U.PORTO
FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

UNIVERSITY OF PORTO MEDICAL SCHOOL

DEPARTMENT OF HYGIENE AND EPIDEMIOLOGY

MASTER IN PUBLIC HEALTH

THESIS

Self-Reported Medication Use and Polypharmacy: A Glance at Non-Steroidal Anti-Inflammatory Drugs Use

CRISTINA P. PINHEIRO

Cristina Pedreira Pinheiro

Self-Reported Medication Use and Polypharmacy:

A Glance at Non-Steroidal Anti-Inflammatory Drugs Use

O Uso Auto-Declarado de Medicamentos e Polimedicação:

Um Olhar Sobre O Uso De Anti-Inflamatórios Não Esteróides

U.PORTO
FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Master in Public Health

University of Porto Medical School

2007

“*Make things as simple as possible. Never simpler*.”

Albert Einstein

Index

Special Thanks

*I wouldn't and couldn't begin this small but of most importance chapter without trying to tell to my Parents, **Rosa** and **Armando**, how immeasurably thankful I am to them for cherishing me with Their immense Love and Joy, for the Strength I've fortunately inherited from Them, the incredible and quite unique Life I've had so far, all the important and decisive Chances, Their Faith in me, Their unconditional Support, Their Trust and Confidence, Their Sacrifices and all the other invisible important things They've provided me and taught me... Je Vous aime de tout mon cœur.*

*To all my **Friends**, Dearest journey Companions, to all Those who kind-heartedly support me and push me forward, thank You so much for doing so!*

To all Those who received me and provided me the opportunity to learn and grow better as a professional, thank You.

To the Department of Hygiene and Epidemiology of Porto University Medical School and all Those who welcomed me and guide me day by day through this new path of mine, thank You.

To Milton Severo, dear colleague, who supervised the statistical analysis of this study, many thanks!

To Professor Henrique Barros who opened the door of the Science of Epidemiology to me, and honoured me by guiding this thesis, thank You so very much.

Cristina

Summary

The concurrent use of many drugs at one same time is called polypharmacy. Whether the consumption of drugs result from physician's prescription or self-medication, there is evidence that polypharmacy is associated to adverse drug events (ADEs), drug-drug interactions, and lack of adherence to medication.

This present study was based on data from the EPI-Porto study follow-up stage – a population-based study designed and carried on by the Department of Hygiene and Epidemiology of Porto University Medical School. We used drug utilization related data that was collected by means of a structured questionnaire applied during a face to face interview with trained interviewers that made inquiries about health related information. The subjects were then asked if they had taken any medication during the 12 months before the interview, and all drugs were registered on a medicine-by-medicine basis along with doses and duration of use.

EPI-Porto study follow up stage inquired 1511 non-institutionalized adults living in Porto from 2005 until February 2007. All reported drugs were classified according to the Anatomic Therapeutic Chemical (ATC) classification system. Drug use was defined as daily use for at least 14 consecutive days, anytime during the previous 12 months. Drug regimens considered are monopharmacy (one only drug), minor polypharmacy (2 to 4 drugs simultaneously), and major polypharmacy (5 or more drugs simultaneously). Since complete drug information was not available for 143 subjects, only 1368 were included in this analysis.

Out of the 1368 subjects included in the analysis, 939 reported the use of at least one drug during the previous 12 months (23.6% men, 45% women). The average use was 2.39 drugs per person (men: 1.99, women: 2.64, $p< 0.001$) or 3.49 drugs per individual on any drug. Among men, 18.0% reported monopharmacy, 29.2% minor polypharmacy, and 14.8% major polypharmacy. Corresponding figures for women were 16.3, 33.8 and 22.7% respectively.

Women were more prone to be under a polypharmacy regimen than men (minor polypharmacy OR, 1.61, 95%CI [1.23-2.12], and major polypharmacy OR, 2.14, 95%CI [1.54-2.96]). Increasing age was also significantly associated to increasing quantity of drugs used, from monopharmacy (OR, 1.05, 95%CI [1.03-1.06]), to minor polypharmacy (OR, 1.10, 95%CI [1.09-1.12]), and major polypharmacy (OR, 1.15, 95%CI [1.13-2.96]). Major polypharmacy was also associated to the number of visits to a physician (OR, 1.55, 95%CI [1.45-1.67]), and the household size, as subjects living by themselves were more prone to take 5 or more drugs (OR, 6.93, 95%CI [3.92-12.24]). After adjustment for sex, age, education, household size, income appreciation and number of visits to a physician, women were still more likely to have taken 5 or more drugs than men (OR, 2.62, 95%CI [1.71-4.03]), as were older subjects (OR, 1.15, 95%CI [1.13-1.17]). Those who visited more a physician during the previous year were also more prone to be under major polypharmacy (OR, 1.49, 95%CI [1.37-1.61]).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) were one of the most reported drugs group (8.5%). Since the prevalence of rheumatic diseases in the study population had already been estimated, we looked for the eventuality of an association between NSAIDs use and the report of any rheumatic disease. Moreover, we also looked for an association between NSAIDs use and polypharmacy regimens. NSAIDs use was significantly higher in women (6.6% women, 1.9% men, $p< 0.001$) and increased in both sexes with age and the report of rheumatic diseases. NSAIDs use significantly decreased with education, MMSE score, household income and household size. Major polypharmacy was found to be the only factor associated to NSAIDs use among the subjects who reported its use but did not report any rheumatic disease. On the other hand, the report of rheumatic diseases alone without NSAIDs use seemed to be associated to the female, elder, less educated and needier subjects. A merge of the cited factors appeared to be associated to the report of both NSAIDs use and rheumatic diseases and therefore may explain the association between NSAIDs use and rheumatic diseases in this sample.

Introduction

Pharmacoepidemiological studies describe patterns of drug use and their subsequent effects at the population level. These studies aim for several targets – the optimised rational use of drugs at the patient, the clinician and the pharmacist level, to avoid all of the different drug concerning problems that aroused in larger extent during the last decades: adverse drug events (ADEs), drug-drug and drug-disease interactions, drug resistance, non-compliance, unadvised self-medication, the concurrent use of contraindicated drugs, prescription and filling errors, the unpredictable outcomes resulting from drug use by pregnant women, infants, and elderly, and the therapeutic regimens conceived for the masses.

Clinical pharmacology, within its core dimensions, has one central principle that specifically regards the individualization of drug therapy by an assertive estimation of the risk/benefit ratio for each individual.[1] There are more than a few considerations to be taken, like the individual's age and gender, its clinical state and medical history, its haemodynamic condition and biochemical alterations, its mental state, the coexistence of chronic diseases – multimorbility, and the present prescribed drug regimens. Along with the physiological modifications due to aging, diseases, or actually induced by drugs or surgical procedures, an individual's biochemical alterations may lead to a theoretically unsystematic turn on a drug's pharmacokinetics and pharmacodynamics. These changes influence the drug's pharmacological behaviour and make possible, or more than certain, inefficacy issues or the occurrence of more or less severe adverse drug events, drug-drug and drug-disease interactions, and consequently belief barriers to medication adherence. Hospital admission, whether compelled by severe drug related events or by chronic diseases aggravation, along with non-compliance are the two major outcomes of the above situations. Each one of them may lead to the other.

Elderly people are more prone to receive inappropriate medications that can potentially add more health problems to their frail condition.[2] Ageing changes in drug's

pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics compromise their expected efficacy, making the elderly individual particularly vulnerable to a wide unpredicted sort of drug related contrarieties. On the other hand, the physiological and anatomical manifestations of ageing leave behind a gradual deterioration in the function of virtually all tissues and organ systems. The process is probably due to a change in the function of cell's macromolecules, particularly DNA, which results in a decreased cell division and increased cell death, and by a malfunction of many of the remaining ones. This phenomenon is, actually, the simple built-in limit to the number of times that cells can divide until they can no longer replicate. [3]

The function of cell's macromolecules may be affected by environmental and genetic factors (genes that code for proteins that regulate the processes of cellular and macromolecular maintenance and repair), and by oxidative stress. Therefore, the exposure to a wide range of chemicals (including, drugs) and pollutants over a lifetime adds undoubtedly several and important outcomes to the ageing process, as the impairment of some organ's functions due to the chemicals' toxicological effects and the installation of metabolism chronic diseases. Moreover, all of these factors, including emergent chronic diseases, are capable and more than likely to interact in an unfavourable way with drugs, no matter how old (or not that old) we are.

Polypharmacy:

- ***Arguments for and Against***

The use of several different drugs by one individual, even when distributed over different periods of time, may cause drug-drug interactions, and other drug related complications, depending on the drug's metabolism and clearance – the drug washout period. However, when several drugs are taken simultaneously – Polypharmacy, the above complications are more then certain to occur.

There is actually no consensual definition for polypharmacy, though it is often defined in terms of the number of medications that are being taken simultaneously at any given time. This approach includes the concurrent use of multiple prescription drugs and over-the-counter medication. This can be quantified as the concurrent use of a fixed number of drugs. However, polypharmacy can be approached through different estimators, such as the number of medications that a person is exposed to over time, the quantity of medications taken on a chronic basis, or as the unnecessary overuse of drugs.[4,5] Several other definitions of polypharmacy have been proposed including the use of more medications than clinically indicated, drug regimens that include more than one unnecessary drug, the use of a drug to treat adverse effects of another drug and inappropriate dosage regimens, but irrespective of the definition, polypharmacy is a word that often has negative connotations.

Inappropriate prescribing, double prescribing, and unadvised medication use and abuse, give rise to a wide set of concerns about polypharmacy.[2] This concurrent use of several different drugs has been associated to the risk of drug-drug interactions, incidence of adverse drug events (ADEs), reduced quality of life, lack of adherence to medication, hospital admission, and drug related mortality.[6-14] The occurrence of such incidents is directly proportional to the sheer number of medications taken and increases with duration of use.[15] With each drug coadministered, the likelihood of an adverse interaction increases exponentially.[16] Several epidemiological studies agreed that the number of medications concurrently used is the most important risk factor for the above complications.[6,17]

Polypharmacy has the potential to cause adverse drug events (ADEs) and drug-induced symptoms that may mimic and be misinterpreted as new medical problems and consequently produce prescribing cascades that lead to the prescription or to the unadvised use of additional drugs, with absolutely no further benefits, on the contrary. Polypharmacy risks and complications also include a cascade of events resulting from

iatrogenia, and increased costs, directly resulting from unnecessary medications and indirectly resulting from hospitalisations caused by iatrogenic illnesses (Figure 1).

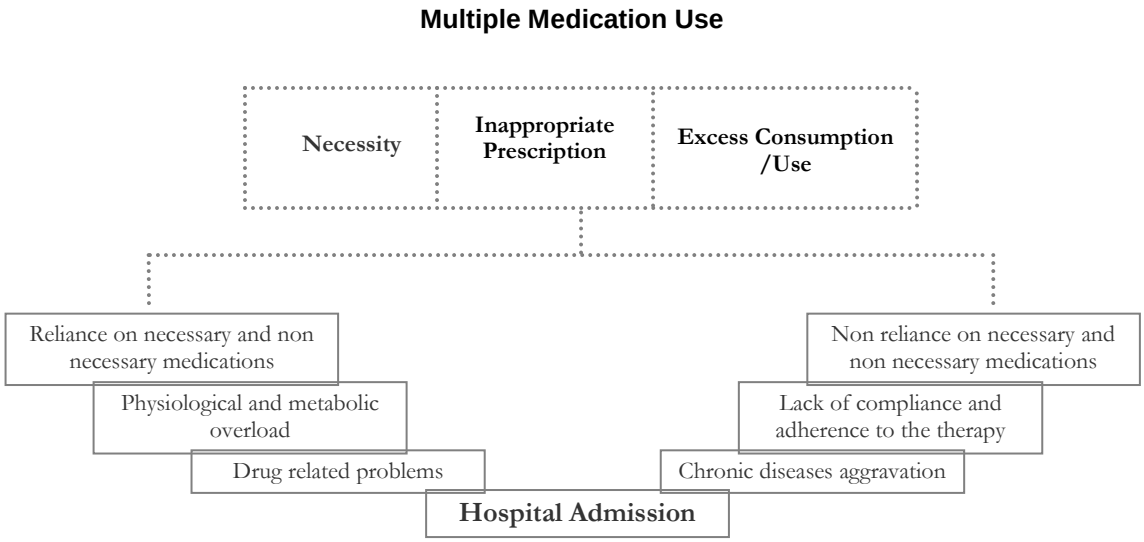


Figure 1 – Cascade of events resulting from the concurrent use of multiple medications – Polypharmacy

Polypharmacy may be unjustified, or vice versa, it may be naturally in accordance with good clinical practice, whether it results from inappropriate prescribing or self-medication. Major causes of polypharmacy include the presence of multiple disease states, thereby necessitating multiple drug therapy, particularly in patients with chronic debilitating disorders; increasing demand for health care; therapeutic advances as well as excessive prescribing (which may be related to poor coordination between practitioners).[18] The number of prescribing physicians has been identified as an independent risk factor for patients being under polypharmacy regimens and for self-reporting an adverse drug event.[19] One possibility is poor communication between multiple providers. Health providers may contribute to polypharmacy directly by excessive or inappropriate prescribing practices or indirectly through their inability to resist client's demands for pharmacologic interventions.[20] Family practitioners and

health professionals are then in a unique position to identify polypharmacy and to modify drug regimens.[21] Interventions performed in this matter of identifying inappropriate medication use suggest that an interpersonal relationship between patients and health care providers, including pharmacists, remains critical to the provision of pharmaceutical care.[22]

Managing medications is complex, particularly for consumers with multiple coexisting conditions for whom benefits and adverse effects are unpredictable and health priorities may be variable.[23] The extent to which the risk of an adverse drug event (ADE) is increased by any combination of drugs can not be predicted, unless the exact risks of each medication are known and the risks of adverse outcomes to each medication are independent of each other.[24] Assessing the potential for adverse drug interactions (ADIs) in a high risk population of an emergency department, Goldberg et al. claimed that the risk of an adverse drug interaction (ADI) rose from 13% for patients taking 2 medications to 82% for patients taking 7 or more medications.[25]

One can then understand why research on polypharmacy is mainly aimed at reducing inappropriate prescription and use of drugs. However, the relationship between polypharmacy and underuse of medication has also been established. The probability of underprescription was shown to also increase significantly with the number of drugs used.[26] If one considers underprescription as inappropriate prescribing then polypharmacy remains associated to inappropriate prescribing and to a treatment-risk paradox.[27-30]

But polypharmacy has become extremely useful in the treatment of complex diseases and emerged in the setting of poorly controlled or complex problems lacking effective treatment algorithms.[31,32] The concurrent use of many medications may be the consequence of evidence-based medical care to optimize the control of complex diseases such as cardiovascular, mental, or metabolic pathologies like diabetes and the associated metabolic risk factors of hypertension and hyperlipidemia.[33,34] Consequently, rational multitargeted polypharmacy and polypills may constitute

modern approaches to complex medication regimens designed with the intention of insuring adequate treatment and patient's safety.[35,36]

A number of studies have pointed some socio-demographic features as determinants of polypharmacy: age, gender, education, employment, social class, and attendance to health care settings. Women, elder, and less educated people have proven to be at increased risk of polypharmacy and inappropriate medication use.[6, 37-39] However, the majority of the existent studies are based on highly selected populations, such as elderly, hospitalized patients and nursing home populations.[40-43] No data are currently available about the prevalence of polypharmacy in the Portuguese population.

Definitions of minor polypharmacy, as the concurrent use of two to four drugs, and major polypharmacy, as the use of five or more, were chosen. These definitions proposed by Bjerrum et al. are common in the literature and useful for comparison between different studies.[44, 45]

- ***Polypharmacy, Rheumatic Diseases and Non-Steroidal Anti-Inflammatory Drugs Use***

Patients with chronic diseases may have a high frequency of polypharmacy irrespective of age, and polypharmacy could be particularly high among patients with rheumatic diseases and associated co-morbidities. Polypharmacy, altered drug metabolism, multiple diseases, and errors in self-medication are all factors seen in these patients which increase the risk for side effects from anti-rheumatic drug therapy.[46] Rheumatic patients are often treated with drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, opioid painkillers, and disease modifying anti-rheumatic drugs (DMARDs) with a high incidence of adverse effects, particularly non-steroidal anti-inflammatory drugs (NSAIDs).

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for analgesic, anti-inflammatory, and antipyretic purposes, and are the most frequently prescribed drugs

to treat pain associated with osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and other musculoskeletal conditions. [47]

The well known common side effects of non-steroidal anti-inflammatory drugs (NSAIDs) are the major therapeutic limitation to the successful management of musculoskeletal diseases and disability.[48] Used mainly to treat chronic pain, such as night or rest pain, non-steroidal anti-inflammatory drugs (NSAIDs) benefits come at the expense of important adverse effects in kidney (inhibition of renal prostaglandin), cardiovascular homeostatic mechanisms, liver, skin, and platelet function, and the risk of clinically important injuries to gastrointestinal mucosa, ultimately resulting in ulceration, perforation, and haemorrhage.[49,50] However, the risk of these gastrointestinal complications varies with duration of use and non-steroidal anti-inflammatory drugs (NSAIDs) dosage.[51] Non-steroidal anti-inflammatory drugs (NSAIDs) are also known to have severe interactions with other drugs and diseases. Predisposing factors for their associated toxicity, particularly gastrointestinal side effects, are indeed age-related physiological changes, underlying conditions and polypharmacy.[52]

But polypharmacy rates have not been well documented in rheumatic diseases. Viktil *et al*. assessed major polypharmacy rates (as the concurrent use of five or more drugs) for all patients with rheumatic diseases admitted to nine Norwegian medical centres. Major polypharmacy was found to be present in 60%, with increasing rates associated with increasing age.[53]

The self-report of rheumatic diseases on the same sample of the Portuguese population that we used had already been assessed at the baseline stage of the EPI-Porto study, in 2004.[54] The former study also estimated that approximately 1.200.000 women and 430.000 men suffered from at least one rheumatic disease in Portugal. At the end of the same year, more than 8.5 million packages of non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed in Portugal, resulting in a total cost of approximately 142 million euros to the national health system – Sistema Nacional de

Sáude (SNS). By the end of 2006, more than 10 million packages of non-steroidal anti-inflammatory drugs (NSAIDs) were sold under prescription in Portugal, resulting in a total cost to the national health system of approximately 80 million euros, a considerably lower sum due to the introduction of new generic drugs into the Portuguese pharmaceutical market .[55]

- ***Ultimate Study Goal***

As a pharmacist, I have always been aware to multiple drug users, whether multiple drug use occurs by prescription filling or self medication, or even by a blend of both. Portuguese reality, our ever ageing population, the growing incidence of chronic diseases, low social support, the partial reimbursement of essential medication being none enough for too many people that needs to chose aimlessly which medications to buy from a prescription when the complete filling is unaffordable, the impoverishment of health and all the direct (economical) and indirect (social) costs, makes it essential to acknowledge polypharmacy, today.

We need more knowledge about the epidemiology of polypharmacy in our population, in order to evaluate the extent of the problem, and to identify which individuals are particularly exposed. Moreover, we also need to keep identifying and preventing every avoidable and inappropriate usage of medication, in order to promote rational drug use and improve the odds of benefiting from it.

Intervention programmes aimed at reducing problems associated with polypharmacy may become a reality and even effective health policies the day when they will focus on the groups of patients with the highest risk. A study designed by the Pharmacy School of Lisbon University, aimed at monitoring drug use in a sample of Portuguese elderly, hit the news in 2007 as a promising enterprise.

However, this study based on the population of Porto is the first study in Portugal assessing the prevalence and the determinants of polypharmacy in randomly selected adults and one of the few in such settings. The side glance at non-steroidal anti-

inflammatory drugs use (NSAIDs) and rheumatic diseases and the association of both to polypharmacy allows focusing not only on one of the most commonly and indiscriminately used drug groups but also on one set of chronic diseases that touches people of any age.

Objectives

The objectives of this population-based study using a sample of Porto population are:

- To describe the self-reported medication use according to gender and age and analyse the occurrence of drug use regimens (monopharmacy, minor and major polypharmacy);

- To determine the prevalence and determinants of each drug use regimen and identify the individuals particularly at risk of polypharmacy;

- To estimate the overall prevalence of NSAIDs use and estimate the association between NSAIDs use, rheumatic diseases and polypharmacy.

The study is described in two parts: Part I and Part II. Each study is presented by an introduction, material, methods, results, and discussion.

Study Setting

The population based study EPI-Porto was designed as a cohort study contemplating a random sample of the city of Porto non-institutionalized inhabitants. Study participants were first recruited from 1999 to 2003 by random digit dialing using households as sampling units, followed by simple random sampling to select one eligible person older than 17 years old among permanent residents in each household, without allowing for replacement if refusals occurred. After being informed about study details, each one of the 2488 participants that accepted to participate was expected to visit the Department of Hygiene and Epidemiology of Porto Medical School to complete a large questionnaire providing information on demographic, social, behavioural (diet, physical activity, smoking and alcohol intake), and clinical characteristics. In the same meeting, anthropometric measurements were to be taken, an electrocardiogram performed and a fasting blood sample drawn. Information at every stage was collected by trained interviewers. Overall participation was estimated as 70.0% but was significantly lower in women (66.3%) than in men (74.7%).[56] The Mini-Mental State Examination (MMSE) was used for the rapid evaluation of cognitive impairment in individuals aged over 64 years. Those participants who scored less than 24 were classified as inadequate to provide reliable information, and were excluded from the study (n= 49 participants).

The follow-up on the EPI-Porto study participants started in 2005 and is still in course. Until February 2007, 1511 participants were re-evaluated and interviewed using similar methods. This study relies on the cross-sectional evaluation of those 1511 participants who were contacted according to the initial inclusion order in the cohort.

The high number of participants not willing to participate or that is unavailable at the moment to attend to the Department of Hygiene and Epidemiology of Porto Medical School for a second evaluation may have introduced substantial selection bias. An analysis about the differences between participants who have not provided further information after inclusion into the primary cohort (977) and the participants followed-

up so far (1511) showed that both populations are similar regarding to gender distribution, mean age and suffering from a chronic disease.

		EPIPorto Follow-up		p-value
		Non-Participants n= 977	**Participants** n= 1511	
Sex	Male	375 (38,4%)	573 (37,9%)	0,425*
	Female	602 (61,6%)	938 (62,1%)	
Age	Median	53,0	53,0	0,659§
	1st Quartile	40,0	44,0	
	3rd Quartile	68,0	63,0	
Education	Median	6,0	9,0	0,006§
	1st Quartile	4,0	4,0	
	3rd Quartile	13,0	13,0	
Chronic Disease	Yes	597 (61,1%)	926 (61,3%)	0,514*
	No	375 (38,4%)	582 (38,5%)	
MMSE	Median	27,0	28,0	0,004§
	1st Quartile	24,0	26,0	
	3rd Quartile	29,0	29,0	

Table 1 – Comparison of participants and non-participants of the study (MMSE – Mini-Mental State Examination). *Pearson χi^2 test; §Mann-Whitney test

Despite what one could think, followed-up participants are neither older nor sicker than non-participants. Nevertheless, they do are more educated than participants who have dropped out the study, and participants aged over 64 at follow-up performed better at the Mini-Mental State Examination than the participants aged 64 at the time of the first evaluation.

Main Results

This study main's objectives were to estimate the prevalence of polypharmacy regimens in the Porto population and the results showed that it was widespread in our study sample, the overall prevalences of minor and major polypharmacy being, respectively, 32.0 and 19.7%. A higher prevalence of polypharmacy for at least 14 days anytime during the 12 months before the interview was found for women (22.7%) than for men (14.8%). On the other hand, the use of a single medication (monopharmacy) was reported by 17% of all subjects.

Summarily, women, older, less educated subjects, as well as those who lived by themselves and those who visited physicians more during the 12 months before the interview were found at higher risk for both minor and major polypharmacy. Even after statistical adjustment, female sex, increasing age and number of visits to physicians were the features strongly associated to major polypharmacy.

But this study also intended to estimate the prevalence of Non-Steroidal Anti-Inflammatory drugs (NSAIDs) in the study population, and to relate it with polypharmacy and having a rheumatic disease. We found that NSAIDs were reported by 8.5% of subjects (1.9% men, 6.6% women) and that the most reported NSAIDs were diclofenac (1.24%), nimesulide (1.10%) and ibuprofen (0.80%). Major polypharmacy, lower education, and the report of rheumatic diseases were indeed found to be associated to NSAIDs use, although among the subjects who did not reported a rheumatic disease, major polypharmacy was the only feature explaining NSAIDs use. Moreover, among the subjects who reported a rheumatic disease, NSAIDs use was associated to female sex, lower education, a worst appreciation of the family income, and major polypharmacy.

Discussion

The importance of ageing in European populations, especially in Portugal, makes it important to determine whether the available therapeutic arsenal is being used in the profit of improved health of individuals and to identify the individuals at risk of eventual adverse drug reactions but the knowledge about the prevalence of polypharmacy has never been estimated for the Portuguese population.

Polypharmacy studies are mainly based on highly selected populations such as hospitalized patients or institutionalized elderly. However, this study based on the population of Porto is the first study in Portugal assessing the prevalence and the determinants of polypharmacy in randomly selected adults and one of the few in such settings. Therefore, direct comparisons with other studies based on highly selected population samples or prescription databases are complicated by the differences beneath each study design: the data collection and the population samples. The use of self-reported data has the strength that not only prescription but over-the-counter (OTC) medication was included but it raises another difficulty for the comparison of our study with others. All reported drugs were registered with no differentiation between OTC and prescribed drugs, while prescription databases studies only take into account the use of prescription drugs. However, the fact that a drug has been purchased does not obligatorily mean that it has been taken. The calculation of mean number of drugs used by gender and age groups showed increasing medication use with increasing age in both sexes – a finding in accordance with other studies whilst comparisons are only partial due to the reasons mentioned above.

Nonetheless, and apart the encouragement to bring the medications to the interview, we did not use any standard interviewing technique recommended to increase subject recall. We may, therefore, have underestimated the prevalence of the different drug use regimens.

Conclusions

Polypharmacy was found to be widespread in the population sample from the EPI-Porto study, in particular among women, older, less educated, and subjects living by themselves. Female sex, increasing age and number of visits to physicians were the major determinants of minor and major polypharmacy.

In this population sample, we found that lower education, having a rheumatic disease, and polypharmacy were associated to NSAIDs use. Polypharmacy alone explained NSAIDs use among subjects who had not reported any rheumatic disease.

References

1 Strom BL, Kimmel SE. *Textbook of Pharmacoepidemiology*. Wiley & Sons, 2006

2 Hooft CS, Jong W´t, Dieleman JP, et al. Inappropriate drug prescribing in older adults: the updated 2002 Beers criteria – a population-based cohort study. *Br J Clin Pharmacol*. 2005; **60**: 137-144

3 Vander J et al. Human Physiology: the mechanisms of body function. McGraw-Hill Publ. 2006

4 Fincke BG, Snyder K, Cantillon C, et al. Three complementary definitions of polypharmacy: methods, application and comparison of findings in a large prescription database. *Pharm Drug Saf*. 2005; **14**: 121-128

5 Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM. The development of polypharmacy. A longitudinal study. *Fam Pract*. 2000; **17**: 261-267

6 Colley CA, Lucas LM. Polypharmacy: the cure becomes the disease. *J Gen Intern Med*. 1993; **8**: 278-283

7 Spina E, Scordo MG. Clinically significant drug interactions with antidepressants in the elderly. Review Article. *Drugs Aging*. 2002; **19**(4): 299-320

8 Hallas J, Harvald B, Gram LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med*. 1990; **228**: 83-90

9 Schmader K, Hanlon JT, Weinberger M, et al. Appropriateness of medication prescribing in ambulatory elderly patients. *J Am Geriatr Soc*. 1992; **8**:143-158

10 Cheng HY. Polypharmacy was associated with mortality in the elderly hispanic population: how strong was the association? *J Gerontol A Biol Sci Med Sci.* 2006; **61**(8): M874

11 Espino DV, Bazaldua OV, Palmer RF, Mouton CP, Parchman ML, Miles TP, Markides K. Suboptimal medication use and mortality in an older adult

community-based cohort: results from the Hispanic EPESE Study. *J Gerontol A Biol Sci Med Sci.* 2006; **61**(2):170-175.

12 Buajordet I, Ebbesen J, Eriksen J, Brørs O, Hilberg T. Fatal adverse drug events: the paradox of drug treatment. *J Intern Med*. 2001; **250**(4): 327-341

13 Iwata M, Kuzuya M, Kitagawa Y, Suzuki Y, Iguchi A. Under-appreciated predictors for postdischarge mortality in acute hopsitalized oldest-old patients. *Gerontology*. 2006; **52**(2): 92-98

14 Ebbesen J, Buajordet I, Erikssen J, Brørs O, Svaar H, Sandvik L. Drug related deaths in a department of internal medicine. *Arch Intern Med*. 2001; **161**(19): 2317-2323

15 Thomas HF, Sweetnam PM, Janchawee B, Luscombe DK. Polypharmacy among older men in South Wales. *Eur J Clin Pharmacol* 1999; **55**: 411-415

16 Cadieux RJ. Drug interactions in the elderly: how multiple drug increases risk exponentially. *Postgrad Med*. 1989; **86**(8): 179-186

17 Roberts SJ. Influences of practice characteristics on prescribing in practices. Multiple regression models depend on explanatory variables included. *BMJ*. 1996; **313**: 1551-1551

18 Queneau P. Pitfalls of polypharmacy, particularly in the elderly. *Bull Mem Acad R Med Belg*. 2006; **161**(6): 408-421

19 Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? *Am J Geriatr Pharmacother*. 2007; **5**(1): 31-39

20 Jones BA. Decreasing polypharmacy in clients most at risk. *AACN Clin Issues*. 1997; **8**(4): 627-634.

21 Ibrahim IA, Kang E, Dansky KH. Polypharmacy and possible drug-drug interactions among diabetic patients receiving home health care services. *Home Health Care Serv Q*. 2005; **24**(1-2): 87-99.

22 Jameson JP, VanNoord GR. Pharmacotherapy consultation on polypharmacy patients in ambulatory care. *Ann Pharmacother*. 2001; **35**(7-8): 835-840.

23 Manias E, Claydon-Platt K, McColl GJ, Bucknall TK, Brand CA. Managing complex medication regimens: perspectives of consumers with osteoarthritis and healthcare professionals. *Ann Pharmacother*. 2007; **41**(5): 764-771

24 Aronson JK. In defence of Polypharmacy. Editors´View. *Br J Clin Pharmacol*. 2004; **57**(2): 119-120

25 Goldberg RM, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high risk population. *Am J Emerg Med*. 1996; **14**(5): 447-450

26 Kuijpers MAJ, Marum RJ, Egberts ACG, Jansen PAF, The OLDY study group. Relationship between polypharmacy and underprescribing. *Br J Clin Pharmacol*. 2008; **65**(1): 130-133

27 Lee DS, Tu JV, Juurlink DN, Alter DA, Ko TD, Austin PC, Chong, A, Stukel TA, Levy D, Laupacis A. Risk-treatment mismatch in the pharmacotherapy of heart failure. *JAMA*. 2005; **294**(10): 1240-1247

28 McAlister F, Oreopoulos A, Norris CM, Graham MM, Tsuyuki RT, Knudtson M, Ghali WA. Exploring the treatment risk paradox in coronary disease. *Arch Intern Med*. 2007;**167**(10): 1019-1025

29 Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc*. 2006; **54**: 1516-1526

30 Ko DT, Mamdani M, Alter DA. Lipid lowering therapy with statins in high-risk elderly patients. *JAMA*. 2004; **291**: 1864-1870

31 Cross RK, Wilson KT, Binion DG. Polypharmacy and Crohn's disease. *Aliment Pharmacol Ther*. 2005; **21**: 1211-1216.

32 Chong SA, Ravichandran N, Poon LY, Verma S. Reducing polypharmacy through the introduction of a treatment algorithm : use of a treatment algorithm on the impact of polypharmacy. *Ann Acad Med Singapore*. 2006; **35**: 457-460

33 American Diabetes Association: Clinical Practice Recommendations 2001. *Diab Care*. 2001; **24**(1): S1-S133

34 Grant RW, Cagliero E, Murphy-Sheehy P, Singer DE, Nathan DM, Meigs JB. Comparison of hyperglycemia, hypertension, and hypercholesterolemia management in patients with type 2 diabetes. *Am J Med*. 2002; **112**: 603-609

35 Williams B, Shaw A, Durrant R, Crinson I, Pagliari A, Lusignan A. Patient perspectives on multiple medications versus combined pills: a qualitative study. *Q J Med*. 2005; **98**: 885–893

36 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ*. 2003; **326**: 1419

37 Flores LM, Mengue SS. Drug use by the elderly in Southern Brazil. *Rev Sau Publica*. 2005; **39**(6): 924-929

38 Mamun K, Lien CTC, Goh-Tan CYE, Ang WST. Polypharmacy and inappropriate medication use in Singapore Nursing Homes. *Ann Acad Med Singapore*. 2004; **33**: 49-52

39 Roth MT, Ivey JL. Self-Reported Medication Use in Community-Residing Older Adults: A Pilot Study. *Am J Geriatr Pharmacother*. 2005; **3**(3):196-204

40 Lechevallier-Michel N, Gautier-Bertrand M, Alpérovitch A, et al. Frequency and risk factors of potentially inappropriate medication in community-dwelling elderly populations: results from the 3C study. *Eur J Clin Pharmacol*. 2005; **60**: 813-819

41 Junius-Walker U, Theile G, Hummers-Pradier E. Prevalence and predictors of polypharmacy among older primary care patients in Germany. *Fam Pract*. 2007; **24**: 14-19

42 Gurwitz JH. Polypharmacy. A new paradigm for quality drug therapy in the elderly? *Arch Intern Med*. 2004; **164**: 1957-1959

43 Brekke M, Hunskaar S, Strand J. Self-reported drug utilization, health, and lifestyle factors among 70-74 year old community individuals in Western Norway. The Hordaland Health Study (HUSK). *BMC Public Health*. 2006; **6**: 121-128

44 Bjerrum L, Søgaard J, Hallas J, Kragstrup J. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. *Eur J Clin Pharmacol* 1998; **54**: 197-202

45 Chen YF, Dewey ME, Avery AJ. Self-reported medication use for older people in England and Wales. *J Clin Pharm Ther*. 2001; **26**: 129-140

46 Iobst WF, Bridges CR, Regan-Smith MG. Antirheumatic agents: CNS toxicity and its avoidance. *Geriatrics*. 1989; **44**(4): 95, 99-100, 102.

47 Zochling J, Bohl-Bühler M, Baraliakos X, Feldtkeller E, Braun J. Nonsteroidal anti-inflammatory drug use in ankylosing spondylitis – a population-based survey. *Clin Rheumatol*. 2006; **25**: 794-800

48 Buchanan WW, Kean WF. Osteoarthritis IV: Clinical therapeutic trials and treatment. *Inflammopharmacology*. 2002; **10** (1,2): 79-155

49 Dunn MJ. The role of arachidonic acid metabolites in renal homeostasis: nonsteroidal anti-inflammatory drugs on renal function and biochemical, histological and clinical effects and drug interactions. *Drugs*. 1987; **33** (1): 56-66

50 Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta analysis. *Ann Intern Med*. 1991; **115**: 787-796

51 Lewis JD, Kimmel SE, Localio AR, et al. Risk of serious upper gastrointestinal toxicity with over-the-counter Nonaspirin Nonsteroidal Anti-inflammatory Drugs. *Gastroenterology*. 2005; **129**: 1865-1874

52 Todesco S. Special considerations in the use of NSAIDs in the elderly. *Eur J Rheumatol Inflamm*. 1994; **14**(1): 7-13

53 Viktil KK, Enstad M, Kutschera J, Smedstad LM, Schjøtt J. Polypharmacy among patients admitted to hospital with rheumatic diseases. *Pharm World Sci*. 2001; **23**(4): 153-1518

54 Costa L, Gal D, Barros H. Prevalência auto-declarada de doenças reumáticas numa população urbana. *Acta Reum Port*. 2004; **29**: 169-174

55 Observatório dos Medicamentos e dos Produtos de Saúde. Instituto Nacional da Farmácia e do Medicamento, INFARMED. 2006

56 Ramos E, Lopes C, Barros H. Investigating the Effect of Non-participation Using a Population-Based Case–Control Study on Myocardial Infarction. *Ann Epidemiol*. 2004; **14:** 437-441

Part I

Self-Reported Medication Use and Polypharmacy in a Random Sample of a Portuguese Population

Introduction

Ageing, comorbidities, self-medication and the increasing knowledge on disease prevention and health maintenance leads to the use of multiple medications at one same time.[1] The concurrent use of many medications may be the consequence of evidence-based medical care to optimize the control of complex diseases such as cardiovascular, mental, or metabolic pathologies like diabetes and the associated metabolic risk factors of hypertension and hyperlipidemia.[2,3] Consequently, rational multitargeted polypharmacy and polypills may constitute modern approaches to complex medication regimens designed with the intention of insuring adequate treatment and patient's safety.[4,5]

However, and more frequently, inappropriate prescribing, double prescribing, and unadvised medication use and abuse, give rise to a wide set of concerns about polypharmacy.[6] This concurrent use of several drugs increases the risk of drug-drug interactions, adverse drug reactions, lack of adherence to medication, hospital admission, and drug related mortality.[7-13] The occurrence of such incidents is directly proportional to the sheer number of medications taken and increases with duration of use.[14] With each drug coadministered, the likelihood of an adverse interaction increases exponentially.[15] Moreover, several studies agreed that the number of medications concurrently used is the most important risk factor for the above complications.[16,17]

There is no consensual definition for polypharmacy. Often, it is defined as the number of medications that are being taken simultaneously at any given time. However,

polypharmacy can be approached through different estimators, such as the number of medications that a person is exposed to over time, the quantity of medications taken on a chronic basis, or as the unnecessary overuse of drugs.[18] A criterion for minor and major polypharmacy (as the concurrent use of 2-4 drugs and 5 or more, respectively) has been proposed (and will be used in this analysis).[19,20]

Age, gender, education, employment, social class, and attendance to health care settings were identified as determinants of polypharmacy. Women, elder and less educated people are at increased risk of polypharmacy and inappropriate medication use. [14,19,21,22] However, these findings were based on highly selected populations, such as elderly, hospitalized patients and nursing home populations. [23-26]

The purpose of this study was to analyse the self-reported drug utilization in a random sample of a Portuguese population in order to determine the prevalence of different drug regimens: monopharmacy, minor and major polypharmacy, and to identify individuals particularly at risk of polypharmacy as a whole.

Subjects and Methods

EPI-Porto cohort study participants were first recruited from 1999 to 2003 by random digit dialing using households as sampling units, followed by simple random sampling to select one eligible person older than 17 years old among permanent residents in each household, without allowing for replacement if refusals occurred; 2.488 subjects accepted to participate and attended to and interview at Porto Medical School where they were submitted to medical examination and to a structured questionnaire comprising social, demographic, behaviour, and health related information. Information at every stage was collected by trained interviewers. The second evaluation of the EPI-Porto study started in 2005 and, until February 2007, 1511 participants were re-evaluated and interviewed using the same questionnaire. This study relies on the cross-sectional evaluation of those 1511 participants who were contacted according to the initial inclusion order in the cohort from 2005 to February 2007.

All reported drugs, doses and frequency of use were registered on a medicine-by-medicine basis and classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[27] The interviewers collected detailed information on the frequency and dosage of both prescription and over-the-counter (OTC) medications used during the previous 12 months. Drug use was defined as daily use for at least 14 consecutive days, anytime during the previous 12 months. Since complete drug information was not available for 143 subjects who admitted during the interview that they were unable to recall every medication used, only 1368 were included in this analysis: 847 female (61.9%) and 521 male (38.1%).

Some of the socio-demographic features assessed during the interview included education, as the highest year of school completed, the household size by number of residents, the appreciation of the subjects family income (the subjects classified their family income as “insufficient”, as “needing to be careful with the expenses”, as “enough” or as “comfortable”), and the number of visits to physicians during the previous 12 months. Later in the analysis, the income appreciation is considered as low (“insufficient” and “careful”) and high (“enough” and “comfortable”).

Pearson Chi-square test was used for the comparisons of socio-demographic characteristics according to monopharmacy, minor and major polypharmacy. To estimate the associations adjusted for all variables multinomial regressions models were used in order to compare subjects under monopharmacy, minor and major polypharmacy with subjects who didn't reported drug use. Statistical analysis was performed with SPSS version 14.0.

Results

Out of the 1368 interviewed subjects, 429 (31.4%) reported no use of drugs over a minimum period of 14 days during the previous 12 months (38.0% of men, mean age 47.4 ± 13.7 years; 27.3% of women, mean age 46.4 ± 13.5 years). On the other hand, 939 (68.6%) had taken at least one drug over a 14 days period anytime during the

previous 12 months (62% of men, 72.7% of women), in total 3274 drugs: 1039 drugs used by 323 men, 2235 drugs used by 616 women. This corresponds to an average use of 2.4 (SD, 2.56) drugs per person (men: 2.0, women: 2.6, $p < 0.001$) or 3.5 (SD, 2.40) drugs per individual on any drug for at least 14 days anytime during the previous 12 months.

The maximal number of concurrently used drugs taken by one person during the considered period was 12 for men as well as for women. Among male subjects, 18.0% reported the use of only one drug (monopharmacy), 29.2% reported 2 to 4 drugs (minor polypharmacy), and, 14.8% reported the use of 5 or more drugs (major polypharmacy). Corresponding figures for women were 16.3, 33.8 and 22.7%, respectively, while the overall prevalences summed 17.0, 32.0 and 19.7% (Table 1).

Almost half medications used (45.4%) belonged to one of the twelve most reported drugs or drug groups: benzodiazepine derivatives (N05BA, reported by 20.1% of subjects), statins (C10AA, 19.1%), platelet aggregation inhibitors (B01AC, 11.2%), ACE-inhibitors and blood glucose lowering drugs except insulin (C09AA and A10B, both reported by 9.7% of subjects), nonsteroidal anti-inflammatory drugs (M01A, 8.5%), proton pomp inhibitors (A02BC, 8.0%), B-blockers (C07A, 7.5%), serotonin selective reuptake inhibitors (N06AB, 7.2%), biphosphonates (M05BA, 6.5%), trimetazidine (C01EB15, 6.1%), and Angiotensin II antagonists (C09DA, 5.7%). Fig.1. shows the prevalence of use for each one of the above drug groups according to gender. Although not included in further analysis, calcium and multivitamin supplements were reported by 5.7 and 5.8% of subjects, respectively.

The age and sex-specific prevalences of drug use are shown in Fig.2. The general trend was a decreased prevalence of no drug use and an increased prevalence of drug use with increasing age, especially for women as the prevalences of monopharmacy and minor polypharmacy rapidly increase around the age of 30. This increase is mainly due to the use of contraceptive drugs alone or along with other drugs such as psycholeptics, specially benzodiazepines, which 8.5% of women in this age group used

compared with 3% in the younger age group, and psychoanaleptics, mostly selective serotonin reuptake inhibitors (SSRIs), which were reported by 5.6% of women in this same age group compared with 2.8% in the age group 20 to 29 years. For men, the increase of monopharmacy and minor polypharmacy prevalences are greater around the age of 40 as men used more cardiovascular drugs such as lipid modifying agents, which 9% of them used compared to only 2.1% in the 30-39 age group. Table 2 describes the most frequently used drugs for each age group according to gender.

Monopharmacy increased with age in both sexes, the prevalence of minor polypharmacy increased till the age of 60 decreasing thereafter for both men and women, while major polypharmacy sharply increases and takes over the others drug use regimens of women around the age of 70-79 that reported an average of 4.4 (SD, 2.8) used drugs.

The mean number of drugs reported by women according to their age groups, increased steadily with increasing age as did the prevalences of monopharmacy and major polypharmacy. Men's mean number of reported drugs by age groups increased till the 70-79 age group and slightly decreased for men aged more then 80 years old group, which may be explained by a decrease in the prevalences of minor and major polypharmacy comparatively to the prevalence of monopharmacy for the same age group. Women older then 80 reported the overall higher mean of used drugs: 4.7 (SD, 2.66).

In agreement with the described variations of drug use regimens prevalences, bivariate analysis (Table 1) showed that females and increasing age were associated with greater drug use, especially major polypharmacy (p for trend<0.001). Low education level, low income, small households, and increasing number of visits to a physician were also found to be associated with increasing drug use and major polypharmacy (p for trend<0.001, Table 1).

The results from the unadjusted multinomial regression models that compared subjects who reported monopharmacy, minor and major polypharmacy to subjects who reported

no drug use are presented in Table 3 and corroborated bivariate analysis results for the above variables as older subjects were more likely to be under monopharmacy (OR, 1.05, 95%CI [1.03-1.06]) alike less educated subjects (OR, 2.12, 95%CI [1.48-3.18]), and those who attended more to a physician during the previous 12 months (OR, 1.23, 95%CI [1.14-1.33]). The odds increased for polypharmacy, both minor and major, and got greater for major polypharmacy. Female subjects had a 61% increased risk of being under a minor polypharmacy regimen than men (95%CI [1.23-2.12]) and a 2.14 OR for major polypharmacy (95%CI [1.54-2.96]), as less educated subjects were also more likely to had used 2 to 4 drugs (OR, 5.95, 95% CI [4.16-8.53]) and 5 or more than more educated ones (OR, 8.48, 95%CI [5.57-12.92]). Subjects that attended more times to physicians during the previous year had also an increased risk for minor polypharmacy that reached around 40% compared to those who never went to see one and a 55% increased risk of being under major polypharmacy (95%CI [1.45-1.67]). Having a 2.6 fold risk for minor polypharmacy, subjects living by themselves were also at a much higher risk for major polypharmacy (OR, 2.61, 95%CI [1.63-4.19]) than subjects living in households of 2, 3, 4 or more persons. Subjects who appreciated their income as “low” had a 2 fold risk for major polypharmacy compared to those with “high” incomes (OR, 2.06, 95%CI [1.51-2.81]) which is 38% higher than the risk of being under minor polypharmacy (OR, 1.68, 95%CI [1.28-2.20]).

Female high risk for minor and major polypharmacy remained after adjustment for age, education, household size, income appreciation, and number of visits to a physician (major polypharmacy OR, 2.62, 95%CI [1.71-4.03], see Table 4). None of the other variables included in the adjusted model showed a significant association to monopharmacy regimen, excepting increasing age (OR, 1.05, 95%CI [1.03-1.06]) and number of visits to a physician (OR, 1.19, 95%CI [1.10-1.29]). The same variables were also associated to minor polypharmacy: the age associated risk increased 5% (OR, 1.10, 95%CI [1.08-1.12]) while the risk associated to the number of visits physicians increased 15% (OR, 1.34, 95%CI [1.24-1.44]). Apart from female sex, the

risk of major polypharmacy was also found to be associated with increasing age (OR, 1.15, 95%CI [1.13-1.17]) and with the number of visits to physicians during the previous 12 months. Subjects who attended more times to a physician had a 50% higher risk of being under major polypharmacy (95%CI [1.37-1.61]).

Discussion

Polypharmacy, frequently defined as the concurrent use of multiple medications, has the potential to cause adverse drug reactions and drug-induced symptoms that may mimic and be misinterpreted as new medical problems and consequently produce prescribing cascades that lead to the prescription or to the unadvised use of additional drugs, with absolutely no further benefits.[28]

The knowledge about the prevalence of drug use regimens such as monopharmacy, minor and major polypharmacy, has never been estimated for the Portuguese population. The importance of ageing in European populations, especially in Portugal, makes it important to determine whether the available therapeutic arsenal is being used in the profit of improved health of individuals and lower burden for societies or not. It is also important to identify the individuals at risk of multiple and concurrent medication use in order to closely monitor the occurrence of eventual adverse drug reactions, and to make possible the development of strategies to improve and optimize drug safety of use: no superfluous drugs, no individual or governmental avoidable costs, improved therapy adherence, and the insurance of lower risks.

Polypharmacy studies are mainly based on highly selected populations such as hospitalized patients or institutionalized elderly. Only a few have been based on data from the general population, usually recurring to prescription databases which are not available in Portugal. The electronic registry of prescription related data – the prescribed medications and the prescription refilling, is yet at an experimental stage.

Therefore, direct comparisons with other studies based on highly selected population samples or prescription databases are complicated by the differences beneath each

study design: the data collection and the population samples. Another difficulty in the comparison of our study with others is that the EPI-Porto study questionnaire did not differentiated prescription drugs from OTC drugs. All reported drugs were registered with no differentiation between OTC and prescribed drugs, while prescription databases studies only take into account the use of prescription drugs.

We found that 31.4% of our sample did not use any medication over a 14 days period anytime during the 12 months previous to the follow-up interview. The overall mean number of reported drugs was 2.39 (SD, 2.56), and the mean number of drugs per individual on any drug for at least 14 days was 3.49 (SD, 2.40) which corresponds to 68.6% of our sample. The average number of reported drugs was found to be subsequently higher as the subjects were older. Women aged 60 years old and more reported an average of 3.99 drugs and women aged over 70 reported an average of 4.47 drugs. Corresponding figures for men were 3.19 and 3.68 drugs. Even though these figures include both prescription and OTC drugs, they are greater than the results presented by studies based on elderly populations like Brekke *et al*. study on self-reported medication use by 70 year old Norwegian elderly living in the community and Chen *et al*. study on self-reported medication use by 65 year old from England and Wales living in both community and institutions.[22,29] On the contrary, the averages of drug use we have found in this sample are smaller than those reported by older primary care patients in Germany. [28]

The prevalence of monopharmacy and polypharmacy, both minor and major, are also difficult to compare because of the same differences in studies design. However, the overall prevalences of 17, 32 and 19.7%, respectively, are quite concerning, especially major polypharmacy that was reported by 14.8% of men and 22.7% of women. Once more, our findings showed evidence of greater medication use, particularly by women and elderly. Prescription-databases studies, which do not include OTC, may underestimate the occurrence of polypharmacy and then partially explain why medication use is more prevalent in our study. Moreover, the fact that a drug has been

purchased does not obligatorily mean that it has been taken. Nonetheless, and apart the encouragement to bring the medications to the interview, we did not use any standard interviewing technique recommended to increase subject recall, such as picture books or calendars, to minimize recall bias, and the effect of time on reported usage seems to model the accuracy of medication use recall, specially over 12 months.[30-32] Recall bias may have occurred if patients with chronic diseases were more likely to remember their medication then others. Other factors studied such as education and age might also have influenced recall bias. We may, therefore, have underestimated the prevalences of the different drug use regimens.

Polypharmacy increases with age, and is more frequent among women, less educated people and among lower social classes.[14,19,21-26] We too found that female sex, increasing age, low education, low income, small households and people living by themselves, and increasing number of visits to a physician during the previous 12 months were associated with increasing drug use and major polypharmacy.

In the multinomial regression models we distributed our population sample into 4 groups according to the different drug use regimens: no drug use (reference group), monopharmacy, minor polypharmacy, and major polypharmacy. After statistical adjustment for sex, age, education, household size, number of visits to a physician and income appreciation, only increasing age and the number of visits physicians were found to be significantly associated to monopharmacy and the odds increased for minor and major polypharmacy. Female sex was found to be associated to polypharmacy, with increasing odds from minor to major polypharmacy, but no association was found with monopharmacy. Indeed, monopharmacy was more prevalent among men between 40 and 89 years old and corresponded to the use of single cardiovascular drugs, such as ACEI, B-blockers, platelet aggregation inhibitors, statins, Angiotensin II – antagonists, and drugs to treat prostate benign hypertrophy.

The most reported drugs in this sample of the Portuguese population were benzodiazepines derivatives: 20.1% of subjects reported their use, 80% of which were

women. Benzodiazepines were common as single medication and as part of minor and major polypharmacy regimens both in men and women. We found that its use in women was frequently associated to antidepressants, mainly SSRIs, in minor polypharmacy regimens. Among French elderly, female sex, antidepressant use, and multiple drug use were also strongly associated to benzodiazepines use.[33] An association between antidepressants use and heterogeneous drug regimens of more than 8 drugs in both young and older patients has also been described.[34] Since drug treatment of depression in old age is known to be associated with an increased risk of adverse drug interactions, the high prevalence of benzodiazepines and SSRIs use in the Portuguese population a major concern. SSRIs, in particular, fluoxetine and paroxetine, the 2 drugs with higher shares in the Portuguese antidepressant pharmaceutical market and the most reported antidepressants in our study are potent inhibitors of CYP2D6 and should be avoided in elderly people when coadministered with antipsychotics, opioids, B-blockers, and antiarrhythmics. Fluoxetine, alone, has also the potential to inhibit CYP2C9 isoenzyme, which has for specific substrates NSAIDs like diclofenac, ibuprofen and naproxen, and their coadministrations were found to be quite common in our sample: 5.90, 1.60 and 0.96%, respectively.[35] The combined use of SSRIs and NSAIDs strongly increases the risk of gastrointestinal adverse effects and should be avoided.[36] This may reflect a low perception of the overall therapeutic regimen of patients when these attend to different professionals to treat coexisting pathologies, or it may be an indication that patients may be continuing the use of antidepressants and antipsychotics even after being told to stop. Indeed, a more effective coordination of care and communication of information about all medications prescribed to their patients between providers could overcome the fact that the number of prescribing physicians may be an independent risk factor for patients self-reporting an adverse drug reaction.[37] A close cooperation between health care practitioners and pharmacists could identify and prevent problems resulting from multiple drug use.

Among the other most reported drugs, platelet aggregation inhibitors and NSAIDs use also deserve close monitoring as they too are very likely to cause severe adverse drug reactions, drug-drug interactions, and drug-diseases interactions.[38-43] Since the identification of inappropriate drug use was not one of the aimed objectives of our study, we did not investigated further potentially harmful associations.

The more our participants reported visits to physicians during the 12 months before the interview, the more drugs they reported to use, and polypharmacy and all its consequent risks may then be the result of overprescrition or overuse of drugs with the single purpose of treating symptoms before a proper diagnosis. That may be the case of benzodiazepines, frequently prescribed for insomnia, or proton-pomp inhibitors to relief upper digestive symptoms or peptic ulcers over a long period of time due to their relatively high tolerance profile.[44] A French inquiry of the national health insurance has noticed that the number of consumers of anxiolytics and hypnotics increased with increasing age while, on the contrary, the prevalence of anxiety symptoms decreased.[45]

Conclusions

The concurrent use of several different drugs, or polypharmacy, was found to be widespread in the population, in particular among women, older people, less educated, and subjects living by themselves. Sex, increasing age and number of visits to physicians were the major determinants of minor and major polypharmacy.

Figure 1

Prevalence of the most reported drug groups (females – *hatched bars*, males – *striped bars*)

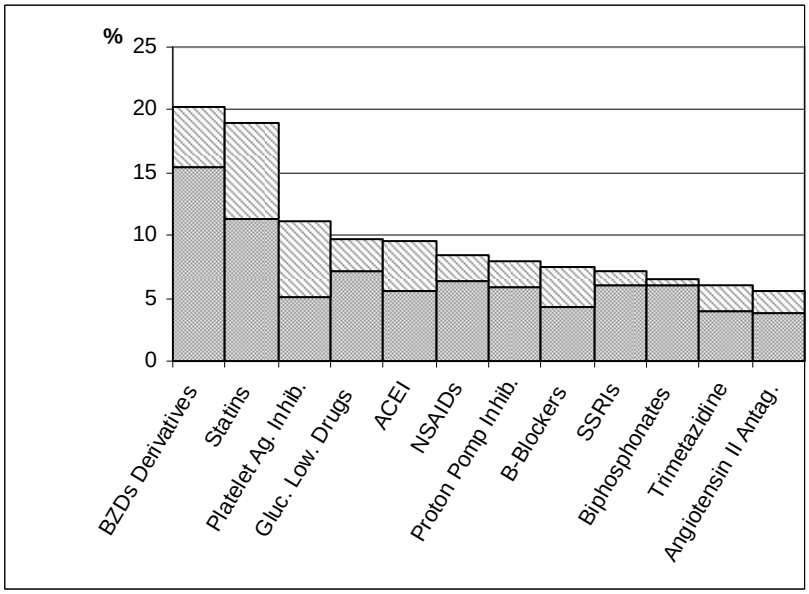
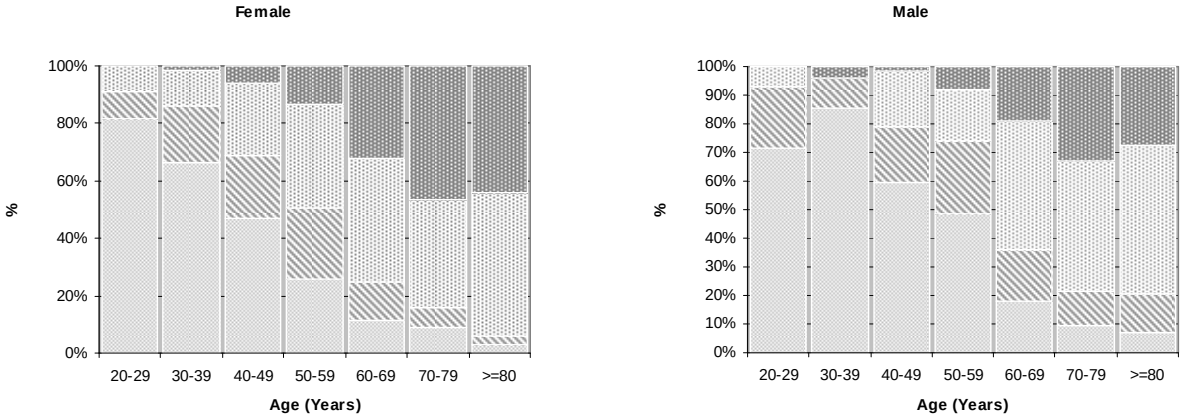


Figure 2

Age-specific prevalences of no drug use (0), monopharmacy (1 drug), minor polypharmacy (2 to 4 drugs) and major polypharmacy (5 or more drugs) in female and male over a 14 days period anytime during the previous 12 months.



Legend: 0 1 2 to 4 5 or more

Table 1

Prevalence of drug regimens according to socio-demographic factors

		n	Use of any drug n (%)	Monopharmacy n (%)	Minor Polypharmacy n (%)	Major Polypharmacy n (%)	p*
Overall		1368	939 (68.6)	232 (17.0)	438 (32.0)	269 (19.7)	
Sex	Male	521	323 (38.0)	94 (18.0)	152 (29.2)	77 (14.8)	<0.001
	Female	847	616 (27.3)	138 (16.3)	286 (33.8)	192 (22.7)	
Age	20-44	268	82 (30.6)	46 (17.2)	29 (10.8)	7 (2.6)	
	45-64	609	422 (69.3)	133 (21.8)	204 (33.5)	85 (14.0)	<0.001
	>= 65	469	431 (91.9)	49 (10.4)	205 (43.7)	177 (37.7)	
Education	0-4	501	419 (83.6)	78 (15.6)	204 (40.7)	147 (29.3)	
	5-11	427	339 (79.4)	70 (16.4)	141 (33.0)	75 (17.6)	<0.001
	>= 12	434	174 (40.1)	90 (20.7)	91 (21.0)	46 (10.6)	
Income Appreciation	Low						
	Insufficient	155	121 (78.1)	26 (16.8)	52 (33.5)	43 (27.7)	
	Careful	485	354 (73.0)	74 (15.3)	172 (35.5)	108 (22.3)	<0.001
	High						
	Enough	484	326 (67.4)	86 (17.8)	150 (31.0)	90 (18.6)	
	Comfortable	241	136 (56.4)	46 (19.1)	63 (26.1)	27 (11.2)	
Household Size	1	189	146 (77.2)	19 (10.1)	67 (35.4)	60 (31.7)	
	2-3	878	626 (71.3)	154 (17.5)	190 (33.0)	182 (20.7)	<0.001
	>= 4	300	166 (55.3)	59 (19.7)	80 (26.7)	27 (9.0)	
Visits to GP	0	176	58 (33.0)	31 (17.6)	23 (13.1)	4 (2.3)	
	1	269	149 (55.4)	53 (19.7)	77 (28.6)	19 (7.1)	
	2-6	762	592 (77.7)	133 (17.5)	287 (37.7)	172 (22.6)	<0.001
	> 6	161	140 (87.0)	15 (9.3)	51 (31.7)	74 (46.0)	

***** Pearson χi^{2} p-value

Table 2

Main reported drugs for each drug regimen according to sex and age (ATC codes)

Age Groups	n	Mean no. of drugs (SD)	Monopharmacy	Minor Polypharmacy	Major Polypharmacy
Female	847				
20-29	33	0.36 (0.93)	Antianemic preparations (B03), Analgesics (N02), Decongestants for topical use (R01A)	SSRIs (N06AB), Antihistamines for systemic use (R06A), Adrenergic inhalants (R03A)	No report
30-39	71	0.59 (1.06)	Laxatives (A06), Antidiarrheals (A07), Sex Hormones (G03), Thyroid Hormones (H03AA), Antianemic preparations (B03), Benzodiazepines (N05BA), Antidepressants (N06A), Decongestants for topical use (R01A)	Benzodiazepines (N05BA), SSRIs,(N06AB) Laxatives (A06), Antianemic preparations (B03), Fibrates (C10AB), Diuretic Sulfonamides (C03BA), Sex Hormones (G03), Thyroid Hormones (H03AA), Angiotensin II – antagonists (C09D)	Biguanides (A10BA), Lipid Modifying Agents (C10A), Diuretics (C03), Antiobesity drugs (A08)
40-49	134	1.21 (1.74)	Statins (C10AA), ACEI (C09AA), Benzodiazepines (N05BA), SSRIs (N06AB)	Benzodiazepines (N05BA), SSRIs (N06AB), ACEI (C09AA), Statins (C10AA), Sex Hormones (G03), Thyroid Hormones (H03AA), B-blockers (C07), Biguanides (A10BA)	Benzodiazepines (N05BA), SSRIs (N06AB), Proton pomp inhibitors (A02BC)
50-59	216	2.08 (2.09)	Angiotensin II – antagonists (C09DA), Statins (C10AA), Thyroid Hormones (H03AA), NSAIDs (M01A), Antidepressants (N06A), Benzodiazepines (N05BA),	Benzodiazepines (N05BA), SSRIs (N06AB), ACEI (C09AA), Statins (C10AA), Sex Hormones (G03), Diuretics (C03), NSAIDs (M01A), Thyroid Hormones (H03AA), Biphosphonates (M05BA), Proton pomp inhibitors (A02BC), Vasoprotectives (C05BA), B-blockers (C07)	SSRIs (N06AB),Benzodiazepines (N05BA), Statins (C10AA), Proton pomp inhibitors (A02BC), Diuretic Sulfonamides (C03BA), ACEI (C09AA), Vasoprotective drugs (C05BA), B-blockers (C07)
60-69	201	3.53 (2.57)	Proton pomp inhibitors (A02BC), Biphosphonates (M05BA), Benzodiazepines (N05BA)	Benzodiazepines (N05BA), Angiotensin II – antagonists (C09), Statins (C10AA), Biphosphonates (M05BA), NSAIDs (M01A), Diuretics (C03), SSRIs (N06AB), Proton pomp inhibitors (A02BC), Sex Hormones (G03CA)	Benzodiazepines (N05BA), SSRIs (N06AB), Angiotensin II – antagonists (C09), Statins (C10AA), Blood glucose lowering drugs exc. Insulin (A10B), Diuretics (C03), B-blockers (C07), Platelet aggregation inhibitors (B01AC), NSAIDs (M01A)
70-79	159	4.43 (2.81)	Lipid modifying drugs (C10A), Diuretics (C03)	Benzodiazepines (N05BA), Statins (C10AA), ACEI (C09A), Biphosphonates (M05BA), Trimetazidine (C01EB15), Platelet aggregation inhibitors (B01AC), Diuretics (C03), Ca^{2+} Channel blockers (C08A), SSRIs (N06AB),	Angiotensin II – antagonists (C09), Benzodiazepines (N05BA), Statins (C10AA), Trimetazidine (C01EB15), Platelet aggregation inhibitors (B01AC), Diuretics (C03), Proton pomp inhibitors (A02BC), Ca^{2+} Channel blockers (C08A), NSAIDs (M01A), Vasoprotective drugs (C05CA), Biphosphonates (M05BA)
≥ 80	33	4.68 (2.66)	Benzodiazepines (N05BA)	ACEI (C09AA), Benzodiazepines (N05BA), Platelet aggregation inhibitors (B01AC),Statins (C10AA)	Trimetazidine (C01EB15), ACEI (C09AA), Benzodiazepines (N05BA), Proton pomp inhibitors (A02BC), Statins (C10AA), Diuretic Sulfonamides (C03CA), Peripheral vasodilators (C04), Vasoprotectives (C05CA), Ca^{2+} Channel blockers (C08A)
Male	521				
20-29	28	0.46 (0.96)	Propulsives (A03FA), Urological preparations (G04), Thyroid Hormones (H03AA), Anxiolytics (N05)	Drugs for functional bowel disorders (A03AA), Laxatives (A06), Anxiolytics (N05), B-blockers (C07A), SSRIs (N06AB)	No report
30-39	48	0.31 (1.04)	Laxatives (A06), B-blockers (C07), NSAIDs (M01), Thyroid Hormones (H03AA),ACEI (C09AA)	No report	Benzodiazepine (N05BA), Lipid Modifying agents (C10A), Urological preparations (G04CA)
40-49	67	0.78 (1.32)	Platelet aggregation inhibitors (B01AC), B-blockers (C07), Antiepileptics (N03AG)	Statins (C10AA), Benzodiazepines (N05BA)	Benzodiazepines (N05BA), SSRIs (N06AB), Statins (C10AA), Platelet aggregation inhibitors (B01AC), B-blockers (C07)
50-59	134	1.34 (2.14)	Statins (C10AA), ACEI (C09AA), NSAIDs (M01A), Vasoprotectives (C05CA)	Statins (C10AA), ACEI (C09AA), Platelet aggregation inhibitors (B01AC), B-blockers (C07), SSRIs (N06AB), Ca^{2+} Channel blockers (C08CA)	Statins (C10AA), ACEI (C09AA), Platelet aggregation inhibitors (B01AC), Proton pomp inhibitors (A02BC), B-blockers (C07), Trimetazidine (C01EB15), Ca^{2+} Channel blockers (C08CA), Antigout preparations (M04A), Benzodiazepines (N05BA),
60-69	112	2.63 (2.19)	Statins (C10AA), Angiotensin II – antagonists (C09DA), Benign prostatic hypertrophy drugs (G04CA)	Statins (C10AA), ACEI (C09AA), Platelet aggregation inhibitors (B01AC), Blood glucose lowering drugs exc. Insulin (A10B), Benzodiazepines (N05BA), Trimetazidine (C01EB15), B- blockers (C07)	Angiotensin II – antagonists (C09), Statins (C10AA), Blood glucose lowering drugs exc. Insulin (A10B), B-blockers (C07), Benzodiazepines (N05BA), Diuretics (C03C), Platelet aggregation inhibitors (B01AC)
70-79	103	3.73 (2.67)	Benign prostatic hypertrophy drugs (G04CA), NSAIDs (M01A), Antigout preparations (M04A), Platelet aggregation inhibitors (B01AC)	Angiotensin II – antagonists (C09), Platelet aggregation inhibitors (B01AC), Statins (C10AA), Benign prostatic hypertrophy drugs (G04CA), Trimetazidine (C01EB15), Benzodiazepines (N05BA)	Angiotensin II – antagonists (C09), Statins (C10AA), Platelet aggregation inhibitors (B01AC) Benzodiazepines (N05BA), Benign prostatic hypertrophy drugs (G04CA), Trimetazidine (C01EB15), Ca^{2+} Channel blockers (C08A), B-blockers (C09)
≥ 80	29	3.52 (2.53)	Angiotensin II – antagonists (C09A), Benign prostatic hypertrophy drugs (G04CA)	Benign prostatic hypertrophy drugs (G04CA), Blood glucose lowering drugs exc. Insulin (A10B), Benzodiazepines (N05BA), Angiotensin II – antagonists (C09)	Platelet aggregation inhibitors (B01AC), Trimetazidine (C01EB15), ACEI (C09AA), Proton pomp inhibitors (A02BC), Diuretics (C03), Statins (C10AA), Benign prostatic hypertrophy drugs (G04CA)

Table 3

Unadjusted individual OR (95%CI) for monopharmacy, minor and major polypharmacy

		n	Monopharmacy	Minor Polypharmacy	Major Polypharmacy
Sex	Female	847	1.26 (0.91-1.74)	1.61 (1.23-2.12)	2.14 (1.54-2.96)
	Male	521	1.0	1.0	1.0
Age		1368	1.05 (1.03-1.06)	1.10 (1.09-1.12)	1.15 (1.13-1.17)
Education	0-4	501	2.12 (1.42-3.18)	5.95 (4.16-8.53)	8.48 (5.57-12.92)
	5-11	427	1.14 (0.78-1.67)	2.28 (1.62-3.19)	2.39 (1.57-3.66)
	>= 12	434	1.0	1.0	1.0
Income Appreciation	Low	640	1.21 (0.87-1.67)	1.68 (1.28-2.20)	2.06 (1.51-2.81)
	High	725	1.0	1.0	1.0
Household Size	1	189	1.00 (0.54-1.87)	2.61 (1.63-4.19)	6.93 (3.92-12.24)
	2-4	878	1.39 (0.96-2.00)	1.93 (1.39-2.67)	3.58 (2.27-5.65)
	> 4	300	1.0	1.0	1.0
Visits to GP		1368	1.23 (1.14-1.33)	1.40 (1.31-1.50)	1.55 (1.45-1.67)

Table 4

Adjusted OR* (95%CI) for monopharmacy, minor and major polypharmacy

		n	Monopharmacy	Minor Polypharmacy	Major Polypharmacy
Sex	Female	847	1.25 (0.88-1.76)	1.75 (1.25-2.45)	2.62 (1.71-4.03)
	Male	521	1.0	1.0	1.0
Age		1368	1.05 (1.03-1.06)	1.10 (1.08-1.12)	1.15 (1.13-1.17)
Education	0-4	501	1.09 (0.66-1.79)	1.61 (1.01-2.56)	1.44 (0.81-2.57)
	5-11	427	0.81 (0.53-1.23)	1.24 (0.83-1.87)	1.09 (0.63-1.86)
	>=12	434	1.0	1.0	1.0
Income	Low	640	1.01 (0.70-1.45)	1.10 (0.78-1.55)	1.22 (0.80-1.85)
	High	725	1.0	1.0	1.0
Household Size	1	189	0.63 (0.33-1.23)	0.69 (0.38-1.27)	1.02 (0.48-2.16)
	2-4	878	0.99 (0.67-1.47)	0.81(0.55-1.20)	1.07 (0.61-1.86)
	> 4	300	1.0	1.0	1.0
Visits to GP		1368	1.19 (1.10-1.29)	1.34 (1.24-1.44)	1.49 (1.37-1.61)

*OR adjusted for all variables in the model: sex, age, education, household size, number of visits to the GP, and income appreciation

References

1 Zarowitz BJ, Stebelsky LA, Muma BK, Romain TM, Peterson EL. Reduction of High-Risk Polypharmacy Drug Combinations in Patients in a Managed Care Setting Pharmacotherapy. *Pharmacotherapy*. 2005; **25**(11): 1636-1645

2 American Diabetes Association: Clinical Practice Recommendations 2001. *Diab Care*. 2001; **24**(1): S1-S133

3 Grant RW, Cagliero E, Murphy-Sheehy P, Singer DE, Nathan DM, Meigs JB. Comparison of hyperglycemia, hypertension, and hypercholesterolemia management in patients with type 2 diabetes. *Am J Med*. 2002; **112**: 603-609

4 Williams B, Shaw A, Durrant R, Crinson I, Pagliari A, Lusignan A. Patient perspectives on multiple medications versus combined pills: a qualitative study. *Q J Med*. 2005; **98**: 885–893

5 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ*. 2003; **326**: 1419

6 Hooft CS, Jong W´t, Dieleman JP, et al. Inappropriate drug prescribing in older adults: the updated 2002 Beers criteria – a population-based cohort study. *Br J Clin Pharmacol*. 2005; **60**: 137-144

7 Hallas J, Harvald B, Gram LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med*. 1990; **228**: 83-90

8 Schmader K, Hanlon JT, Weinberger M, et al. Appropriateness of medication prescribing in ambulatory elderly patients. *J Am Geriatr Soc*. 1992; **8**:143-158

9 Cheng HY. Polypharmacy was associated with mortality in the elderly hispanic population: how strong was the association? *J Gerontol A Biol Sci Med Sci.* 2006; **61**(8): M874

10 Iwata M, Kuzuya M, Kitagawa Y, Suzuki Y, Iguchi A. Under-appreciated predictors for postdischarge mortality in acute hopsitalized oldest-old patients. *Gerontology*. 2006; **52**(2): 92-98

11 Ebbesen J, Buajordet I, Erikssen J, Brørs O, Svaar H, Sandvik L. Drug related deaths in a department of internal medicine. *Arch Intern Med*. 2001; **161**(19): 2317-2323

12 Krähenbühl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. Drug-related problems in hospitals: a review of the recent literature. *Drug Saf*. 2007; **30**(5): 379-407

13 Buajordet I, Ebbesen J, Erikssen J, Brørs O, Hilberg T. Fatal adverse drug events: the paradox of drug treatment. *J Intern Med*. 2001; **250**: 327-341

14 Thomas HF, Sweetnam PM, Janchawee B, Luscombe DK. Polypharmacy among older men in South Wales. *Eur J Clin Pharmacol* 1999; **55:** 411-415

15 Cadieux RJ. Drug interactions in the elderly: how multiple drug increases risk exponentially. *Postgrad Med*. 1989; **86** (8): 179-186

16 Colley CA, Lucas LM. Polypharmacy: the cure becomes the disease. *J Gen Intern Med*. 1993; **8**: 278-283

17 Roberts SJ. Influences of practice characteristics on prescribing in practices. Multiple regression models depend on explanatory variables included. *BMJ*. 1996; **313**: 1551-1551

18 Fincke BG, Snyder K, Cantillon C, et al. Three complementary definitions of polypharmacy: methods, application and comparison of findings in a large prescription database. *Pharm Drug Saf*. 2005; **14**: 121-128

19 Bjerrum L, Søgaard J, Hallas J, Kragstrup J. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. *Eur J Clin Pharmacol* 1998; **54:** 197-202

20 Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM. The development of polypharmacy. A longitudinal study. *Fam Pract*. 2000; **17**: 261-267

21 Flores LM, Mengue SS. Drug use by the elderly in Southern Brazil. *Rev Sau Publica*. 2005; **39**(6): 924-949

22 Chen YF, Dewey ME, Avery AJ. Self-reported medication use for older people in England and Wales. *J Clin Pharm Ther*. 2001; **26**: 129-140

23 Mamun K, Lien CTC, Goh-Tan CYE, Ang WST. Polypharmacy and inappropriate medication use in Singapore Nursing Homes. *Ann Acad Med Singapore*. 2004; **33**: 49-52

24 Roth MT, Ivey JL. Self-Reported Medication Use in Community-Residing Older Adults: A Pilot Study. *Am J Geriatr Pharmacother*. 2005; **3**(3): 196-204

25 Lechevallier-Michel N, Gautier-Bertrand M, Alpérovitch A, et al. Frequency and risk factors of potentially inappropriate medication in community-dwelling elderly populations: results from the 3C study. *Eur J Clin Pharmacol*. 2005; **60**: 813-819

26 Junius-Walker U, Theile G, Hummers-Pradier E. Prevalence and predictors of polypharmacy among older primary care patients in Germany. *Fam Pract*. 2007; **24**: 14-19

27 Guidelines for ATC Classification; 2007. WHO Collaborating Centre for Drugs Statistics Methodology, Oslo.

28 Gurwitz JH. Polypharmacy. A new paradigm for quality drug therapy in the elderly? *Arch Intern Med*. 2004; **164**: 1957-1959

29 Brekke M, Hunskaar S, Strand J. Self-reported drug utilization, health, and lifestyle factors among 70-74 year old community individuals in Western Norway. The Hordaland Health Study (HUSK). *BMC Public Health*. 2006; **6**: 121-128

30 Atkin P, Stringer R, Duffy J et al. The influence of information provided by patients on the accuracy of medication records. *Med J Aust*. 1998; **28**: 394-400

31 Lewis JD, Strom BL, Kimmel SE, et al. Predictors of Recall of over-the-counter and prescription non-steroidal anti-inflammatory drug exposure. *Pharmacoepidem Dr S*. 2006; **15**: 39-45

32 Kimmel SE, Lewis JD, Jaskowiak J, Kishel L, Hennessy S. Enhancement of medication recall using medication pictures and lists in telephone interviews. *Pharmacoepidemiol Drug Saf*. 2003; **12**(1): 1-8.

33 Fourrier A, Letenneur L, Dartigues JF, Moore N, Begaud B. Benzodiazepine use in an elderly community-dwelling population. Characteristics of users and factors associated with subsequent use. *Eur J Clin Pharmacol*. 2001; **57**(5): 419-425

34 Silkey B, Preskorn SH, Golbeck A, et al. Complexity of medication use in the Veterans Affairs healthcare system: Part II. Antidepressant use among younger and older outpatients. *J Psychiatr Pract*. 2005; **11**(1): 16-26

35 Spina E, Scordo MG. Clinically significant drug interactions with antidepressants in the elderly. Review Article. *Drugs Aging*. 2002; **19**(4): 299-320

36 de Jong JCF, van den Berg PB, Tobi H, de Jong-van den Berg LTW. Combined use of SSRIs and NSAIDs increases the risk of gastrointestinal adverse effects. *Br J Clin Pharmacol*. 2002; **55**: 591-595

37 Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? *Am J Geriatr Pharmacother*. 2007; **5** (1): 31-39

38 Lanas A, Perez-Aisa MA, Feu F, et al. A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with Nonsteroidal Antiinflammatory Drug Use. *Am J Gastroenterol*. 2005; **100**:1685-1693

39 Monster TBM, de Jong PE, de Jong-van dem Berg LTW. Drug-induced renal function impairment: a population-based survey. *Pharmacoepidem Dr S*. 2003; **12**: 135-143

40 Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly people. *Ann Int Med*. 1991; **114** (4): 257-263

41 Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta analysis. *Ann Intern Med*. 1991; **115**: 787-796

42 Lewis JD, Kimmel SE, Localio AR, et al. Risk of serious upper gastrointestinal toxicity with over-the-counter Nonaspirin Nonsteroidal Anti-inflammatory Drugs. *Gastroenterology*. 2005; **129**: 1865-1874

43 Lindblad CI, Hanlon JT, Gross CR, et al. *Consensus Statement* Clinically Important Drug-Disease Interactions and Their Prevalence in Older Adults. *Clin Ther.* 2006; **28**: 1133-1143

44 Legrain S. Consommation Médicamenteuse chez le Sujet Agé. Consommation, Prescription, Iatrogénie et Observance. Haute Autorité de Santé. RAPPORT, DOCUMENT PAPIER, 2005/09, FRA, FRE. HAS/SEP/SL/AD/CC. 2005

45 Lecadet J, Bidal P, Baris B, Vallier N, Fender P, Allemand H. Médicaments psychotropes: consommation et pratiques de prescription en France métropolitaine: I – Données nationales, 2000. *Rev Méd Assur Mal*. 2003; **34**(2): 75-84

Part II

Non-Steroidal Anti-Inflammatory Drugs Use, the Self-Report of Rheumatic Diseases and Polypharmacy

Introduction

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used for analgesic, anti-inflammatory, and antipyretic purposes, and are the most frequently prescribed drugs to treat pain associated with osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and other musculoskeletal conditions. [1]

The well known common side effects of NSAIDs constitute the major therapeutic limitation to the successful management of musculoskeletal symptoms and disability.[2] Used mainly to treat chronic pain, NSAIDs benefits come at the expense of important adverse effects in kidney (inhibition of renal prostaglandin), cardiovascular homeostatic mechanisms, liver, skin, and platelet function, and the risk of clinically important injuries to gastrointestinal mucosa, ultimately resulting in ulceration, perforation, and haemorrhage.[3,4] However, the risk of this gastrointestinal complications varies with duration of use and NSAID dosage. [5]

Potentially severe adverse events tend to overcome long-term oral NSAIDs advantages, leading to the recommendation of acetaminophen as the first-line pharmacological treatment for symptomatic OA. [6,7]

Elderly people suffering from rheumatic diseases are particularly prone to use NSAIDs.[8,9] NSAIDs are also the first choice as over-the-counter (OTC) pain medications. [10]

There is limited knowledge regarding the prevalence of NSAIDs use in Portugal population as for the prevalence of polypharmacy. Although polypharmacy has no consensually accepted definition, it is generally defined in terms of the number of

medications that are being taken at any given time; a simultaneous use of many drugs, which increases the odds of adverse drug reactions (ADRs), medication errors, drug-drug interactions, and low medication adherence.[11] The association between rheumatic diseases, particularly rheumatoid arthritis and osteoarthritis, and polypharmacy has already been established.[12,13] A criterion for minor polypharmacy (concurrent use of two to four drugs) and major polypharmacy (concurrent use of 5 or more drugs) has been proposed and is used in this analysis. [14]

After a previous study in Porto, it was possible to estimate that approximately 1.200.000 women and 430.000 men suffered from at least one rheumatic disease in Portugal.[15] By the end of 2006, more than 10 million packages of NSAIDs were prescribed in Portugal, resulting in a total cost to the national health system of approximately 80 million euros.[16]

The purpose of this study was to estimate the prevalence of self-reported NSAIDs use, and to analyse its relation to the self-report of rheumatic diseases and polypharmacy using a representative sample of the Porto population.

Subjects and Methods

EPI-Porto cohort study participants were first recruited from 1999 to 2003 by random digit dialing using households as sampling units, followed by simple random sampling to select one eligible person older than 17 years old among permanent residents in each household, without allowing for replacement if refusals occurred; 2.488 subjects accepted to participate and attended to and interview at Porto Medical School where they were submitted to medical examination and to a structured questionnaire comprising social, demographic, behaviour, and health related information. Information at every stage was collected by trained interviewers. The second evaluation of the EPI-Porto study started in 2005 and, until February 2007, 1511 participants were re-evaluated and interviewed using the same questionnaire. This study relies on the

cross-sectional evaluation of those 1511 participants contacted according to the initial inclusion order in the cohort from 2005 to February 2007.

Subjects were evaluated and questioned about whether their physician had ever diagnosed them any rheumatic disease and if they were taking any medication. All drugs, doses and frequency of use were registered on a medicine-by-medicine basis. The interviewers collected detailed information on the frequency and dosage of both prescription and over-the-counter (OTC) medications used during the previous 12 months. Drug use was defined as daily use for at least 14 consecutive days, anytime during the same 12 months period. All reported drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system within the NSAID and Anti-Rheumatic drugs therapeutic class (M01A) which includes: Butylpyrazolidines (M01AA), Acetic Acid derivatives and related substances (M01AB), Oxicams (M01AC), Propionic Acid derivatives (M01AE), Fenamates (M01AG), Coxibs (M01AH), and other NSAID and anti-rheumatic agents (M01AX).[17] The differentiation to the fifth level of the ATC codes (drugs) was made for a second level of analysis, which includes drugs such as ibuprofen (M01AE01), naproxen (M01AE02), nimesulide (M01AX17), celecoxib (M01AH01), diclofenac (M01AB05), aceclofenac (M01AB16), indomethacin (M01AB01), acemethacin (M01AB11), azapropazone (M01AX04), and meloxicam (M01AC06). Acetaminophen (N02BE01) was also included in the analysis so that the prevalence of use in subjects who self-reported a rheumatic disease could be assessed and then compared with the use of NSAIDs.

Since complete drug information was not available for 143 subjects who admitted during the interview that they were unable to recall every medication used, only 1368 subjects were included in the analysis. Some of the socio-demographic features assessed during the interview included education, as the highest year of school completed, the household size by number of residents, and an appreciation of the family income (the subjects classified their family income as “insufficient”, as “needing to be careful with the expenses”, as “enough” or as “comfortable”). Later in the

analysis, the income appreciation is considered as low ("insufficient" and "careful") and high ("enough" and "comfortable"). All subjects older than 64 were submitted to the Folstein's Mini-Mental State Examination (MMSE) so that their cognitive function could be assessed and possible cognitive disorders screened.[18]

Logistic and multinomial regressions were computed to estimate all associations. Multinomial regression was used to compare four different groups: subjects who did not reported neither NSAIDs use nor rheumatic diseases, subjects who did reported NSAIDs use but no rheumatic diseases, subjects who did not reported NSAIDs use but did reported at least one rheumatic disease, and, finally, subjects who reported both NSAIDs use and rheumatic diseases. We considered the first group as the reference category. Statistical analysis was performed using SPSS statistical package, version 14.0.

Results

Out of all 1368 subjects (61.9% women, 38.1% men, mean age 57.4 ± 14.72 years) included in the analysis, 939 (68.60%) reported they had taken at least one drug during the previous 12 months. NSAIDs use was reported by 116 subjects (8.5%, 6.6% women, 1.9% men, overall mean age 66.2 ± 10.3 years): 1.8% reported a NSAID from the Acetic Acid derivatives or related drugs group, 0.6% reported an Oxicam, 1.5% reported a NSAID from the Propionic Acid derivatives group, nearly 1% reported a Cox-2 Inhibitor NSAID, and 3.4% reported another NSAID. The most reported NSAIDs were diclofenac (1.24%), nimesulide (1.10%), ibuprofen (0.80%), celecoxib (0.66%), and naproxen (0.51%) (Table 1).

The mean number of drugs reported by NSAIDs users was higher than the average number of drugs per individual on any drug during 14 days (4.84 ± 2.80 vs. 3.49 ± 2.40). The prevalence of NSAIDs use was significantly higher in women (10.6% of women vs 5.1% of men, $p<0.001$), (OR, 2.27, 95%CI [1.45-3.56]). NSAIDs use also significantly increased with age and with polypharmacy ($p<0.001$), both minor and

major, but it significantly decreased with education, household income and household size (Table 2).

Self-reported rheumatic diseases were more frequent among female, older, less educated subjects, and NSAIDs users. However, 35.3% of participants who reported to take a NSAID did not report any rheumatic disease and might have been using the drug for a different reason. The prevalence of NSAIDs use found for each rheumatic disease were: 38.1% for rheumatoid arthritis (RA), 25% for ankylosing spondylitis (AS), 23% for hands osteoarthritis, 22.7% for knee osteoarthritis, and 24.3% for hip osteoarthritis, while no one who reported systematic lupus eritematosum (SLE) or psoriatic arthritis (PA) reported NSAIDs use. Acetaminophen use (0.66%) does not seem to be associated with the report of rheumatic diseases.

Table 3 shows the age and sex adjusted associations between NSAIDs use and education, monopharmacy, minor and major polypharmacy and the report of rheumatic diseases. The adjusted analysis demonstrated that major polypharmacy (OR= 3.31, 95%CI [1.66-6.67], p= 0.001), higher education (OR= 0.53, 95%CI [0.32-0.88], p= 0.014), and the report of rheumatic diseases (OR= 3.34, 95%CI [2.14-5.22], p< 0.001) were significantly associated to NSAID use.

In order to classify subjects based on values of a set of the above predictor variables, ie, to establish the comparison between the association of NSAIDs use and the above factors and the association of the same factors and the report of rheumatic diseases, a multinomial regression model was used (Table 4). The results showed that major polypharmacy is the only factor that was associated to NSAIDs use among the subjects who reported its use but did not report any rheumatic disease. On the other hand, the report of rheumatic diseases alone without NSAIDs use seemed to be associated to the female, elder, less educated and needier subjects. A merge of the cited factors appears to be associated to the report of both NSAIDs use and rheumatic diseases and therefore may explain the association between NSAIDs use and rheumatic diseases in this sample.

Discussion

Results indicated that 8.5% of subjects reported NSAIDs use over at least a 14 days period during the 12 months previous to the interview with significant overall difference between males and females, while 24.6% reported a rheumatic disease. These findings suggest that not every potential rheumatic subject was under a NSAID treatment during the 12 months before the follow-up interview, although there was a significant association between NSAIDs use and the self-report of rheumatic diseases.

Major polypharmacy over a 14 days period during the previous 12 months was also found to be strongly associated with NSAIDs use. Female, older and less educated subjects were more prone to have used a NSAID, as they were more prone to suffer from a rheumatic disease and to have used more than 5 different drugs during the previous 12 months. Similar findings were reported by Lechevallier–Michel et al. after a population based study in France, though their aim relied on inappropriate medication use.[19] It seems that less educated elderly women are a sensitive population regarding medication use, mostly inappropriate medication use. Since NSAIDs are some of the most frequent prescription and OTC drugs in old age and have been associated with severe adverse reactions and hospital admissions related to gastroduodenal pathologies and cardiovascular events, this finding rises several concerns about NSAIDs appropriateness of use by rheumatic and polimedicated elderly.

Lower incomes and smaller households were also positively associated to the risk of NSAIDs use. This makes particularly sense since older and less educated people are more likely to live by themselves with little economic resources. However, the multinomial regression analysis showed that lower incomes were evenly associated to the report of rheumatic diseases alone and along with NSAIDs use.

The MMSE was administered to 461 subjects (98.3% of all subjects older than 65 years). The results showed that increasing scores (on 0-30 scale) were negatively associated to NSAIDs use, suggesting that cognitively impaired elderly were more prone to have used or to use NSAIDs when compared to subjects with no cognitive

impairment. However, there is evidence that cognitively impaired elderly are usually less likely to be prescribed analgesic drugs the more severe is their disability once they are less able to communicate and remember pain episodes.[20] Our finding may be simply due to the fact that illiteracy and poorer education are quite common among the Portuguese population, and our sample isn't any different. Therefore, a poorer understanding of the MMSE questionnaire has certainly led to lower scores without indicating cognitive impairment, but it may also be explained by our population being a community sample with no institutionalized subjects.

There are two major biases in this study that may lead us to underestimate NSAIDs use in this sample. First, we have only included non-aspirin NSAIDs, even though 500 mg acetylsalicylic acid (ASA), as well as 100mg/day and 150mg/day ASA, are along with trimetazidine, the most commonly prescribed antithrombotic therapies to the subjects in this study. Second, apart the encouragement to bring the medications to the interview, no standard interviewing techniques recommended to increase subject recall, such as picture books or calendars, were used to minimize recall bias, though the effect of time on reported usage seems to model the accuracy of medication use recall, specially over 12 months. [10,21,22] Recall bias may have occurred if patients with chronic diseases were more likely to remember their medication then others. Indeed, it is likely that patients with more severe diseases such as RA know to a greater extent which and how many NSAIDs they might have used. Other factors studied such as education, age and mental state also influence recall bias. Differential misclassification may have also occurred if NSAIDs users were more likely to report their rheumatic diseases, and therefore, it may have biased the presented prevalence estimates.

In 1999, when this community sample was first evaluated regarding the prevalence of self-reported rheumatic diseases, the findings accounted that 23% of the 1238 inquired subjects, at the time, reported one (RA,1.6%, LES, 0.2%, AS, 0.6%). Osteoarthritis (OA) was found to be more frequent in women than men (7.4% *vs*. 2.2% reported hip arthritis, while 14.2% *vs*. 5.9% reported knee arthritis) and to increase with age. These

former results are quite similar to those found in this evaluation though a slight increase in all diseases prevalences was noticed, specially for RA (2.9%), AS (0.14%) and OA (35.4%).

Despite the increasing trend for rheumatic diseases incidence, NSAIDs are still the most commonly used drugs to treat rheumatic diseases and musculoskeletal symptoms in this sample with no place for acetaminophen. Clinical trials evaluating acetaminophen tolerability in OA management have proven its favourable use at doses of 4g/d, for periods of up to 12 weeks.[23-25] Longer clinical trials did also accounted acetaminophen's hepatic and renal safety when used at high daily doses over 1 and even 2 years.[26,27] However, the best treatment, NSAIDs or acetaminophen, differs in individual patients.[28,29]

Conclusions

In this population sample, the prevalence of NSAIDs use was of NSAIDs use was of 8.5%. Lower education, having a rheumatic disease, and polypharmacy were associated to NSAIDs use. Polypharmacy alone explained NSAIDs use among subjects who had not reported any rheumatic disease. NSAIDs use alone or along other drugs by adults affected by rheumatic diseases, especially elderly women, deserves a more serious insight.

Table 1

Prevalence of use of different NSAIDs in the sample population

	Subjects n = 1368 (%)	Females n = 847 (61.9%)	Males n = 521 (38.1%)
NSAID Chemical Groups			
Acetic Acid derivatives			
Diclofenac	17 (1.24)	14	3
Aceclofenac	6 (0.44)	5	1
Etodolac	1 (0.07)	1	0
Indol Derivatives			
Indomethacin	1 (0.07)	0	1
Acemethacin	4 (0.30)	3	1
Oxicams			
Piroxicam	2 (0.14)	2	0
Meloxicam	5 (0.37)	4	1
Tenoxicam	1 (0.07)	1	0
Propionic Acid Derivatives			
Ibuprofen	11 (0.80)	6	5
Naproxen	7 (0.51)	6	1
Ketoprofen	2 (0.14)	2	0
Flurbiprofen	1 (0.07)	1	0
Pirazolonic Derivatives			
Azapropazon	2 (0.14)	2	0
Sulfanilamidic Derivatives			
Nimesulide	15 (1.10)	11	4
COX-2 Selective Inhibitors			
Celecoxib	9 (0.66)	8	1
Etoricoxib	3 (0.22)	2	1
Rofecoxib	1 (0.07)	0	1
Other Non-specific NSAIDs	34 (2.05)	23	11
Acetaminophen	9 (0.66)	8	1

Table 2

Crude associations between NSAID use and socio-demographic and health characteristics

		n	NSAIDs Users n (%)	OR (95% CI)	p for trend
Sex	Male	521	26 (5.0)	1	
	Female	847	90 (10.6)	2.27 (1.45-3.56)	
Age	20-44	269	3 (1.12)	1	
	45-64	609	53 (8.7)	8.42 (2.61-27.19)	< 0.001
	>=65	469	60 (12.8)	12.96 (4.02-41.74)	
Education	<=4	501	78 (15.6)	1	
	5-11	427	23 (5.4)	0.30 (0.19-0.49)	< 0.001
	>=12	434	15 (3.5)	0.20 (0.11-0.34)	
Drug Regimen	0 drug	429			
	Monopharmacy	232	9 (3.9)	1.00	
	Minor Polypharmacy	438	42 (9.6)	2.27 (1.18-4.36)	<0.001
	Major Polypharmacy	269	65 (24.2)	4.63 (2.41-8.88)	
Household Size	1	189	25 (13.2)	2.23 (1.19-4.18)	
	2-3	878	72 (8.2)	1.31 (0.77-2.20)	0.013
	>= 4	300	19 (6.3)	1	
Income Appreciation	High	725	38 (5.24)	1	
	Low	640	77 (12.0)	2.49 (1.66-3.73)	
Rheumatic Disease	Yes	336	115 (34.2)	6.63 (4.42-9.95)	
	No	1032	41 (3.97)	1	
EPI-Porto Sub-Sample					
MMSE		461	60 (13.0)	0.90 (0.84-0.96)	0.004

Table 3

Adjusted OR* for NSAID use

		OR* (95% CI)
Education	0-4	1.00
	5-11	0.53 (0.32-0.88)
	>=12	0.47 (0.22-1.01)
Rheumatic Disease	No report	1.00
	Report	3.34 (2.14-5.22)
Drug Regimen	Monopharmacy	1.00
	Minor Polypharmacy	1.88 (0.95-3.72)
	Major Polypharmacy	3.31 (1.66-6.67)

* OR Adjusted for Sex, Age, Income, and Household Size

Table 4

Results from the multinomial regression analysis

		NSAIDs Use and No Rheumatic Disease OR [95%CI]	Rheumatic Disease and no NSAIDs Use OR [95%CI]	NSAIDs Use and Rheumatic Disease OR [95%CI]
Sex	Male	1.00	1.00	1.00
	Female	0.80 [0.39-1.64]	2.79 [1.88-4.13]	3.44 [1.66-7.15]
Age	20-44	1.00	1.00	1.00
	45-64	1.65 [0.35-7.71]	4.34 [1.50-12.52]	5.00 [0.64-38.88]
	>=65	1.48 [0.29-7.62]	7.12 [2.40-21.13]	4.54 [0.56-36.54]
Education	0-4	1.99 [0.77-5.14]	1.94 [1.17-3.23]	3.14 [1.28-7.72]
	5-11	0.77 [0.27-2.18]	1.47 [0.88-2.44]	1.44 [0.56-3.74]
	>= 12	1.00	1.00	1.00
Drug Regimen	Monopharmacy	1.00	1.00	1.00
	Minor Polypharmacy	0.95 [0.36-2.49]	0.80 [0.52-1.24]	2.71 [1.01-7.26]
	Major Polypharmacy	3.10 [1.18-8.15]	1.49 [0.92-2.40]	6.13 [2.23-16.81]
Household Size	1	1.79 [0.56-5.72]	1.36 [0.72-2.56]	0.85 [0.34-2.09]
	2-3	0.82 [0.35-2.39]	1.40 [0.84-2.32]	0.78 [0.39-1.58]
	>= 4	1.00	1.00	1.00
Income Appreciation	Low	1.56 [0.77-3.17]	1.70 [1.19-2.43]	1.81 [1.01-3.25]
	High	1.00	1.00	1.00

References

1 Zochling J, Bohl-Bühler M, Baraliakos X, Feldtkeller E, Braun J. Nonsteroidal anti-inflammatory drug use in ankylosing spondylitis – a population-based survey. *Clin Rheumatol*. 2006; **25**: 794-800

2 Buchanan WW, Kean WF. Osteoarthritis IV: Clinical therapeutic trials and treatment. *Inflammopharmacology*. 2002; **10** (1,2): 79-155

3 Dunn MJ. The role of arachidonic acid metabolites in renal homeostasis: nonsteroidal anti-inflammatory drugs on renal function and biochemical, histological and clinical effects and drug interactions. *Drugs*. 1987; **33** (1): 56-66

4 Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *Ann Intern Med*. 1991; **115**: 787-796

5 Lewis JD, Kimmel SE, Localio AR, et al. Risk of serious upper gastrointestinal toxicity with over-the-counter Nonaspirin Nonsteroidal Anti-inflammatory Drugs. *Gastroenterology*. 2005; **129**: 1865-1874

6 Eccles M, Freemantle N, Mason J. North of England evidence based guideline development project: summary guideline for non-steroidal anti-inflammatory drugs versus basic analgesia in treating the pain of degenerative arthritis. The North of England Non-Steroidal Anti-Inflammatory Drug Guideline Development Group. *BMJ*. 1998; **317** (7157): 526-530

7 American College of Rheumatology Subcommittee on Osteoarthritis Guidelines: Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum*. 2000; **43** (9): 1905-1915

8 Beer MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med*. 1997; **157** (14): 1531-1536

9 Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly people. *Ann Intern Med*. 1991; **114** (4): 257-263

10 Lewis JD, Strom BL, Kimmel SE, et al. Predictors of Recall of over-the-counter and prescription non-steroidal anti-inflammatory drug exposure. *Pharmacoepidem Dr S*. 2006; **15**: 39-45

11 Thomas HF, Sweetnam PM, Janchawee B, Luscombe DK. Polypharmacy among older men in South Wales. *Eur J Clin Pharmacol*. 1999; **55:** 411-415

12 Viktil KK, Enstad M, Kutschera J, Smedstad LM, Schjøtt J. Polypharmacy among patients admitted to hospital with rheumatic diseases. *Pharm World Sci*. 2001; **23** (4): 153-158

13 Treharne GJ, Douglas KMJ, Iwaszko J, Panoulas VF, Hale ED, Mitton DL, Piper H, Erb N, Kitas GD. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. *Musculoskelet. Care*. In press 2007

14 Bjerrum L, Søgaard J, Hallas J, Kragstrup J. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. *Eur J Clin Pharmacol*. 1998; **54:** 197-202

15 Costa L, Gal D, Barros H. Prevalência auto-declarada de doenças reumáticas numa população urbana. *Acta Reum Port*. 2004; **29**: 169-174

16 Observatório dos Medicamentos e dos Produtos de Saúde. Instituto Nacional da Farmácia e do Medicamento, INFARMED. 2006

17 Guidelines for ATC Classification; 2007. WHO Collaborating Centre for Drugs Statistics Methodology, Oslo.

18 Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive sate of patients for the clinician. *J Psychiatr Res*. 1975; **12** (3): 189-198

19 Lechevallier-Michel N, Gautier-Bertrand M, Alpérovitch A, et al. Frequency and risk factors of potentially inappropriate medication in a community-dwelling elderly populations: results from the 3C study. *Eur J Clin Pharmacol*. 2005; **60**: 813-819

20 Cornali C, Franzoni S, Gatti S, Trabucchi M. Diagnosis of chronic pain caused by osteoarthritis and prescription of analgesics in patients with cognitive impairment. *J Am Med Dir Assoc*. 2006; **7**: 1-5

21 Atkin P, Stringer R, Duffy J et al. The influence of information provided by patients on the accuracy of medication records. *Med J Aust*. 1998; **28**: 394-400

22 Kimmel SE, Lewis JD, Jaskowiak J, Kishel L, Hennessy S. Enhancement of medication recall using medication pictures and lists in telephone interviews. *Pharmacoepidemiol Drug Saf*. 2003; **12**(1): 1-8.

23 Bradley JD, Brandt KD, Katz BP, et al. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med*. 1991; **325**: 87-91

24 Pincus T, Koch GG, Sokka T, et al. A randomized, double blind, cross-over clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum*. 2001; **44**: 1587-1598

25 Geba GP, Weaver AL, Polis AB et al, for the Vioxx, Acetaminophen, Celecoxib Trial (VACT) Group. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: A randomized trial [published correction appears in *JAMA*. 2002; **287**: 989]. *JAMA*. 2002; **287**: 64-71

26 Temple AR, Benson GD, Zinsenheim JR, Schweinle JE. Multicenter, randomized, double-blind, active-controlled, parallel-group trial of the long-term (6-12 months) safety of acetaminophen in adult patients with osteoarthritis. *Clin Ther*. 2006; **28** (2): 222-235

27 Williams HJ, Ward JR, Egger MJ, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. *Arthritis Rheum*. 1993; **36**: 1196-1206

28 Oddis CV. New perspectives on Osteoarthritis. *Am J Med* 1996; **100** (suppl 2A)**:** 10-15

29 Wegman ACM, van der Windt DAWM, de Haan M, Devillé WLJM, Chin A Fo CT, de Vries PGM. Switching from NSAIDs to paracetamol: a series of n of 1 trials for individual patients with osteoarthritis. *Ann Rheum Dis*. 2003; **62:** 1156-1161