Va. Summary

The elderly population is expanding rapidly throughout the world. Among this age group, multiple chronic and degenerative disorders, frequently accompanied aging, are highly prevalent. Also development of new drugs, growing evidence of their benefits in older adults and more aggressive marketing strategies contribute to steady increase in the number of medications prescribed to the elderly, particularly in developed countries. Clinicians thus spend larger proportion of their practices by managing pharmacotherapeutic strategies in geriatric patients and sufficient knowledge of the rational and safe geriatric drug use become an important part of the daily clinical practice. More attention should be therefore given to the training of physicians and pharmacists in geriatric pharmacology, pharmacoepidemiology and medication errors on pregraduate and postgraduate level.

According to the United Nations' Initiative (1999), all nations should prepare their healthcare, social and economic systems for demographic aging of their populations. One of the principle preventive strategies is also to ensure efficient, safe yet cost- effective pharmacological treatment which can contribute to improved quality of life of senior citizens. Research data show increasing proportion of prescribing errors in the elderly and the need to adopt effective measures in this area in order to prevent serious and costly consequences of such practices. Studies available from the US and Canada have documented that suboptimal prescribing significantly impact the elderly population health and national economy, and indirect costs for medications highly exceed the direct expenditures. Simple limitation of drug use and minimizing the direct medication costs therefore does not seem to be an effective way how to reduce future economic burden and more complex strategies should be implemented. Major interest in drug area should be devoted to rational and cost-effective drug use. Unfortunately, the lack of national pharmacoeconomic studies considering total expenditures for pharmacotherapy (in general, but particularly in senior population), contributes to underestimation of this problem in many European countries.

To emphasize the need of specific geriatric knowledge among physicians and pharmacists, we focused our work on description of crucial differences between geriatric and middle-age prescribing. The work comprehensively reviews major pharmacological changes accompanying aging and their impact on the therapeutic value of some medications. Main focus has been devoted to the concept of "potentially inappropriate drugs in the elderly" which contrary to the United States and Canada is still unknown or not accepted in many European countries. In the Czech Republic, our work represents the pioneer work providing comprehensive and detail information about this concept. Before we started to promote this area, expert criteria were unknown in our country and even now they are not enough respected by prescribing physicians, pharmacists and other healthcare professionals.

Also experimental part of the dissertation thesis gives important results. It represents the first comparative estimate of potentially inappropriate medication use in several European countries. The study warns against the different approaches across Europe in potentially inappropriate medication use and belongs to important decision-making tools for the European drug policy.

The author of the dissertation thesis and her tutors promote this area at home and abroad since the year 2001. During the 5 years of the postgraduate studies the first author presented works related to this topic at 8 international and European conferences, 6 national conferences and 3 scientific meetings abroad. Results of the work were published at 2 English professional journals (JAMA, IF (impact factor) 2004= 21.455 and Eur J Clin Pharmacol, IF 2004= 2,083) and 11 national journals. The dissertation thesis is going to be released as an educational material for pregraduate and postgraduate training of physicians and pharmacists in geriatric drug use.

The dissertation thesis has been divided into three parts:

I/ The first part comprehensively describe major physiological and pathological changes accompanying aging and their impact on pharmacology, efficacy and safety of some medications.

II/ Second part has been devoted to specific criteria of medications potentially inappropriate in the elderly defined as medications, that rather should be avoided in the old age because of potential ineffectiveness or frequent adverse drug events in older adults. Safer alternatives should be preferred, if available, particularly in high-risk elderly.

III/ The third, experimental part of the work, evaluates the use of potentially inappropriate medications in home care elderly, residing in metropolitan areas of 8 European countries. The prevalence of potentially inappropriate medication use in individual countries, different approaches and predictive factors associated with such a prescribing are described here. This original research work has been published at the Journal of the American Medical Association in March 2005.

Major conclusions related to invididual chapters:

Chapter 1- Age-related pharmacological changes

This chapter summarizes major physiological and pathological changes accompanying aging that might significantly impact pharmacology, tolerability and safety of some medications. It is important to point out, that age-related changes reflect rather the biological than chronological age and inter-/ intraindividual variations in the aging process along with different pathologies in older individuals contribute to substantial heterogeneity among geriatric patients. This heterogeneity does not enable simple prescribing decisions.

Some age-related changes occur with the higher probability and should be considered during the routine prescription process, e.g. pharmacodynamic sensitivity to highly anticholinergic and sedating medications, mild impairment in renal functions (present in nearly every second elderly patient), changes in drug distribution, decrease in hepatic first-pass effect, etc. Other changes may accompany only specific disorders or specific clinical conditions (e.g. severe renal impairment, significant decline in dopaminergic transmission, etc.).

Optimal way of geriatric prescribing is of course thorough evaluation of the drug regimen and individual application of the knowledge of geriatric pharmacology, pharmacoepidemiology and medication errors. However, it is hardly to expect such detail skills in primary prescribers, because recent medical and pharmaceutical knowledge are too broad. For primary prescribing practice simpler, general recommendations are needed. But, no general rule can fit to every patient and physicians must be aware of conditions, when general recommendations are not valid and present a substantial risk for the patient.

One of the general, specific approaches of geriatric prescribing is also awareness to medications having unpredictable pharmacokinetics, high risk of toxicity, highly accumulating in the aging body, causing frequent adverse drug events in the elderly or accelerating the age-related changes (e.g. cognitive impairment in patients treated with highly anticholinergic drugs). Most of these medications that pose the risk particularly for

older adults have been identified in the past 15 years by geriatric experts and are known under the term "medications potentially inappropriate in the elderly".

Chapter 2- Expert criteria of medications potentially inappropriate in the old age

Different lists of medications potentially inappropriate in the elderly have been published until now: Beers´s criteria 1991, 1997 and 2003, Mc Leod 1997 criteria and Zhan 2001 criteria. They were first created for specific conditions of the US and/or Canadian drug market, using at that time recent evidence of geriatric studies. The main reason for developing these criteria was decreasing awareness of prescribing physicians to medications with high-risk potential in the elderly and their routine or unnecessary prescription. It has been documented that more than half of preventable medication errors occur at the time of prescription and limited use of potentially inappropriate medications minimizes the probability of the occurrence of adverse drug events in the elderly.

However, it is necessary to emphasize that inappropriateness of these medications is relative not absolute and under certain conditions even "potentially inappropriate drug" can be beneficial for the selected patient. The term "potentially inappropriate medications" thus emphasizes the fact that the use of these medications is connected with the higher probability of adverse drug events in geriatric patients than in the middle-age population, or than in elderly subjects treated with safer alternatives. Because even a small change in clinical conditions (e.g. acute medical problem, dehydration, malnutrition or newly prescribed medication) can increase the risk of serious drug-related problems in the users of potentially inappropriate medications, decision not to use safer approaches should be medically justified and careful and regular monitoring of adverse drug events performed.

Expert criteria of medications potentially inappropriate in the elderly have been developed using statistical Delphi method, based on the consensus of specialists from different fields of geriatric medicine and pharmacy. Although there is missing comprehensive evidence that implementation of these criteria always leads to better outcomes (probably also because individualized therapy is superior to general rules), this fact does not question clinical advantages of this approach.

Chapter 3- Use of potentially inappropriate medications in home care elderly in Europe

Results of our analysis brought the first comparative estimates of potentially inappropriate medication use in a larger sample of European home care elderly (2 707 elderly patients, residing in metropolitan areas of 8 European countries: Prague- Czech Republic, Copenhagen- Denmark, Helsinki- Finland, Reykjavik- Iceland, Milano/Monza- Italy, Rotterdam- the Netherlands, Oslo- Norway and Maidstone and Ashford- United Kingdom). Because no specific criteria of potentially inappropriate medications have been developed in European conditions, we used all until now published foreign criteria to gather the most comprehensive evaluation of this issue in Europe.

Previous US studies have documented (using Beers´s 1997 methodology) that 21% of community-living elderly and 23% of Medicare-managed care older adults used in 2001 and 2003, respectively, at least 1 potentially inappropriate medication. In our sample we obtained similar results (19.8%) when all published criteria have been used, but significantly lower prevalence (10.4%) using the same approach (Beers 1997 criteria), in agreement with small-scale national studies from Northern Europe and Italy. The striking difference was described between the Czech Republic (the only Eastern European country in our sample), where 41.1% of inappropriate medication users were identified, and Western Europe (15.8%). Important differences were documented also among the Western European countries, where

the prevalence of potentially inappropriate medication use ranged between 5.8% in Denmark and 26.5% in Italy.

Results of our study disclosed several problematic areas related to potentially inappropriate medication use in Europe that should be further studied:

a/ The need for specific European criteria of potentially inappropriate medications

The percentage of potentially inappropriate medications approved for the clinical use in individual European countries varied substantially- from 31.6% medications from the total list approved in Norway to 70.9% in Italy. Several substances with comparable harmful pharmacological properties (e.g. flunitrazepam) were frequently prescribed in Europe, but unknown in the US and Canada and not included in existing criteria. Specific lists of potentially inappropriate medications should be created in Europe, based on previously defined country-specific criteria.

b/ The need for more effective feed-back strategies related to potentially inappropriate medication use in many European countries

Results of our study confirm important impact of inequalities in socioeconomic background, regional marketing strategies and local prescribing habits on the prevalence of potentially inappropriate medication use. In some countries, effective regulatory measures contributed to lower prevalence of inappropriate medication use- e.g. in Denmark, where drug utilization reviews were provided to prescribing physicians, or in the United Kingdom, where Beers´s criteria has been implemented in prescribing guidelines and clinical pharmacists' auditing.

On the other hand, high prevalence of potentially inappropriate medication use has been documented in European countries, where specific regulatory measures were missing (Czech Republic, Italy and Finland). Most commonly used inappropriate medications differed substantially in individual countries, independently on the prevalence of major chronic diseases- e.g. amiodarone and ticlopidine were extensively prescribed in Italy, psychotropic medications (amitriptylin, long-acting benzodiazepines) in Finland; and pentoxyphylline, high-dose digoxin and long-acting benzodiazepines in the Czech Republic.

Because the use of potentially inappropriate medications mostly represent the cheaper way of geriatric prescribing (in terms of the direct costs), national pharmacoeconomic studies considering total expenditures on pharmacotherapy should be performed to determine weather implementation of the expert criteria is cost-effective in individual countries.

c/ The need for rational acceptance of the expert criteria

In our study, we documented higher prevalence of potentially inappropriate medications in countries, where expert criteria were unknown (Czech Republic) or criticized and not respected (Italy, Finland). Similarly, using the newest Beers 2003 approach we determined nearly twice as high prevalence of inappropriate medication use than with the use of older Beers 1997 criteria. This result might indicate higher awareness of physicians to medications included in older, better known Beers´s recommendations.

In the future it is necessary to define factors influencing prescribers´ decision to use potentially inappropriate medications. Differences in prescribing guidelines, defining conditions when to use potentially inappropriate medications, should be harmonized across the Europe.

d/ The need for more thorough implementation of risk-management strategies in high-risk elderly

Several US studies have documented that the use of potentially inappropriate medications contribute to adverse outcomes in the elderly - e.g. to more common adverse drug events, to functional status decline and to the increase in health and social care provision and total costs. Adverse drug events are more prevalent in high-risk elderly patients (e.g. with the high degree of morbidity, using a lot of medications, treated with psychotropic drugs, etc.). All of these characteristics were identified in our study among the factors significantly associated with potentially inappropriate medication use. Findings of the study thus indicate that prescribing to high-risk elderly is often burdened with prescribing errors and fundamental preventive strategies are insufficiently implemented in these patients.

As one of the principal aims of the medical care for seniors in Europe is to ensure equal, safe and appropriate drug treatment to all elderly patients, drug policies and regulatory measures related to potentially inappropriate medication use should be harmonized in the future in member states. It is necessary to establish prescribing limits for some inappropriate medications, to harmonize clinical guidelines, approve safer drug alternatives, etc. Our study demonstrated significant variations across Europe in potentially inappropriate medication use and the possibility to improve prescribing habits in some countries. Future effort in this area should be devoted to educational and risk-management strategies and pharmacoeconomic and epidemiological studies evaluating the impact of potentially inappropriate prescribing on the healthcare economy.