Anticholinergic or sedative medication without strong opioid	472	80.1	412	73.2
Strong opioid in combination with anticholinergic or sedative medication	35	5.9	6	1.1
Strong opioid in combination with any anticholinergic and sedative drug	24	4.1	6	1.1
Strong opioid in combination with anticholinergic drug (nonusers of sedatives)	11	1.9	0	0
Strong opioid in combination with any sedative drug (nonusers of anticholinergics)	0	0	0	0

Note: Some drugs are included in more categories listed in the table if they had anticholinergic and sedative characteristics.

For every value in "N" column the denominator is the number expressing 100% in acute and ambulatory care (overall cohort N=589, N=563).

[1] denominator is 335 which is the number of patients suffering from any pain in acute care

[2] denominator is 334 which is the number of patients suffering from any pain in ambulatory care

4.2.6.3. Analyses of associations of anticholinergic burden of drug regimens and anticholinergic side effects in the studied sample (including and excluding opioid treatment)

4.2.6.3.1. Prevalence of anticholinergic negative symptoms in the studied sample

This part of analysis is limited in terms of the number of anticholinergic side effects as not all of them were assessed in acute and ambulatory care. Symptoms which were considered as anticholinergic but were only evaluated in acute care were: blurred vision, hallucination, delirium and confusion. These side effects were not included in our analysis as it was not possible to evaluate them in both types of care. Potential ACH side effects which could have been evaluated in both cohorts are listed in the Table 3.7. Also, we could not be certain if these side effects were caused due to the inappropriate combinations of medications or if there were other possible reasons (confounding factors). We need to also consider that some adverse effects occurred in the past, which can be one of the limits of this analysis.

Of the potential symptoms that could be associated with or potentiated by ACH drug use, atrial fibrillations were documented with the highest prevalence in 34.1% acute care patients and in 21.3 % of ambulatory care patients. About 14.6 % of patients in acute cares and 8.5 % in ambulatory care suffered from constipation and 10.7 % and 7.5 % experienced other types of

arrhythmia, respectively. Symptoms such as tachycardia and dry mouth were experienced by similar proportion of patients in acute and ambulatory care (around 3.0 %).

The significance difference between these two cohorts were noticed in the prevalence of cognitive impairment and dementia- the prevalence in ambulatory care was very high (34.8 %), while in acute care lower (12.9 %).

At least one symptom potentially associated with anticholinergic side effects occurred in 35.0 % of acute care patients and 37.8 % of ambulatory care patients. 17.3% and 15.3% of acute care and ambulatory care patients experienced at least two anticholinergic symptoms.

Table 4.14: Prevalence of symptoms related to potential ACH side effects in the studied sample

Systemic anticholinergic side effects	Acute care		Ambulatory care	
	N	(%)	N	(%)
	589	100	563	100
*atrial fibrillation	201	34.1	120	21.3
constipation	86	14.6	48	8.5
*other type of arrhythmia	63	10.7	42	7.5
palpitations	28	4.8	22	3.9
tachykardia	20	3.4	17	3.0
dry mouth	17	2.9	17	3.0
*urinary retention	11	1.9	6	1.1
CNS anticholinergic symptoms				
cognitive impairments, dementia	76	12.9	196	34.8
at least 1 of these symptoms	206	35.0	213	37.8
2 and more of these symptoms	102	17.3	86	15.3
3 and more of these symptoms	30	5.1	25	4.4

For every value in "N" column the denominator is the number expressing 100% in acute and ambulatory care (overall cohort N=589, N=563).

**side effect occured in the past or present*

4.2.6.3.2. Number of anticholinergic medications prescribed to seniors in the studied sample

The majority of patients used medications with some anticholinergic properties as part of their medical plan. About a third (33.6 %) of acute care patients were using at least one anticholinergic drug and almost the same proportion of patients – 23.3 % and 24.3 % used two or three and more

anticholinergic drugs.

In case of ambulatory patients, the number of individuals using one, two or three and more anticholinergic medications was almost the same in all these categories (26.6 %, 23.6 %, 21.0 %).

Table 4.15: Number of anticholinergic drugs used by patients in the studied sample

Number of anticholinergic drugs	Acute care		Ambulatory care	
	N	(%)	N	(%)
	589	100	563	100
0	111	18.8	161	28.6
1	198	33.6	150	26.6
2	137	23.3	133	23.6
3+	143	24.3	119	21.1

For every value in "N" column the denominator is the number expressing 100% in acute and ambulatory care (overall cohort N=589, N=563).

4.2.6.3.3. Anticholinergic activity of prescribed drug regimens

Each anticholinergic drug had assigned a number 0-3 expressing the magnitude of its anticholinergic activity; number 1 was the weakest and 3 was the strongest ACH activity. We can see that the proportions of patients were distributed almost equally among all categories of drug regimens divided according to their ACH activity (drug regimens with no ACH activity (around 0, (0-0.49)), mild ACH activity (around 1 (0.5-1.49)), moderate (around 2 (1.5-2.49) and strong (around 3 and more (2.5 and more)).

One third of acute care patients (31.6 %) was using anticholinergic drug regimens with the activity 0.6-1.4 (mild ACH activity) followed by 27.5 % of patients experiencing the strongest activity. Whereas 28.6 % ambulatory care patients mostly took anticholinergic drug regimens with the weakest anticholinergic activity (0-0.5). The other categories 0.6-1.4, 1.5-2.4, 2.5+ were prescribed in 1/5 to 1/4 of patients (with ranging prevalence from 22.2 % to 25 %) (see Table 4.17).

Table 4.16 : Anticholinergic activity of prescribed drug regimens in the studied sample

Anticholinergic activity	Acute care		Ambulatory care	
	N	(%)	N	(%)
	589	100	563	100
0-0.5	116	19.7	161	28.6
0.6-1.4	186	31.6	136	24.2
1.5-2.4	125	21.2	125	22.2
2.5+	162	27.5	141	25

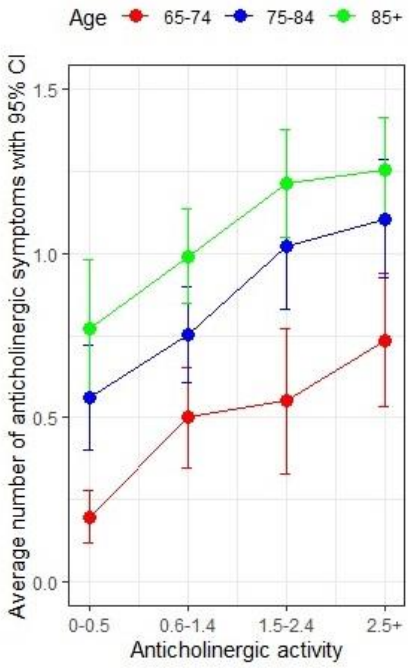
For every value in "N" column the denominator is the number expressing 100% in acute and ambulatory care (overall cohort N=589, N=563).

4.2.6.4. Analyses of associations between increased prevalence of ACH symptoms and the use of ACH drug regimens

4.2.6.4.1. Association between ACH activity of drug regimens, age and the occurrence of potentially ACH symptoms

Graph 4.3. clearly describes that the number of anticholinergic symptoms is increasing with age and with the anticholinergic activity of drug regimen. The majority of anticholinergic symptoms occurred in the age category 85 years and older while the smallest number of ACH were found in patients between 65 and 74 years old.

Graph 4.3: Association between anticholinergic activity of drug regimens, age and the occurrence of potentially ACH symptoms in assessed patients



4.2.6.4.2. Association between ACH activity of drug regimens, other factors and the occurrence of potentially ACH symptoms

Number of anticholinergic symptoms significantly increased with anticholinergic activity and age, however, differences between ambulatory and acute care were tiny, Graph 4.4.

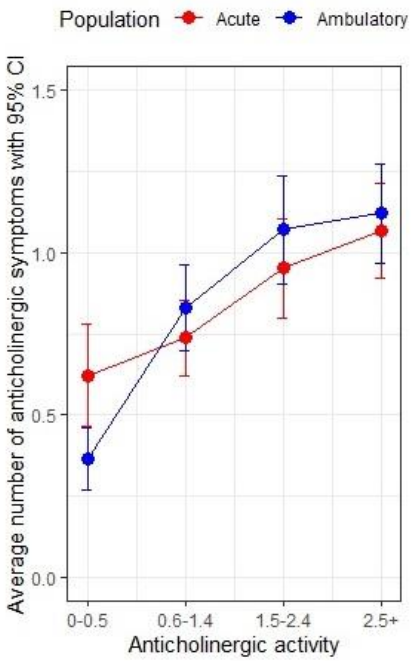
Patients who suffered from pain had more anticholinergic side effects than those without pain (however, the trend was not statistically significant), see graph 4.5. The cause of this trend cannot be specifically determined, probably polypharmacy in patients treated for pain might played an important role.

Regarding graph 4.6. women experienced a higher number of anticholinergic symptoms than men. However, the differences were small between these two groups so we can conclude that gender did not play a statistically significant role in the occurrence of anticholinergic symptoms.

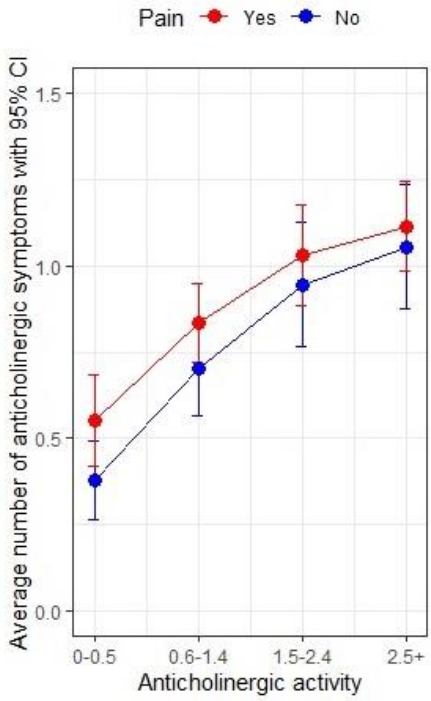
Also, it can be seen that use of opioids use (use of tramadol and other weak or strong opioids) had almost no influence on the average number of anticholinergic symptoms seen in assessed patients as it can be seen in graph 4.7.

Relationship between number of anticholinergic drugs and its activity is not causative. It is cross-sectional study so the time consequences are unknown. We cannot definitely determine if a patient has had already anticholinergic symptoms before the anticholinergic medication was started or not, we cannot either determine other confounding factors.

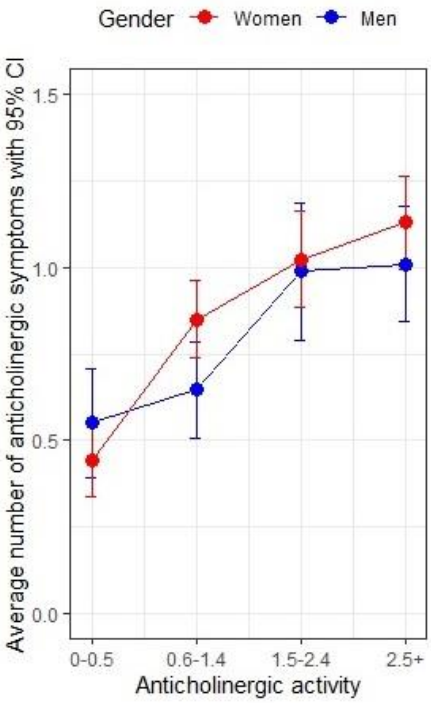
Graph 4.4: Association between number of anticholinergic symptoms and anticholinergic activity of drug regimens in acute and ambulatory care



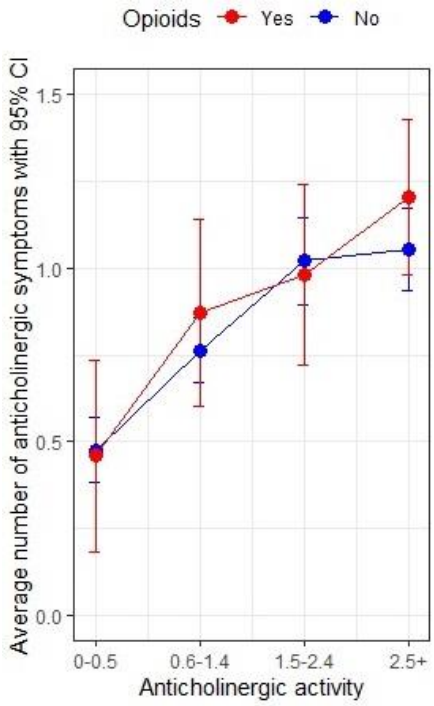
Graph 4.5: Association between number of anticholinergic symptoms and anticholinergic activity of drug regimens in patients with pain and without pain



Graph 4.6: Association between number of anticholinergic symptoms and anticholinergic activity of drug regimens in women and men



Graph 4.7: Association between number of anticholinergic symptoms and anticholinergic activity of drug regimens in patients taking and no-taking opioids



It should be observed that there was a notable correlation between the number of anticholinergic medications and the anticholinergic activity of drug regimens (Kendall's rank correlation tau=0.960, p<0.001).

In summary, the table 4.18 shows that patients between 75 and 84 years old and 85 year and above had higher odds (2.5 times and 3.8 times, respectively) of having more anticholinergic symptoms than seniors who were in the age category between 65 and 74 years old. Anticholinergic activity 0.6 – 1.4, 1.5 – 2.4 and 2.5+ respectively increased odds of experiencing more potential ACH symptoms 2.1 times, 3.1 times and 3.8 times respectively in comparison with the drug regimen having ACH activity of 0-0.5. The effects of gender, type of care (acute, ambulatory), pain (yes, no) and opioids (taking, not taking) on the number of anticholinergic symptoms were not significant.

Table 4.17: Effect of age and anticholinergic activity of prescribed drug regimen on the number of potential ACH symptoms (0,1,2,3+)

Values		OR	95% CI	p-value
Age	65-74	1,0		
	75-84	2.5	(1.8; 3.3)	<0.001
	85+	3.8	(2.8; 5.2)	<0.001
Anticholinergic activity	0-0.5	1		
	0.6-1.4	2.1	(1.5; 2.9)	<0.001
	1.5-2.4	3.1	(2.2; 4.5)	<0.001
	2.5+	3.8	(2.7; 5.3)	<0.001

5. DISCUSSION

Older people are more exposed to the risk of taking more medication and polypharmacy due to multiple comorbidities. As a result, there is a higher risk of accumulation of different drugs leading to adverse reactions [94]. Since it is predicted that the population of older people increase significantly over the upcoming decades following by rise of the number of chronic diseases and polypharmacy, focus on the right assessment, rationality of drug use and appropriate management of medication treatment is necessary.

Data, which were used for our study, were data of more than 1000 seniors (1152) assessed during the EUROAGEISM H2020 project and majority of patients were 78 years old. Data were collected in four different cities across multiple types of healthcare facilities - ambulatory care (589 individuals), acute care (563 individuals) and pharmacy practices (450 individuals). Since pharmacy practice protocol was not so detail, we used for the purposes of our analyses particularly data of seniors assessed in acute and ambulatory care in our project. To our knowledge, this study is one of the biggest current studies assessing characteristics of pain, use of opioids and their potentially negative consequences amongst the geriatric population in the Czech Republic.

Patients´ assessments were primarily conducted by interviewing patients and information were clarified using patients' medical records and healthcare staff interviews. It is necessary to state that for some areas of assessment researchers faced difficulties to get all information needed. One of the reasons was for example that patients did not remember all over the counter medications which they used. It is also questionable whether patients (particularly in ambulatory care) followed all recommendations and dietary regimes suggested by healthcare professionals. Undoubtedly, this study has limitations in gathering some information, but they are not major in order to remarkably influence results of this rigorous thesis.

Our research focused mainly on older individuals who suffered from pain and specifically we focused on evaluation of patients using opioids. More than half of the patients in our cohort (58%) experienced pain – interestingly almost the same number of older adults in acute care had pain as in ambulatory care. Studies have consistently shown that women experience more pain than men (for example Fillingim et al., 2009; Bartley and Fillingim, 2016; Pieretti et al., 2016) [23, 95]. The same pattern can be seen in our study – 184 (16.0 %) men and 485 (42.1 %) women suffered from pain. Biological, psychological and social factors might be reasons for the gender differences. At the same time there was a higher number of women assessed in our sample than men (typical proportions as in all geriatric studies) which could influence the final percentages as well. However, some studies suggest that men and women may have different response to opioids pain relief which can be also affected by age and comorbid mental disorders [96]. In the meta-analysis

of Averitt et al. published in 2019 [97], which compared several studies conducting research about inherent differences in how the central nervous system of males and females responds to pain and opioids, authors found out that both (preclinicial and clinical research) indicated females are less responsive to opioid medications and they tend to use prescribed opioids at higher doses and for a longer period of time than men. However, the role of these factors is usually omitted when it comes to the prescription of opioids for pain control. More clinical trials should be urgently conducted on the use of opioid medications for pain considering influencing factors in men and women.

Looking at the figures expressing breakdown of chronic, acute and breakthrough pain, we can see that almost the same number of patients suffered from chronic (29.0 %) and acute pain (29.2 %) in acute care. However, in ambulatory care the majority of patients (55.4 %) suffered from chronic pain. The study from 2021 [98] analysing pain prevalence in a hospital setting concluded that one fifth (21.7 %) of patients suffered from chronic pain – 20.4 % of the study sample reported pain between 5 till 8 on NRS point scale and moderate and severe pain was reported by 7 % of individuals. Acute pain was more frequent and was stated by 37 % to 53 % of acute care patients. Another study conducted by Wenzel et al. published in 2020 [99] revealed data presenting that up to 50 % of older adults (> 65 years) and 68.5 % outpatient adults (≥ 18 years) reported chronic pain in the primary healthcare setting.

There were four main characteristics of pain which were assessed as part of pain analyses. It was frequency of pain, localization of pain, cause of pain and medication which were used in patients suffering from pain. The majority of patients in acute care (58.8 %) experienced pain several times per day. Whereas ambulatory care patients suffered from pain mostly 2-3 times per week (54.8 %). There were ten different localizations which were evaluated as places of pain. Legs (26.9 %) and chest (11.6 %) were the most common mentioned localizations in acute care while knees (32.6 %) and spine (24.0 %) were the most frequent at patients with pain in ambulatory care.

Various conditions such as osteoarthritis, neuropathy and vertebral algic syndrome were observed at patients with pain in acute care. Osteoarthritis provided a strong link with pain in almost half of the patients suffering from pain in ambulatory care. This is also stated in the study Zimmer et al. from 2020 where arthritis is as one of the most prevalent condition in older adults when assessing pain [23]. Apart from arthritis conditions, musculoskeletal disorders, neuropathic pain, ischemic pain and pain due to cancer and its treatment were listed as the most common among older adults. Vertebral compression fractures were extremely common at older women [100]. Postsurgical pain can be another reason for development of pain (acute or chronic). A study by Lee and colleagues [101] reported that there are about 40 million surgical procedures annually occurring in the United States and 10 % to 15 % of operated individuals will develop chronic pain.

Chronic conditions, including those that are physical and psychological in nature, have been found to have independent influences on pain which is acknowledge in the study mentioned above. Unfortunately, the links between these categories and pain were not analyzed in our thesis which might be a limiting factor to explicitly determine cause of pain in patients in our cohort.

A large part of this thesis is dedicated to pain management and use of opioids. We considered this topic extremely important as the opioid prescriptions increased from 2004 to 2016 in most of the European countries. Even though some Eastern European countries still have a low consumption of opioids, there was a parallel increase of opioid-related harms and the number of dispensed opioid drugs as well. Opioids are mostly prescribed for acute and chronic noncancer pain in some Western and Northern European countries [26, 102]. Because the risks and magnitude of the use of opioids are currently under closer monitoring, the prevalence of the use opioids and their risks were analyzed also in our study in seniors assessed in acute and ambulatory care.

We divided opioids into three groups for our thesis: patients using any type of opioids, patients with pain using weak opioids or their combinations and patients with pain using strong opioids and their combinations. More women than men in our cohort used any type of opioids and opioids were used to treat pain in most cases.

Any type of opioid was used by 132 (22.4 %) acute care patients who mostly took weak opioids or their combinations (70.5 %). Only a small number (10.5 %) of patients with pain in ambulatory care used any type of opioid and there were very few patients who used a strong opioid or their combinations in acute as well as in ambulatory care. From non-pharmacological strategies and use of other services, rehabilitation (41.3 %) and home care (37.0 %) were the most common healthcare services provided to patients taking opioids in acute and ambulatory care respectively. Opioids were also used for acute pain in 50.8 % and for chronic pain in 41.7 % of patients in the acute care. In ambulatory care they were mostly used for chronic pain (93.2 %). This could have been influenced by the number of patients in ambulatory care who mostly experienced chronic pain.

Doses of opioids prescribed for individuals were not assessed in our study. However, many studies mentioned [103, 104, 105] it is recommended to reduce the dose of opioids in older adults by 25 % to 50 % or increasing the time between doses compared with younger patients due to physiological changes. Opioids administered to seniors tend to be more potent and have a longer duration of action causing a higher risk for adverse effects in these patients. In other studies opioids were prescribed in 24 % for chronic pain for older adults residing in nursing homes or for outpatients at geriatric clinic [106]. In terms of acute pain and opioid prescription, opioids were prescribed for 18.7 % emergency departments discharges in the USA [107]. Opioid drugs are essential to treat short-term acute painful episodes. However, distinction between acute, chronic

and chronic non-cancer pain and cancer pain must be made as their significance and management vary [108].

The majority of our cohort stated that they had pain in one location. About a third of acute care patients had opioid prescribed and only one fifth of ambulatory patients took opioids as part of their medication plan. Opioid medication was mostly used for fractures (22.0 %) in acute care to relieve immediate pain. However, in ambulatory care opioids were mostly used for chronic conditions such as vertebral algic syndrome (39.0 %) or osteoarthritis (37.3 %). When putting a patient on a long-term opioid treatment, the potential negative consequences of opioid need to be addressed. There is still a little evidence suggesting that opioids improve function or quality of life beyond 3 months in people with chronic pain conditions [102]. A study conducted in Finland [109] among aged home care patients revealed similar results to our study. Opioids were used for musculoskeletal disorders in four-fifths of the study population. The most frequent were vertebral osteoporotic fractures (21.6 %), degenerative spinal disorders (20.9 %) and osteoarthritis (20.6 %). Whereas acute fractures or fall related injuries and muscular pain were less common indication of opioids within this group. Another study [110] which included dental (23.2 %) and postsurgical pain (17.4 %) as one of the indications of opioids stated that these were the most common clinical indications in the cohort. Patients suffering from musculoskeletal pain and trauma-related pain had opioids as part of their pain management in 12.0 % and 11.2 %, respectively.

Apart from opioids, we assessed other analgesics and coanalgesics which were used mostly probably also as part of the pain treatment. In overall cohort in acute care, there was 29.4 % of patients using pyrazolone derivates which was also the group of analgesic medications mostly used in ambulatory care (12.6 %). Antipsychotics and antidepressants were mostly used as coanalgesics medication in 21.4 % and 21.2 % of seniors in acute care. Data presented by Deng and colleagues [111] collected in the hospital among older adults showed that coanalgesics were used by 25.0 % of patients before hospitalization and by 28.2 % when they were discharged. Antipsychotics and antidepressants were also mostly present as coanalgesics in ambulatory care. It can be seen that antidepressants were used in about 6.2 % more patients in ambulatory care than in acute care. However, use of antipsychotics was about 2.0 % less in ambulatory care then in acute care. We cannot explicitly state if these types of medication were prescribed to treat pain or if they were used to treat other conditions, but their coanalgetic effect might be expected in drug regimen. A study conducted by Barros et al. [112] suggested that self-medication is practiced by 78.4 % of patients with chronic pain, however, we cannot assess over the prescribed drugs and had mostly information of prescription medication. This fact could be one of the limitations of our study as stated above, particularly in the sample of patients assessed in ambulatory care. Only analgesics (without co-

medication) were used by 30.8 % respondents in our assessments. Unfortunately, we cannot be absolutely convinced that our respondents gave us full answer about all medication which they used to manage their pain at home. Therefore, our results might be not completely accurate.

We also observed sedative and anticholinergic medication in our cohort as these medications can reinforce sedative and anticholinergic side effects of opioids. Anticholinergic or sedative medication were used without weak opioids at 69.3 % of patients at acute care and at 65.9 % respondents in ambulatory care. However, combination of these classes of medications together with opioids was prescribed at 16.8 % and 8.3 % patients in acute and ambulatory care respectively, and these were mostly combinations with anticholinergic drugs, not sedative medications. Strong opioids in combination with anticholinergic or sedative medication was found rarely in our cohort (5.9 % acute care, 1.1 % ambulatory care). A recent study [113] indicated that at least 66% of community dwelling older adults were exposed to at least one anticholinergic or sedative medication, which is corresponds to our figures. The most common medication with these properties were codeine/paracetamol (20.1 %), tramadol (11.5 %) and zopiclone (9.5 %). These figures correlate with our study as 15.8 % of ambulatory patients suffering from pain took at least one weak opioid or their combinations.

The probability of experiencing any anticholinergic side effects increases with the number of anticholinergic medication and their anticholinergic activity. Cumulative anticholinergic effects, known as anticholinergic burden, is associated with peripheral and central adverse outcomes. At least one of the anticholinergic symptoms were experienced by 35.0 % of acute care patients and 37.8 % ambulatory care patients; 2 or more anticholinergic side effects appeared at 17.3 % acute care and 15.3 % ambulatory care patients. The most common was atrial fibrillation in both cohorts (34.1 % acute care, 21.3 % ambulatory care) followed by constipation (14.6 % acute care, 8.5 % ambulatory care). The number of anticholinergic drugs taken by each patient was pretty much fairly spread in the cohort. The majority of acute care patients (33.6 %) took 1 anticholinergic drug, 2 and 3 anticholinergics were taken by 23.3 % and 24.3 % of patients respectively. Whereas, 26.6 % ambulatory care patients used 1 anticholinergic drug, 23.6 % of ambulatory patients used 2 anticholinergic drugs and 21.1 % 3 anticholinergic drugs. In 2017, Lampela et al. [114] assessed exposure to ACH medication in population aged 75 years and older. They reported the proportion of people using at least one ACH drug as 60.1 % while study conducted Iran in 2021 by Raei et. al [115] stated that ACH medication was used in one third of the cohort. Other studies in New Zealand published by Narayan et al. in 2013 [116] and by Nishtala et al in 2014 [117] showed that about 40 % older adults were exposed to ACH medications. The median of 2 anticholinergic drugs per patient aged 65 years and older was reported in the study published by Tristancho-Pérez et al. in

2021 [118]. These differences might be due to variances in the population study – number of comorbidities, average number of drugs and the type of setting of care.

The most commonly used methods helping to prevent development of anticholinergic side effects are tools helping to monitor Serum Anticholinergic Activity (SAA) or anticholinergic burden, such as the Anticholinergic Drug Scale (ADS) and Anticholinergic Cognitive Burden Scale (ACB) [119, 120].

Anticholinergic activity of drug regimens was determined in our study by reading various studies and comparing various anticholinergic drugs scales, which can be considered as a strength of our study. We used combination of various scales even if the most commonly used scale for determining anticholinergic activity is the scale of Boustani et al from 2008, because we considered our approach as more precise [121].

The anticholinergic activity drug regimen from 0.6 to 1.4 was present at 31.6 % of acute care patients while the activity between 0.0-0.5 was noticed at 28.6 % of ambulatory care patients. From our study we can see a clear correlation between number of anticholinergic symptoms, their activity and age of the patients. With the increasing age the average number of anticholinergic symptoms increased linearly with anticholinergic activity. Patients with pain suffered from more anticholinergic symptoms which could be caused by a higher number of used medication and larger chance of interactions with other medication. At the same time the occurrence of anticholinergic symptoms (in relation to anticholinergic activity of drug regimens) did not depend on the type of healthcare setting, gender of the patients and opioid use.

Epidemiological studies have shown that at least 50 % of the older population uses one or more drugs with anticholinergic (ACH) properties and patients above the age of 65 years are at higher risk of experiencing anticholinergic side effects [118, 122]. This is mainly due to physiological changes such as a decline in renal and liver function influencing drug elimination, changes in body mass distribution or increased blood-brain barrier permeability [122, 123]. The majority of studies confirm that there are usually combinations of anticholinergic medications that cause an adverse reaction and together provide a high anticholinergic load [113, 124, 125].

Our study has other strengths and limitations, that must be also emphasized. Methodological strengths that we can emphasize four our study is that all patients were prospectively assessed in the same time period, using the same methodology and particularly using GCA (comprehensive geriatric assessment) method which is considered as one of the most actual methods also for pain evaluation and assessment in older adults. Moreover, substantial number of patients (over 550) were assessed in both settings of care, in regionally different bigger healthcare facilities and every patient at the age 65 years and older that fulfilled inclusion criteria was included in the study during

assessment period. Refusal rate was very low, below 5 %. Also, various sources of information (patient interviews, medical records and healthcare staff interviews) were combined to obtain complete information. Limitation of our study is that patients were not selected by randomized sampling and we excluded older adults suffering from severe cognitive impairment, so our study did not refer on results for severely cognitively impaired patients. Also, cross sectional design of our study did not allow us to test real associations between use of ACH drugs and negative symptoms, because time-dependency of the exposition and the occurrence of side effects could not be determined.

Rational use of analgesics and particularly opioids is nowadays important issue of the quality of healthcare provision. It is essential to establish adequate and appropriate management of pain as untreated pain can be a common cause of frequent side effects and also agitation, particularly in older patients. Improving multidisciplinary approach and coordination between specialists and primary care providers can optimize management of pain in older adults [126, 135].
U.S. Department of Health and Human Services published in 2019 a final report on pain management best practices for the future which reflects findings from various research about epidemiology of pain and the treatment [127]. Policy makers are not only concerned about controlling opioid prescribing but also about controlling overall costs of analgesics. Multiple areas were identified as potential gaps for improvement in managing chronic pain and patient outcomes.

The current gaps which were identified included:
1) Underutilization of non-opioid therapies in the perioperative, inflammatory, musculoskeletal and neuropathic injury pain.
2) There should be guidelines developed for specific group of patients rather than applying policies for the large population of individuals.
3) Opioids tend to be used early in pain due to lack of awareness about guidance in appropriate pain treatment approaches.
4) Chronic pain is often ineffectively managed as there is not enough understanding and education regarding clinical indication and effective use of non-opioid medications for acute and chronic pain management.
5) Pain specialists are not involved in the multidisciplinary approach of diagnosing and treating pain in patients early enough in the treatment phase.
6) Guidelines for opioid prescribing need to be provided emphasizing potential risk of opioids adverse effects [128, 129, 130, 131].

Nonetheless, we can see huge commitment of the WHO and other organizations to guarantee to each patient the best available treatment for pain. Large disparities in the availability and usage of

opioid analgesics still exist across Europe, especially in Southern and Eastern parts. On the other hand, attention should be paid to opioid use in a few countries in Western and Central Europe (particularly in Switzerland, Germany and Spain) which display high levels of consumption in order to avoid the risk of abuse [68, 131, 132, 133]. For the Czech Republic, the consumption of opioids was 376.58 morphine milligrams equivalents (MME) per 1000 inhabitants per day which belongs to the highest quartile of opioid consumption in 2019 in comparison with the rest of the world [131].

Our study confirmed that the majority of patients in the observed cohort had prescribed weak opioids as part of their pain management plan. Strong opioids or combination with more opioids as part of the drug regimen of individuals were found very rarely; there is a higher chance that opioids provided analgesia regarding their potential and likeliness of triggering side effects due to their overprescribing was decreased. However, we found that the majority of patients used opioids together with other sedative and anticholinergic medication which can lead to a higher sedative and anticholinergic burden.

6. CONCLUSION

This thesis described assessment of pain, pain management, characteristics of different opioids and their potential side effects. Theoretical part was also focused on physiological and pharmacological changes of ageing and changes in the prevalence of pain and efficacy and risks of analgesics and other medications used to treat pain.

Due to the EUROAGEISM H2020 project, we could gain valuable data about medication use in older people in various healthcare facilities in the Czech Republic and analyze in this thesis particularly aspects of the prevalence of pain and prevalence of different analgesics and other co-medications in drug regimens. We analyzed data of seniors 65+ from acute care and ambulatory care which enabled us better comparisons.

More than half of the cohort in both settings of care suffered from pain – it was mainly acute or chronic pain in acute care and chronic pain in ambulatory care. Majority of geriatric patients (53.4 %) in acute care used various analgesics, opioids or their combinations were used by 35.2 % of patients. In acute care patients used analgesics by 28.1 % and 17.4 % used opioids or their combinations, usually weak opioids or their combinations. The percentage of strong opioids was extremely low in both types of healthcare. Another part of the thesis described anticholinergic burden of patients treated for pain in both opioid and non-opioid users. Atrial fibrillation was the most observed anticholinergic side effect in acute and ambulatory care 34.1 % and 21.3 %, respectively. Whereas urinary retention was the least appeared anticholinergic side effects at 1.9 % of acute care patients and 1.1 % of ambulatory patients. By studying associations between anticholinergic burden of drug regimens and prevalence of anticholinergic symptoms, we concluded that the number of anticholinergic symptoms was higher in older people at least 85 years old, inpatients suffering from pain and dependent on anticholinergic drug burden, but independent on gender, setting of care or opioid drug use. Moreover, number of anticholinergic symptoms (potential side effects) linearly increased with anticholinergic activity. Patients with pain are more likely to have more anticholinergic side effects as they might take a higher number of different medications.

Strong opioids or their combinations were sporadically prescribed in both types of health care. Similarly, the majority of anticholinergic drug regimens had lower anticholinergic activity. So, we can assume that medication regimes with strong opioids or their combinations in drug regimen with high anticholinergic activity were not common in prescription of seniors assessed in the EuroAgeism H2020 project in the Czech sample. However, other analgesics and weak opioids and their combinations were common. In order to clearly determine tested associations, we would need

to conduct a longitudinal study which would enable to better identify time-sequences of exposition and related complications in the studied sample.

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LIST OF ACRONYMS

Acronym	Description
ACH	anticholinergic
ATC code	Anatomical Therapeutic Chemical code
BZD	benzodiazepine
BZDs	benzodiazepines
CGA	Comprehensive Geriatric Assessment
CNCP	chronic non-cancer pain
COX-2	Cycloooxygenase-2
GI	gastrointestinal tract
MMSE	Mini-mental state examination
MOR	μ-opioid receptors
NICE	The National Institute for Health and Care Excellence
NRS	numeric rating scale
NMDA	N-methyl-D-aspartate
NSAID	Non-steroidal anti-inflammatory drug
NSAIDs	Non-steroidal anti-inflammatory drugs
OUD	opioid use disorder
PIM	potential inappropriate medication
SD	Standard deviation
VERTAS	vertebral algic syndrome
VAS	Visual Analogue Scale
WHO	World Health Organization

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ATTACHMENT NUMBER 1

Abstract and poster presented at the 49th ESCP virtual symposium on clinical pharmacy 19.10.2021–21.10.2021 Clinical pharmacy, working collaboratively in mental health care

COMPARISONS OF THE RATIONALITY OF SELECTION OF ANALGESICS PRESCRIBED TO COMMUNITY AND HOSPITAL-RESIDING SENIORS IN THE CZECH REPUBLIC: RESULTS FROM THE EUROAGEISM H2020 PROJECTS

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Background and objective: The right diagnosis of pain and its management is often not properly tackled. If that is so, however, we might see better prognosis of neuropsychiatric disorders. The aim of our study was to identify and compare the prevalence and efficacy of weak opioids and other analgesics by implementing a Visual Analogue Scale
in community and hospital settings at older patients in the Czech Republic.

Setting and Method: : Data of 1159 Czech seniors 65+ were prospectively assessed in the EuroAgeism H2020 project in 2019 with the use of study protocols. The sample consisted of 589 patients in acute care and 563 patients in ambulatory care in 4 different cities across regions. Descriptive statistics were applied using R-software (version 4.0.3) for a pilot description of major sample characteristics and weak opioid use.

Results: This study demonstrates that a little bit more than half (58.12%) of the patients suffered from pain (41.7 % chronic pain, 18.9 % acute pain, 4.7% breakthrough pain). It was found out that 176 (15,3%) patients took an opioid medication which half (50%) were weak opioids and combinations of weak opioids together with other analgesics were found in 5% of the patients and 1.3% of seniors were treated by combinations of more opioids. Patients mostly suffered from pain

2-3 times per week and several times per day in 22.3% and 21.0% respectively. Legs (11.0%) and fractures (5.0%) were indicated as the primal location and cause of a pain.

Conclusion: Our pilot findings confirmed significant differences in opioid use in ambulatory and acute care. In terms of efficacy of the analgesics, the strong opioids had the biggest impact on the pain in ambulatory care. However, weak opioids together with NSAID were most efficient in acute care.

Grants: E*uroAgeism Horizon 2020 MSCF-ITN-764632, Inomed NO.CZ.02.1.01/0.0/0.0/18_069/0010046, Progress Q42- Faculty of Pharmacy, Charles University, START/MED/093 CZ.02.2.69/0.0/0.0/19_073/0016935, SVV260 551 and I-CARE4OLD H2020 - 965341*

PREVALENCE OF PAIN AND RATIONALITY OF USE OF ANALGESICS IN COMMUNITY-RESIDING AND ACUTELY HOSPITALIZED SENIORS IN THE CZECH REPUBLIC: RESULTS FROM THE EUROAGEISM H2020 ESR7 AND THE INOMED PROJECTS

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Background and Study Aim

The proper diagnosis of pain and its appropriate management are crucial, particularly in older patients (in order to prevent somatic and neuropsychiatric complications, chronification of pain and worsening of some co-morbidities, eg. geriatric dementia and depression).

The **aim of our study** was to identify and compare the prevalence of pain, its main characteristics and the rationality of analgesic drug use in community-residing and acutely hospitalized older patients in the Czech Republic.

Main outcome measures

Pilot analysis: the prevalence of pain (including assessment of all comprehensive pain characteristics, as well as pain intensity before and after medication treatment using VAS- visual analogue scale), selection of analgesics (with a special focus on prescribing of weak opioids) and comparisons of prescribing patterns between acute and ambulatory care in the Czech Republic.

Table 1:
Sociodemographic characteristics with regard to pain and usage of weak opioids

	Overall cohort				Patients with pain				Patients using weak opioids and their combinations			
	Acut care		Amb. care		Acut. care		Amb. care		Acut. care		Amb care	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Age (yrs)												
65-74	193	32.8	117	20.8	102	30.4	43	12.9	23	24.7	7	13.2
75-84	227	38.5	169	30	125	37.3	84	25.1	37	39.8	9	17
85-94	153	26	241	42.8	95	28.4	174	52.1	29	31.2	33	62.3
95+	16	2.7	36	6.4	13	3.9	33	9.9	4	4.3	4	7.5
Gender												
women	333	56.5	444	78.9	207	35.1	278	49.4	54	9.2	42	7.5
men	256	43.5	119	21.2	128	21.7	56	9.9	39	6.6	11	2

Table 3:
Prevalence of major types of pain (acute, chronic, breakthrough pain) and treatment with weak opioids

	Acute care				Ambulatory care			
	N	%	weak opioids and combin.	%	N	%	weak opioids and combin.	%
Chronic pain	171	29	40	6.8	312	55.4	50	8.9
Acute pain	172	29.2	54	9.2	48	8.5	13	2.3
Break-through pain	44	7.6	8	1.4	11	2.0	4	0.7

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3/Works of the Scientific group "Ageing, Polypharmacy and Changes in the Therapeutic Value of Drugs in the Aged" (Chair Assoc. Prof. D. Fialová), financially supported by the Scientific Program Progress Q42-KSKF2, Faculty of Pharmacy in Hradec Králové,SVV program 260 551, START project No START/MED/093 CZ.02.2.69/0.0/0.0/19_073/0016935) and I-CARE4 OLD H2020 project ID: 965341

Method

Data of 1159 Czech seniors 65+ (N=589 acute care, N= 563 ambulatory care) selected from 4 cities of 4 different regions were prospectively collected in the EuroAgeism H2020 ESR7 international project in 2018-2019 using protocols of comprehensive geriatric assessment (including over 300 socio-demographic, clinical, functional and medication-related geriatric characteristics). Descriptive statistic was applied using R-software (version 4.0.3) to determine prevalence and major characteristics of pain, as well as prescription of analgesics with a special focus on weak opioids.

Results

In the total sample, more than half of seniors (58.1%) suffered from pain (41.7% seniors reported chronic pain, 18.9 % acute pain and 4.7% breakthrough pain). The highest prevalence was documented for pain experienced 2-3 times a week (22.3%) and several times a day (21.2%). 10.2% patients in acute care and 5.0% in ambulatory care took opioids ($p<0.001$). Of those, half (50%) were treated by weak opioids, 5% by combination of weak opioids with other analgesics, 3.2% by strong opioids and 1.3% by combinations of more opioids. During assessment of pain intensity reduction (according to VAS) strong opioids were the most efficient in ambulatory care (in average reduction of VAS from 8 to 2) whereas weak opioids combined with NSAIDs were the most used and efficient in acute care (reduction VAS from 6 to 1).

Table 2:
Prevalence of use of analgesics with a special focus on weak opioids

Characteristics of pain treatment (medication use)	Acutecare		Amb. care	
	N	(%)	N	(%)
Patients with pain	335	58	334	59
Patients with pain taking any analgesics	179	30	94	17
Patients with pain taking any opioid (or their combinations)	118	20	58	10
Patients with pain taking more than one opioid (or their combinations)	13	2	2	0
Patients with pain taking strong opioid (or their combinations)	31	5	6	1
Patients with pain taking tramadol (without fixed combinations)	24	4	16	3
Patients with pain taking tramadol (or fixed combinations) or weak opioids (or their combinations) (not using other analgesics)	50	9	38	7
Patients with pain taking tramadol (or fixed combinations) or weak opioids (or their combinations) and other analgesics	43	7	15	3
Patients with pain taking tramadol (or fixed combinations) or weak opioids (or their combinations) and paracetamol (no other strong analgesics)	14	2	4	1
Patients with pain taking tramadol (or fixed combinations) or weak opioids (or their combinations) and NSAID (no other strong analgesics)	5	1	7	1
Patients with pain taking tramadol (or fixed combinations) or weak opioids (or their combinations) and NSAID (no other strong analgesics) and paracetamol	1	0	1	0

Conclusion

Our pilot findings confirmed significantly higher prevalence of analgesic drugs use in acute than ambulatory care in seniors in the Czech Republic. In ambulatory care, pain was not under sufficient control by analgesic medications. Weak opioids (particularly tramadol) were prescribed in about 1/3 of users of analgesics in both settings of care.

ATTACHMENT NUMBER 2

Abstract for 50th ESCP symposium on clinical pharmacy 19.10.2021–21.10.2022

Polypharmacy and ageing – highly-individualized, person-centered care

Analyses of Pain Treatment and Opioid Drug Use in seniors in Acute and Ambulatory Care: results from the INOMED and the EuroAgeism H2020 projects

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Introduction: Key issue in geriatric treatment is the selection of the most appropriate and safest drug regimen. Geriatric patients often suffer from multiple disorders and particularly seniors with unresolved pain tend to use polypharmacy, often irrational. This study focused on description of pain prevalence and use of opioids in seniors in 2 settings of care (acute care and ambulatory care) in the Czech Republic and on analyses of negative outcomes associated with use of opioids in combined drug regimens.

Main outcome measures: Prevalence of pain, use of analgesics including opioids; correlation analyses between sedative/anticholinergic symptoms (peripheral and central) and sedative/anticholinergic activity of drug regimens (with and without use of opioids).

Methods: Data were collected in seniors 65+ in acute care (N=589) and ambulatory care (N= 563) in the period 2018-2019. Patients were assessed in 4 regionally different facilities (for each setting) using standardized EuroAgeism H2020 ESR7 protocol (embedding over 350 characteristics of Comprehensive Geriatric Assessment- CGA). R-software, version 4.0.5., was used to analyse pilot descriptive results. Correlations between sedative/anticholinergic symptoms (peripheral and central) and sedative/anticholinergic activity of drug regimens (with and without use of opioids) were evaluated using Kendall rank correlation coefficient and differences in categorical variables adjusted for age (>=80, <80) and gender using the Cochran-Mantel-Haenszel test.

Results: There were 56.5% of women assessed in acute care and 78.9 % in ambulatory care. The highest proportion of study subjects was in the age group 75-84 years (38.5%) in acute care and in the age group 85-94 years in ambulatory care (42.8 %) ($p<0.001$). Pain was reported by 58.9 % and 59.3% seniors in acute care and ambulatory care, respectively, and the use of opioids (any) by 22.4% and 10.4% of patients, respectively (of opioid drugs, tramadol and its combinations were

mostly prescribed in both settings of care). Rare were combinations of opioids with sedative drugs, therefore correlation between sedative burden and sedative symptoms (with and without opioid use) could not be tested. However, frequent were co-prescribing of opioids with several medications having anticholinergic properties in one drug regimen. When testing association between symptoms and anticholinergic burden (with or without opioid drug in the drug regimen), results showed a significant correlation between number of anticholinergic drugs and their anticholinergic activity (Kendall's rank correlation tau=0.960, $p<0.001$) and number of anticholinergic symptoms was increasing with the number of anticholinergic drugs ($p<0.001$) and their activity ($p<0.001$). However, there were no significant difference in increase of ACH symptoms when opioids were added into drug regimens, both in acute and ambulatory care patients.

Conclusion: Pain prevalence and use of opioids (particularly tramadol alone or in various combinations) was very frequent in seniors in acute and ambulatory care. However, significant increase in the risk of sedative symptoms (due to rare combinations of opioids with other sedatives) or anticholinergic symptoms (due to non-significant correlation analysis) was not confirmed after adding opioid into drug therapy. Results of these pilot analyses must be proved by multivariable analyses.

Key words: seniors, rationality of pharmacotherapy, pain, opioids

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