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Prevalence and Risk of Polypharmacy Amongst Elderly in the Outpatient Setting

A Retrospective Cohort Study in the Emilia-Romagna Region, Italy

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Abstract

Background: Polypharmacy, the simultaneous taking of many medications,
has been well documented and is a topic of much concern for those looking to
improve the quality of care for the elderly. Elderly patients often develop

complicated and multi-factorial health states that require extensive pharmacotherapy, leaving this population at risk for exposure to drug-drug interactions and other adverse events. Previous literature supports an association between an increase in the rate of adverse events as the number of drugs taken by a patient increases.

Objective: We sought to evaluate the prevalence of polypharmacy, and to determine patient characteristics that are predictive of exposure to polypharmacy, in the elderly population of the Emilia-Romagna region in Italy.

Methods: We conducted a retrospective cohort study of the 2007 Emilia-Romagna outpatient pharmacy database linked with patient information available from a demographic file of approximately 1 million Emilia-Romagna residents aged ≥65 years. The cohort was comprised of 887 165 elderly subjects who had at least one prescription filled during the study year. Using the World Health Organization's defined daily dose (DDD) to determine the duration of treatment for a given drug, we defined a polypharmacy episode as overlapping treatment with five or more medications occurring for at least one day. The prevalence of polypharmacy was measured together with subject characteristics found to be predictive of polypharmacy exposure.

Results: A total of 349 689 elderly people in the population (39.4%) were exposed to at least one episode of polypharmacy during the study period. The prevalence of polypharmacy substantially increased with age and with a higher number of chronic conditions. Over 35% of those exposed to polypharmacy were exposed for 101 or more days of the year. The top three classes of medications involved in polypharmacy were antithrombotics, peptic ulcer disease and gastro-oesophageal reflux disease agents and ACE inhibitors. The odds of exposure to polypharmacy were higher for older subjects, males and subjects living in urban areas.

Conclusions: This study provides evidence that the prevalence of polypharmacy in the elderly in Emilia-Romagna is substantial. Educational programmes should be developed to inform clinicians about the magnitude of the polypharmacy phenomenon and the patient characteristics associated with polypharmacy. Raising physicians' awareness of polypharmacy may help to ensure safe, effective and appropriate use of medication in the elderly.

Introduction

Polypharmacy, the simultaneous taking of many medications, has been well documented in the US and Europe.[1-3] It is a topic of much concern for those looking to improve the quality of care for the elderly, as patients in this population often develop complicated and multi-factorial health states. As the incidence of chronic disease increases, so does the need for pharmacotherapy.[2,4] This inherently places the elderly at risk of exposure to polypharmacy.

Polypharmacy in the elderly has been correlated with increased age,[2,5] and with specific diseases, including cardiovascular diseases, rheumatic diseases and respiratory illnesses.[6] Previous studies have also demonstrated that as the number of concomitant medications increases in elderly patients, so does the risk of adverse drug events.[7-9] Furthermore, polypharmacy has been found to be associated with risk of emergency department visits, hospitalizations, hospital

readmissions and death in the elderly.[7,10,11] The risk of morbidity and mortality associated with polypharmacy, combined with the trend of population aging worldwide, makes polypharmacy an area of prime concern and a potential target for decreasing preventable adverse events.

Despite being a well recognized problem in the elderly population, a universally accepted, formal definition for polypharmacy has yet to be established.[1,12] Several studies have categorized polypharmacy into different levels based on the number of medications taken.[1,2,13-15] More specific definitions quantify polypharmacy by the number of simultaneous medications taken by a patient. The definition that is most frequently used is the simultaneous use of five or more medications. Based on this definition, prevalence estimates for polypharmacy in the outpatient setting vary from 4% to 42% in the elderly population.[3-6,16-23]

While polypharmacy in the elderly has been described in several European countries, the literature on the topic in Italy is scant. The availability of a large, linkable outpatient pharmacy database in Emilia-Romagna, Italy, a large northern region with a population of about 4 million inhabitants, provides an excellent opportunity to evaluate the prevalence of polypharmacy in the elderly and to determine patient characteristics that are predictive of exposure.

Methods

The study protocol was approved by the Institution Review Board of Thomas Jefferson University, Philadelphia, Pennsylvania, USA.

Study Design and Population

We conducted a retrospective cohort study of medication use in the elderly using the Emilia-Romagna outpatient prescriptions database from January 1, 2007 to December 31, 2007. This database includes all medications reimbursed by the 2007 National Pharmaceutical Formulary (PFN, Prontuario Farmaceutico Nazionale).[1] The characteristics of the database have been described elsewhere.[24] We linked prescription claims in the pharmacy database with data from a 2007 demographic file of 960 359 elderly Emilia-Romagna residents

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1 The PFN includes all medications marketed in Italy. It has a positive and a negative drug list, outlining which medicines will be reimbursed and which need to be paid for in full by patients, respectively. All essential medications, such as cardiovascular and antihyperglycaemic drugs, are reimbursed by the PFN; non-essential medications such as benzodiazepines, as well as any over-the-counter medications such as antitussive and cold drugs, are not reimbursed. All Italian citizens are entitled to access essential healthcare services, including PFN-reimbursed medications.

(aged ≥65 years as at January 1, 2007).[2] The study cohort was comprised of 887 165 elderly subjects who had at least one prescription filled during the study year (92.3% of the Emilia-Romagna elderly population).

Study Definitions and Measures

For the purposes of this study we defined polypharmacy as the simultaneous use of five or more medications, a definition that has been widely used in previous studies.[3,13,18,19,23,25] Medications were classified using the Anatomical Therapeutic Chemical (ATC) classification index, and were further differentiated to the fifth level of classification (e.g. B01AA03 represents warfarin).[26] Duration of therapy was calculated assuming that daily drug intake was equal to the defined daily dose (DDD), as determined by the WHO.[26] In addition, it was assumed that subjects completed the duration of therapy for all filled prescriptions. Treatment was assumed to have begun on the day that the prescription was filled. The number of drugs taken on each day of the year was then calculated for each subject, and occurrence of polypharmacy was tabulated from this information.

One-year prevalence was defined as the number of individuals who had at least one episode of polypharmacy during the study period. Subjects exposed to polypharmacy were also stratified by the total number of days of exposure. Incidence of polypharmacy was determined using a method previously described by Bjerrum et al.[13] Subjects with first-time polypharmacy occurrence were identified for each month. As such, elderly exposed to polypharmacy for the first time in the final 3 months of 2007 were assumed to represent true incident cases. The mean monthly first-time occurrence during the final 3 months of 2007 was assumed to represent the monthly incidence of polypharmacy.

Subject Characteristics

Information on subjects' age, sex and geographic location was retrieved from the demographic file. Level of co-morbid disease was calculated using the Chronic Condition Drug Group (CCDG) score. The CCDG score classifies up to 31 chronic conditions based on consumption of specific medications.[27] The CCDG score for an individual reflects the extent to which a person is affected by

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2 Because of the reimbursement process, information in the Emilia-Romagna pharmacy database is very accurate. The pharmacy database includes a unique, anonymous patient identification number, which has been used to link the pharmacy database with the demographic file. The linkage between the demographic file and the pharmacy database was virtually complete.

chronic conditions (i.e. higher CCDG scores reflect a higher number of chronic conditions).

Data Analysis

The unit of analysis for the study was the individual subject. Descriptive statistics were generated for all variables of interest. A bivariate analysis was used to compare the characteristics of drug users exposed to polypharmacy and those not exposed using chi-squared (χ^2) tests for categorical variables. A multivariable logistic regression analysis was used to identify factors that were predictive of polypharmacy exposure. Subject characteristics that were incorporated in our model as independent variables included sex (dichotomously), age (categorically) and geographic location (categorically). The CCDG score was not included in our model because in a separate analysis it was shown to be correlated with the number of medications a subject received (r = 0.71), and hence inherently correlated with polypharmacy. A p-value <0.05 was considered significant for all analyses. All data analysis was completed using SAS® version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results
Subject Characteristics and Medication Use

Of the 887 165 elderly drug users in the region, the mean ± SD age of the study population was 75.5 ± 7.5 years. Females made up 58.3% of the study population (table I). The mean ± SD number of distinct medications (i.e. having different ATC codes) taken during the study period was 6.3 ± 4.2. Total per-patient drug utilization during the study period was as follows: 39.3% used between one and four distinct drugs, 28.4% used between five and seven drugs, 17.4% used between eight and ten drugs, 10.2% used between eleven and fourteen drugs and 4.7% used fifteen or more drugs.

Table I

Prevalence of Polypharmacy

Of the elderly drug users in the region, 349 689 (39.4%) had at least one episode of polypharmacy exposure during the study period (table I). People exposed to polypharmacy were more likely to be older male and have a higher number of co-morbidities. Approximately one-third (36.1%) of elderly exposed to polypharmacy were prescribed 11 or more distinct medications in the study period. Of those exposed to polypharmacy, 47.6% were exposed for a total of

≤50 days, 16.8% for 51–100 days, 20.1% for 101–200 days and 15.5% for ≥200 days.

All of the following drug classes were used by more than one-third of subjects exposed to polypharmacy: antithrombotics; peptic ulcer disease and gastro-oesophageal reflux disease agents; ACE inhibitors; antihyperlipidaemic agents; β-adrenoceptor antagonists; and NSAIDs (table II).

Table II

Incidence of Polypharmacy

Figure 1 shows the number of individuals exposed to polypharmacy for each month of the study period according to the month in which the first episode of polypharmacy occurred. The mean monthly occurrence of new exposures to polypharmacy in the last 3 months of the study period was 11 235. Therefore, the estimated incidence of subjects exposed for the first time to polypharmacy was 1.3% per month.

Fig. 1

Logistic Regression Analysis

The multivariable logistic regression analysis demonstrated that age, sex and geographic location were correlated with exposure to polypharmacy (table III). Using subjects aged 65–74 years as the referent group, risk of exposure to polypharmacy increased as age increased (odds ratios [OR] 1.76 for age 75–84 years and OR 1.83 for age ≥85 years). The odds of exposure were lower in females than males (OR 0.85). Finally, there was a slightly lower risk of polypharmacy exposure for patients in rural areas (hill and mountain locations; OR 0.98 and 0.96, respectively) than in urban areas (plain location).

Table III

Discussion

To our knowledge, this is the first large, population-based study documenting the prevalence of polypharmacy in Italy. The evidence generated by this investigation supports three main conclusions. First, we noted that a large number of elderly subjects in Emilia-Romagna are exposed to polypharmacy. Second, we observed that new exposures to polypharmacy occur at a consistent rate and affect a significant number of elderly subjects. Third, our evidence demonstrated that a large number of the polypharmacy exposures extend over a long period of time. Taken as a whole, these findings are cause for concern for

both practitioners and healthcare policy decision makers in Emilia-Romagna because of the correlation that has been demonstrated between polypharmacy and inappropriate prescribing in this population.[28] Additional research is needed to determine if, and to what extent, this phenomenon exists in other regions of Italy.

The data used in our study afford us confidence that the results generated are an accurate reflection of the patterns of medication use by the elderly in Emilia-Romagna. Other polypharmacy studies frequently rely on pharmacy data collected upon patient admission to and/or discharge from a hospital,[29] during patient interactions with data collectors (either at home, over the phone or in an office setting)[4,5,8,14,30-32] or from patient and/or physician recall,[3] all of which are methods that leave room for inaccuracies in data collection. Because the outpatient pharmacy database used in our study was initially collected at the site of dispensation and was used for reimbursement purposes, the data used in our study have a much lower likelihood of containing error.

We found the prevalence of polypharmacy in our study cohort of elderly patients to be 39.4%. This prevalence falls in the high end of the range reported in previous studies conducted in outpatient settings that used the same definition of polypharmacy (4–42%).[3,6,16-19,23] While some of the variability in the reported prevalence among studies is undoubtedly due to variations in clinician practices and patient behaviours in different countries, it may also be a result of differences in the sample age,[3,4,16,17] the nature of the data source[3,16-19] and the units of analysis.[6,18,23] Thus, comparisons between polypharmacy studies can be extremely cumbersome and difficult to interpret. Despite the challenges faced in comparing polypharmacy investigations, it is clear that polypharmacy is a significant problem in the elderly and warrants additional attention. Further research in this area may help to determine the necessity and most appropriate mechanism for interventions tailored to the needs of different countries and populations.

As was expected, our results show that as the number of chronic conditions increases, so does polypharmacy exposure. Clearly, patients with multiple chronic conditions must be treated with appropriate pharmacotherapy. For example, a patient with non-insulin dependent (type II) diabetes mellitus must be treated with at least one medication, and often multiple medications, to manage this chronic disease. If this patient also has hypertension and hyperlipidaemia, then it is quite likely that appropriate treatment of these conditions would result in exceeding the polypharmacy threshold. For this reason, it is challenging to

determine, based on the number of chronic conditions alone, whether or not the exposure to polypharmacy is appropriate. Future research exploring how the presence of chronic conditions affects health outcomes may help uncover when interventions to address polypharmacy would be beneficial.

Our multivariable analysis showed that older age, male sex and geographic location were significantly associated with the risk of exposure to polypharmacy. The correlation between polypharmacy exposure and increased age is supported by previous literature.[2,5] Our findings reinforce these reports. This association is of considerable concern because of the implications of overuse of medications in the elderly. Predisposing factors in the elderly, such as the decline in renal function that accompanies the aging process,[33] increase the potential for drug-drug and/or drug-disease interactions, drug toxicities and other adverse drug events.

In our study, males were found to be more likely to be exposed to polypharmacy. We found only one other study that reported a positive correlation between male sex and polypharmacy exposure.[34] Conversely, many studies have reported a correlation between polypharmacy and female sex.[4-6,14,30] Such discrepancies among study findings could be due to differences in physicians' prescribing attitude toward sexes, as well as to differences between sexes in educational and socioeconomic characteristics.[35] Further research exploring the relationship between sex and polypharmacy is warranted.

Elderly living in urban areas (plain locations) were found to be more likely to be exposed to polypharmacy than those living in rural areas (hill and mountain locations). One possible explanation for this result may be that providers practicing in urban areas differ in their characteristics and, as a result, in their prescribing patterns. There is evidence that provider attributes, such as sex, and practice characteristics, including structure and workload, are predictive of polypharmacy exposure in their patients.[36] However, information on provider and practice characteristics was not available in our database. Future research exploring the relationship between polypharmacy and provider characteristics may be of interest.

The presence of antithrombotics and NSAIDs among the drug categories commonly used by elderly people exposed to polypharmacy is of great concern because of the potential for adverse drug events with these agents. Antithrombotics such as warfarin have a narrow therapeutic window and a high number of drug-drug interactions that put these patients at risk.[37,38] In addition,

NSAIDs are found on published lists of medications to be avoided in the elderly because of the high number of NSAID related adverse events and potential drug interactions in this population.[28,39,40]

Several of the medication classes that were identified as commonly used by patients exposed to polypharmacy in our study have also been reported in previous investigations.[2,5,6,8,22] Bjerrum et al.[6] reported that elderly patients exposed to polypharmacy frequently used cardiac therapies and analgesics (including NSAIDs). Flaherty et al.[8] reported that gastrointestinal agents and ACE inhibitors were among the most frequently used medications in a cohort of older patients discharged from a home care agency. Knowledge of medication classes that are commonly part of polypharmacy regimens may assist physicians in identifying elderly patients for whom particular attention should be paid when reviewing the appropriateness, safety and efficacy of their drug therapy.

Limitations

Our study has several limitations. First, we cannot say with certainty whether or not prescribed medicines were actually used by patients. Next, we used DDDs to estimate the duration of therapy for each prescription in order to determine overlapping of treatments and therefore identify polypharmacy exposures. The WHO Collaborative Centre for Drug Statistics and Methodology defines the DDD as "the assumed average maintenance dose per day for a drug used for its main indication in adults."[41] DDD is a useful estimator for calculating durations of treatment.[42] However, substantial differences may exist between the doses determined using DDDs and the actual prescribed dose. This may be particularly true for drugs such as antithrombotics, which require individualized dosing for each patient because of the narrow therapeutic window. In addition, the elderly may require more frequent dosage adjustments because of issues such as renal and hepatic impairment. Because each prescription is tailored to the patient's age, sex, weight and other factors that may affect the drug's pharmacokinetics and pharmacological activity, DDDs provides only a rough estimate of the duration of therapy. It is possible that some misclassification of polypharmacy occurred, but this is not likely to have substantially impacted our results.

The Emilia-Romagna database does not include prescription medications not reimbursed by the PFN, such as benzodiazepines, or any non-prescription medications such as over-the-counter medications, herbal remedies or dietary supplements. A correlation between non-prescription medication use and polypharmacy in the elderly has been reported in the literature.[3] These treatments also carry the risk of interactions and adverse events,[43-46] and

therefore are relevant in the discussion of polypharmacy. For these reasons, it is reasonable to conclude that our results are a conservative estimate of the true prevalence of polypharmacy in Emilia-Romagna.

The use of CCDG scores as a proxy for patient co-morbidities is a viable method but has its limitations. There are some diseases that have no pharmacological treatment and are therefore not accounted for in the CCDG score. In addition, many medications may be used for the treatment of more than one disease. It may therefore be impossible to differentiate whether the use of one medication, in a patient taking multiple medications, is for the treatment of a separate co-morbidity or is part of a multi-drug regimen for a single disease. While it is not possible for us to know whether we more frequently over-estimated or under-estimated the CCDG scores, it is likely that these errors cancelled each other out in the aggregate.

Conclusions

Our study results add to the growing evidence that a significant proportion of the elderly are exposed to polypharmacy. However, it is important to emphasize that polypharmacy is not synonymous with inappropriate treatment. Many elderly patients who are taking more than five medications may have appropriate indications for all of these therapies and may lack any major risk for adverse events, such as drug-drug or drug-disease interactions. However, the risk of these adverse events increases as the number of medications that a patient takes simultaneously increases. Therefore, it is highly desirable that physicians identify and keep under surveillance patients exposed to polypharmacy. Raising awareness of the characteristics of those elderly most likely to be exposed to polypharmacy, in conjunction with studies describing the risks associated with increased medication use in this population, may help to ensure safe, effective and appropriate use of medication in the elderly.

In summary, our analysis found that the prevalence of polypharmacy exposure in the elderly population of Emilia-Romagna is of great magnitude. Several factors that may be used to screen patients for risk of polypharmacy exposure were identified. This study provides clinicians in the region with information that they may use to improve the quality of care provided to their elderly patients.

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Fig. 1. Proportion of subjects exposed to polypharmacy for the first time by month during 2007. Elderly exposed to polypharmacy for the first time in the final 3 months of 2007 (see grey bars) were assumed to represent true incident cases, as per the method described by Bjerrum et al.[13] Thus, the mean monthly first-time occurrence during the final 3 months of 2007 was assumed to represent the monthly incidence of polypharmacy.

Table I. Bivariate comparison of characteristics of the patients according to exposure to polypharmacy

Characteristic	Subjects not exposed to polypharmacy (n = 537 476)		Subjects exposed to polypharmacy (n = 349 689)	
	n	%	n	%
Age (y)*				
65–74	294 354	54.8	142 921	40.9
75–84	181 100	33.7	153 227	43.8
≥85	62 022	11.5	53 541	15.3
Sex				
Female	318 931	59.3	198 438	56.7
Male	218 545	40.7	151 251	43.3
Geographic location*				
Mountain (rural)	29 497	5.5	19 140	5.5
Hill (rural)	148 786	27.7	96 101	27.5
Plain (urban)	359 193	66.8	234 448	67.0
CCDG score*				
0–1	293 485	54.6	20 422	5.8
2–3	230 183	42.8	187 502	53.6
≥4	13 808	2.6	141 765	40.5
No. of drugs prescribed*				
1–4	348 405	64.8		
5–7	150 670	28.0	101 452	29.0
8–10	32 590	6.1	122 162	34.9
11–14	5 481	1.0	85 042	24.3
≥15	330	0.1	41 033	11.7

CCDG = Chronic Condition Drug Group; * p < 0.05.

Table II. Anatomical Therapeutic Chemical (ATC)[26] level 3 drug classes most frequently used by subjects exposed to polypharmacy

ATC class (level 3)	Description	Female (n = 198 438) [%]	Male (n = 151 251) [%]	All (n = 349 689) [%]
B01A	Antithrombotics	65.8	75.9	70.1
A02B	PUD and GERD agents	50.0	46.6	48.5
C09A	ACE inhibitors	34.1	41.9	37.5
C10A	Antihyperlipidaemics	34.8	40.9	37.4
C07A	β-adrenoceptor antagonists	35.5	39.0	37.0
M01A	NSAIDs	41.3	28.8	35.9
C03C	High-ceiling diuretics	31.7	32.0	31.8
C08C	Selective calcium	29.7	32.1	30.8

	channel antagonists			
N06A	Antidepressants	27.3	15.9	22.4
C01D	Vasodilators	18.4	22.9	20.3
R03B	Non-adrenergic inhalers	17.1	21.0	18.8
A10B	Antihyperglycaemics (excluding insulin)	17.2	19.8	18.3
C09C	ARBs	18.2	16.5	17.5
C09B	ACE inhibitor combination products	17.0	15.5	16.4
R03A	Adrenergic inhalers	14.3	18.2	16.0
C09D	ARB combination products	17.4	13.0	15.5
G04C	BPH products	0.2	32.6	14.2
S01E	Antiglaucoma preparations and miotics	12.5	11.2	11.9
C01B	Antiarrhythmics, class I and III	6.7	8.1	7.3
A10A	Insulin and analogues	3.9	4.0	3.9

ARB = angiotensin II type 1 receptor antagonist (angiotensin receptor blocker);
BPH = benign prostatic hyperplasia; **GERD** = gastro-oesophageal reflux disease;
PUD = peptic ulcer disease.

Table III. Multivariable logistic regression of patient characteristics associated with polypharmacy exposure

Characteristic	Odds ratio	95% CI
Age (y)		
65–74	1.00	Referent
75–84	1.76	1.74, 1.78*
≥85	1.83	1.80, 1.85*
Sex		
Male	1.00	Referent
Female	0.85	0.846, 0.861*
Geographic location		
Plain (urban)	1.00	Referent
Hill (rural)	0.98	0.97, 0.98*
Mountain (rural)	0.96	0.94, 0.98*

* $p < 0.05$ vs referent.