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Polypharmacy and potentially inappropriate medications: a cross-sectional analysis among 451 nursing homes in France

Running head: Suboptimal prescribing in nursing homes

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Abstract

Purpose: The quality of drug therapy is an important issue for nursing homes. This study aimed to assess the prevalence of polypharmacy and potentially inappropriate medications (PIMs) in a large sample of nursing home residents by using the data recorded during the preparation of pill dispensers.

Methods: This is a cross-sectional study that included 451 nursing homes across France. Information about the medications received by the 30,702 residents (73.8% women) living in these nursing homes was extracted from the system that assists the preparation of pill dispensers in pharmacies. The anonymized database included age, sex, and medications prescribed to residents, as well as nursing home characteristics (capacity, legal status). Factors associated with excessive polypharmacy (≥ 10 different drugs) and PIMs according to the Laroche list were studied using multilevel regression models.

Results: The average number of drugs prescribed was 6.9 ± 3.3 and excessive polypharmacy concerned 21.1% of the residents ($n=6,468$). According to the Laroche list, 47.4% of residents ($n=14,547$) received at least one PIM. Benzodiazepines (excessive doses, long-acting benzodiazepines, and combination of benzodiazepines) and anticholinergic medications (hydroxyzine, cyamemazine, alimemazine) accounted for a large part of PIMs. Individual characteristics (age, gender) influenced the risk of receiving PIMs whereas nursing home characteristics (capacity, legal status) influenced the risk of excessive polypharmacy.

Conclusions: This study shows that polypharmacy and PIMs remain highly prevalent among nursing home residents. Main PIMs concerned psychotropic and anticholinergic medications.

Key words: aged, frail elderly, inappropriate prescribing, information system, nursing homes, polypharmacy

Introduction

As people live longer, they accumulate health problems and drug prescriptions. The addition of medications increases the risk of adverse drug effects and of drug-drug and drug-disease interactions [1,2]. Polypharmacy was shown to be the main determinant of iatrogenic effects of medications [3,4]. In addition, age-associated changes in body composition (sarcopenia) and organ function (decrease in renal and metabolic clearance) can cause changes in the pharmacokinetic/pharmacodynamics properties of medications, and hence modify the safety profile of medications [5].

In order to avoid adverse drug reactions in older people, the benefit-risk balance of each drug should be considered, as well as the risk of interactions. Lists of Potentially Inappropriate Medications (PIMs) were published to help adapt the drug regimen in older people, notably the Beers' criteria, which were first published in 1991 to assess medication appropriateness in nursing homes [6]. Reasons for inappropriateness include an unfavorable benefit-risk ratio, the absence of clear indication or efficacy [7]. This list had been updated several times [8,9] and other lists have been developed, notably to have guidelines that take into account the national specificities in terms of commercialized drugs and practices. In France, Laroche et al published a French list of PIMs in 2007 [10]. This list included 34 general criteria and 5 additional criteria where the PIM is related to an underlying condition.

Studies that compared drug regimen between institutionalized people and old people living in community have shown higher rates of polypharmacy and PIMs among institutionalized people [11-13]. Inappropriate drug use was shown to increase the risk of adverse health outcomes (hospitalizations, emergency department visits, death) in nursing home residents [14-16]. The quality of drug therapy is an important issue for nursing homes and the use of psychotropic medications and polypharmacy have been proposed as indicators of quality of care in nursing homes [17,18]. Indicators of the quality of drug therapy should be monitored

regularly to identify areas for improvement and evaluate the efficacy of interventions. Data about drug therapy in nursing homes can be retrieved from medical records but also from insurance claims and pill dispenser systems. These last options should develop with the increasing willingness of stakeholders involved in health and quality of care to share their data for quality purposes.

In this context, this study aimed to describe the drugs' prescriptions of old people living in nursing homes in terms of polypharmacy and PIMs, by using the data collected during the preparation of pill dispensers.

Material and methods

Study design and population

This is a cross-sectional study that analyzed the drugs prescribed to the 30,702 persons living in the 451 nursing homes that used a pill dispenser supplied by the company Medissimo (Poissy, France) at the time of the analysis. The pill dispenser contains 28 days of treatment, with as many compartments as drugs and time of administration. It is prepared by qualified staff in pharmacy. During the preparation, information about the individuals and their prescriptions is entered in specific software to ensure traceability. Although the pharmaceutical forms that cannot be placed in the pill dispenser (sachets, creams, drops, etc.) are given in their original packaging, information about these drugs are still recorded in the information system. Data from March 25th to March 31st 2014 were extracted from the information system and communicated anonymously to the UMR 1168 for analysis. Medissimo received the approval of the National Commission for Data Protection and Liberties (CNIL, authorization n°1067312).

Data

The database included the following information:

- Residents: sex, month and year of birth;
- Drugs: Anatomical Therapeutical Classification (ATC) code, dosage, time and date of administration;
- Nursing homes: legal status (public, private not-for-profit, private for-profit) and capacity (number of places).

Indicators of suboptimal prescribing

The number of drugs prescribed was determined for each day of the week. In order to take into account drugs administered weekly (for instance bisphosphonates), the assessment of polypharmacy considered the day of the week where the number of medications was the most important. Polypharmacy was defined as five medications or more and excessive polypharmacy as 10 medications or more. This definition included systemic drugs, as well as topical ones.

PIMs were those listed in the Laroche list [10]. Briefly, the French panel consensus list is based on the 2003 Beers criteria but several drugs or therapeutic drug classes were not selected, because they were not available on the French market (such as mataxalone, guanabenz, barbiturates, except phenobarbital) or because the drugs were not judged inappropriate by the French experts (such as amiodarone and nonsteroidal anti-inflammatory drugs, except indometacine). Conversely, some criteria were added to the Beers criteria, notably the concomitant use of two (or more) nonsteroidal anti-inflammatory drugs and the concomitant use of two (or more) psychotropic drugs from the same therapeutic class. The drugs or the drug-classes proposed in this list are to be avoided when possible in the elderly, because of questionable efficacy and/or of unfavorable benefit-risk ratio. We excluded the 5 criteria that required information about underlying conditions because the database did not include clinical information.

Statistical analyses

Indicators of suboptimal prescribing were described in terms of prevalence. Factors related to excessive polypharmacy and to the fact of receiving at least one PIM were investigated among variables related to residents (age and sex) and nursing homes (legal status and capacity) by using Chi-2 test. Multilevel logistic regression models were used to study the independent effect of each variable, with an individual level and a nursing home level in order to take into account the correlation between subjects of a same nursing home. Indeed, the intraclass correlation coefficient obtained in empty models indicated that 8.0% and 3.4% of the total variance of excessive polypharmacy and of at least one PIM was explained by the nursing home level respectively. Analyses were performed using Stata® software v13 and the level of significance was set at 5%.

Results

Population

Of the 451 included nursing homes, 57.7% were private-for-profit (n=260), 29.9% were private-not-for-profit (n=135), and 12.4% were public facilities (n=56). The mean number of places per nursing home was 85 +/- 33. Residents included 22,655 women (73.8%) and 8,047 men (26.2%). After exclusion of 904 potentially erroneous values of age considering the context (i.e. age <60 or >110), the mean age was 87.4 +/- 7.6. The mean number of drugs prescribed was 6.9 +/- 3.3. The most prescribed drugs are listed in the Table 1.

Polypharmacy, PIMs, and anticholinergic drugs

Polypharmacy (5 to 9 medications) and excessive polypharmacy (≥ 10 medications) concerned 54.9% (n=16,854) and 21.1% (n=6,468) of the residents respectively. Potentially

inappropriate prescribing was found in 14,547 residents (47.4%). PIMs and their rationale are listed by order of frequency in the Table 2. Additional information about drugs participating in the different PIMs is given in Appendix 1. Psychotropic medications were a leading cause of PIMs, because of inappropriate dosage, molecule or association. Notably, 2,876 residents (9.4%) received at least two different benzodiazepines during the study period. The prescription of drugs with anticholinergic properties was another frequent PIM. Considered together, drugs with anticholinergic properties were prescribed in 12.2% of the residents (n=3,738). Among them, hydroxyzine was largely prescribed, in 3.4% of the residents (n=1,217). Other notable PIMs involved antihypertensive drugs (4.6% of the residents, n=1,415), cerebral vasodilators and muscle relaxants, especially baclofene.

Factors associated with suboptimal prescribing

Factors associated with suboptimal prescribing are described in Table 3. Men and older residents were at lower risk of PIMs. Private for-profit nursing homes had lower levels of excessive polypharmacy compared to public nursing homes, as well as intermediate- size compared to small- size nursing homes. Overall, individual characteristics influenced the risk of receiving PIMs whereas nursing home characteristics influenced the risk of excessive polypharmacy.

Discussion

Main findings

Taking advantage of technologies used to secure the administration of drugs in nursing homes, indicators of quality of drug therapy could be calculated in a large population of nursing home residents. Excessive polypharmacy and PIMs concerned a large part of the

study population, 21.1% and 47.4% respectively. Areas for improvement mostly concerned psychotropic and anticholinergic medications.

Polypharmacy

The prevalence of excessive polypharmacy found in this study was close to the estimate of the SHELTER study. Among voluntary nursing homes in 7 European countries + Israel, the prevalence of excessive polypharmacy was 24.3% [19]. The health outcomes associated with polypharmacy in old people living in community have been extensively studied. Risks associated with polypharmacy include falls, hospitalizations, and mortality [20,21]. In the context of nursing homes, polypharmacy has been recognized as a major cause of adverse drug events [22], notably falls [23]. The increased risk of adverse drug events associated with polypharmacy may be explained by the increased risk of receiving psychotropic medications and PIMs. In addition, polypharmacy increases medication regimen complexity and the risk of errors during the preparation and dispensation of medications [24].

PIMs

The prevalence of PIMs was relatively high compared to studies in community that reported a prevalence of PIMs about 20% [25,26]. Comparison with other studies that assessed PIMs in nursing homes is complicated by methodological differences between studies regarding the PIMs criteria and data source. The literature shows that the prevalence of PIMs in nursing homes varies widely between studies, from 15% to 89% [27,28]. Two studies previously used the Laroche list [10] in the context of nursing homes and reported prevalence of PIMs about 22% [29,30]. Our higher estimate (47.4%) can be explained by differences in the number of criteria considered. Indeed, the prevalence reported by Cool et al in 175 nursing homes in the South region of France refers to medications with unfavorable benefit-risk ratio only, PIMs

due to questionable efficacy being considered separately [29]. In the German study by Kolzsch et al, the authors could not identify overdosing of benzodiazepines and concomitant use of drugs from a same therapeutic class, whereas these criteria accounted for a large part of the PIMs in our study population [30]. More generally, our estimate is in line with a recent review of literature that estimated the prevalence of PIMs in nursing homes at 49.8% (all criteria of PIMs considered, studies published since 2005) [31].

Psychotropic and anticholinergic medications accounted for a large part of PIMs in this study. Though there are clear national and international recommendations to avoid the use of long-acting benzodiazepines in old people [32,8,33,10], they were still prescribed in 7.2% of the residents in the present study. Among benzodiazepine users, those receiving long-acting molecules were shown to be at increased risk of falls [34,35]. Furthermore, long-acting benzodiazepines would increase the risk of onset of dementia assumed in benzodiazepine users [36]. The use of excessive doses of short- or intermediate- half-life benzodiazepines, as well as the prescription of multiple benzodiazepines, was another worrying result. Though to a lower extent compared to long-acting molecules, short- and intermediate- half-life benzodiazepines also increase the risk of adverse effects such as cognitive impairment, delirium, drowsiness, and falls [10,37]. Moreover, the combination of several psychotropics does not necessarily ameliorate the symptoms, and may increase the risk of interactions and side-effects [38].

Using data from reimbursement of medications in 2012, Beuscart et al reported that 22.3% of people living in nursing homes in the North region of France received anticholinergic drugs, hydroxyzine in two third of the cases [39]. Though anticholinergic drugs were far less prescribed in our study (12.2%), hydroxyzine was still the most prescribed anticholinergic drug, probably because it is considered an alternative to benzodiazepines in the treatment of anxiety. However, drugs with anticholinergic properties can cause peripheral side effects such

as dry mouth and constipation, as well as central side effects, namely falls, dizziness, delirium, and cognitive decline [40].

Factors associated with suboptimal prescribing

The increased risk of PIMs observed in women is quite surprising. Indeed, gender had no influence on PIMs in any of the 11 studies that studied this relationship [12,41,30,42-44,29,45,46,14,47]. This result may reflect the fact that women live longer, but with a heavier burden of comorbidity, and hence medications. Though we did not confirm the inverse association between excessive polypharmacy and age previously found in the SHELTER study [19], we observed a significant decrease in the prevalence of PIMs with advanced age, consistently with previous studies in nursing homes [12,48,49,30,15,44]. This phenomenon may be explained by the reduction of pharmacotherapy in people with limited life expectancy, especially in demented people who are less likely to receive PIMs according to the literature [14, 15, 16, 29, 40, 43, 46].

Contrary to the results published by Beers et al in 1992 that reported an increased risk of PIMs among large nursing homes [6], we found that intermediate- size nursing homes had lower rates of polypharmacy and PIMs compared to small ones. In addition, private-for-profit nursing homes had lower rates of polypharmacy compared to public nursing homes. These results indicate that organizational factors can play a role in the quality of drug prescribing. In a qualitative study in long-term aged care, Tariq et al actually identified multiple system-related factors that could influence the risk of prescribing errors [50]. They were related to communication systems, team coordination and staff management. Organizational differences between nursing homes should be further investigated in order to identify levers to reduce PIMs. Emphasis should be given to the communication between staff and doctors who come

to visit their patients in the nursing home and to the implementation of comprehensive geriatric evaluation and multidisciplinary medication review [51].

Strengths and limitations of the study

The main strength of this study is the size of the study population, covering 6.6% of the total number of places in nursing homes in France [52]. All the nursing homes using the pill dispenser Mono28® were included in this study. This is hence a real life evaluation of the quality of drug therapy, as opposed to studies in samples of nursing homes willing to participate where a selection bias can be expected. Nevertheless, the included nursing homes were not representative of French nursing homes in terms of legal status. Indeed, the proportion of private-for-profit nursing homes was higher in our study sample compared to national statistics (58% versus 43%) and the proportion of public nursing homes was lower (12% versus 26%). The mean capacity of the included nursing homes was comparable to national statistics (85 places versus 83 places).

The use of multi dose systems to assess medications in nursing homes can restrict information to tablets and capsules that can be placed in the multi dose system [12]. Because information was collected during the preparation of all the medications prescribed in the pharmacy, this study overcame this limitation and provided information about other formulations than tablets and capsules (inhalers, sachets, drops, syrups, injectable, etc.). Moreover, information was sufficiently detailed to allow the assessment of PIMs based on inappropriate dosage. Nevertheless, we did not have information about the health and diseases of the residents. This prevented us from studying drug-disease interactions. However, an underestimation of the overall prevalence of PIMs in this study because of the exclusion of drug-disease interactions is unlikely because most of the criteria of the Laroche list [10] that consider drug-disease interactions deal with the prescription of anticholinergic drugs (e.g. drugs with anticholinergic

properties in patients with prostate closed-angle glaucoma or chronic constipation), which are also considered in other criteria.

Though the choice to use the Laroche list [10] was the most relevant with regards to the French context, this list has not been updated since its publication in 2007. Many drugs had been withdrawn from the market since then and maybe some other recommendations could be added. For instance, several studies have recently been published concerning the adverse effects of prolonged use of proton-pump inhibitors (fractures, pneumonia, death) [53], resulting in their inclusion in the 2015 update of the Beers criteria [9]. Considering the high prevalence of use of proton-pump inhibitors in the study population (esomeprazole was used by 17% of the included residents), a part of misuse is likely.

Because data were collected during the routine process of preparation of the pill dispensers by the pharmacy staff and not by trained investigators, we registered about 2.9% of abnormal values of age. These individuals had to be excluded from multivariate analyses. Nevertheless, they did not differ from the rest of the study population in terms of mean number of medications prescribed. Errors regarding medications are very unlikely because the pill dispenser once prepared is checked by a pharmacist.

Conclusion

By using the data collected in routine during the preparation of pill dispensers for nursing homes, this study shows that excessive polypharmacy and inappropriate prescribing concern a large part of nursing home residents. Further studies are required 1/ to understand individual and organizational factors associated with suboptimal prescribing and 2/ to assess the consequences of each criteria of suboptimal prescribing, in terms of adverse health outcomes and subsequent costs, in order to refine the list of indicators of quality of drug therapy and operationalize their monitoring.

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Table 1. List of the most prescribed drugs in the 30,702 residents included in the study

Drug's name	N (%)
Acetaminophen	10,964 (35.7)
Aspirin	9,517 (31.0)
Macrogol	6,588 (21.5)
Furosemide	6,576 (21.4)
Esomeprazole	5,225 (17.0)
Levothyroxin	4,297 (14.0)
Potassium choride	3,903 (12.7)
Zopiclone	3,764 (12.3)
Escitalopram	3,693 (12.0)
Bisoprolol	3,563 (11.6)
Oxazepam	3,516 (11.5)
Alprazolam	3,172 (10.3)
Associations containing calcium	3,116 (10.2)

Table 2. Prevalence of potentially inappropriate medications (PIMs) in the 30,702 residents included in the study

PIM	Reason	N (%)
Dose of short- or intermediate- half-life benzodiazepines > half the dose given in young subjects	Questionable efficacy and increased risk of cognitive impairment, delirium, drowsiness, falls	5,371 (17.5)
Use of two or more psychotropic drugs from the same therapeutic class during the study period	Questionable efficacy and increased risk of adverse effects	4060 (13.2)
Long-acting benzodiazepines	Increased risk of cognitive impairment, delirium, drowsiness, falls	2,199 (7.2)
Anticholinergic histamines	Anticholinergic effects	1,256 (4.1)
Short-acting calcium-channel blockers	May cause postural hypotension, myocardial infarction, and stroke	1044 (3.4)
Anticholinergic antipsychotic drugs	Anticholinergic effects, second choice drugs	891 (2.9)
Anticholinergic antidepressants	Anticholinergic effects, potential for cardiotoxicity, second-choice drugs	639 (2.1)
Anticholinergic hypnotic drugs	Anticholinergic effects	614 (2.0)
Anticholinergic antispasmodic drugs	Anticholinergic effects	531 (1.7)
Cerebral vasodilators	Questionable efficacy	442 (1.4)
Centrally acting antihypertensives	Sedation, hypotension, bradycardia,	412 (1.3)

	syncope	
Muscle relaxants	Sedation, falls	318 (1.0)
Concomitant use of anticholinesterase drugs and drugs with anticholinergic properties	Antagonistic mechanisms	280 (0.9)
Antiarrhythmics	Unfavorable benefit-risk ratio of digoxine > 0.125 mg/j and disopyramide	194 (0.6)
Other drugs with anticholinergic properties: antiemetics, cough suppressants, nasal decongestants, or antidrowsiness drugs	Anticholinergic effects and questionable efficacy	161 (0.5)
Nitrofurantoïne	Potential for pulmonary toxicity and lack of efficacy in case of renal failure	89 (0.3)
Stimulant laxatives	Worsening of irritable bowel syndrome	38 (0.1)
Gastrointestinal antispasmodic drugs with anticholinergic properties	Anticholinergic effects and questionable efficacy	26 (0.1)
Dipyridamole	May cause orthostatic hypotension and more-effective alternatives available	10 (0.0)
Use of two or more non-steroidal anti-inflammatory drugs during the study period	No enhancement of efficacy and increased risk of adverse effects	8 (0.0)
Long-acting sulfonylureas	Prolonged hypoglycemia	8 (0.0)
Ticlopidine	Blood and hepatic adverse effects	4 (0.0)

Cimetidine	Confusion, drug-drug interactions	4 (0.0)
Reserpine	Drowsiness, depression, gastrointestinal disorders	0

Table 3. Factors associated with suboptimal prescribing in the 28,600 residents included in the multivariate analysis

Variable	Excessive polypharmacy			At least one PIM		
	N (%) ^a	aOR ^b (95%CI)	p	N (%)	aOR ^b (95%CI)	p
Gender						
Women	4,787 (21.1)	1		10,829 (47.8)	1	
Men	1,681 (26.0)	1.00 (0.94-1.07)	0.927	3,718 (46.2)	0.87 (0.82-0.91)	<0.001
Age (tertiles, years)						
60-85.5	2,143 (21.4)	1		5,379 (53.6)	1	
85.6-91.1	2,090 (21.2)	0.99 (0.92-1.06)	0.824	4,442 (45.0)	0.70 (0.66-0.74)	<0.001
91.2 and over	2,070 (21.0)	0.99 (0.93-1.07)	0.822	4,245 (42.9)	0.64 (0.60-0.67)	<0.001
Legal status of the nursing home						
Public	855 (22.7)	1		1,837 (48.7)	1	
Private not-for-profit	1,981 (22.6)	0.96 (0.79-1.16)	0.658	4,202 (48.0)	0.94 (0.82-1.08)	0.353
Private-for-profit	3,632 (20.0)	0.81 (0.68-0.98)	0.026	8,508 (46.8)	0.93 (0.82-1.08)	0.255
Number of places in the nursing home						
1-78	2,334 (22.7)	1		4,987 (48.4)	1	
79-94	2,041 (19.8)	0.83 (0.72-0.95)	0.006	4,824 (46.8)	0.94 (0.85-1.03)	0.173
95-242	2,091 (20.7)	0.92 (0.80-1.06)	0.243	4,724 (46.8)	0.94 (0.85-1.04)	0.509

^a Prevalence of excessive polypharmacy and PIM according to individual and organizational factors. For instance, the prevalence of excessive polypharmacy is 21.1% among women and 26.0% among men.

^b Odds Ratio of the multilevel logistic regression model adjusted for all the variables included in the table.