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Frailty of Elderly People and the Consumption of Medications: Inappropriate Polypharmacy and Prescriptions

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Ageing is not a homogenous process. Some people are more frail than others: they are less able to deal with stressful events because their physiological reserves are insufficient (impaired nutrition, loss of muscular mass, etc.) and undergo negative consequences in terms of health and healthcare (hospitalisation, institutionalisation, death, etc.). For a number of years the French National Health Authority (Haute Autorité de Santé, HAS) has focused on the detection and treatment of frailty, in order to improve healthcare for the elderly. The proposed initiatives include the adjustment and simplification of the patients' medicinal treatments.

The originality of this study lies in its analysis of the relation between the use of medications and frailty, by taking into account both the quantity and the quality of the medications prescribed for elderly people aged 65 years or over. The study was carried out based on the data provided by the Health, Health Care and Insurance Survey (Enquête Santé et Protection Sociale, ESPS), conducted by the Institute for Research and Information in Health Economics (Institut de Recherche et Documentation en Économie de la Santé, IRDES) in 2012, merged with healthcare claims data from the French National Health Insurance system (Assurance Maladie), which provides a record of health care consumption. It suggests that polypharmacy and the use of certain potentially inappropriate medications — anticholinergic medications — are associated with frailty in elderly people.

Frailty in elderly people is now well recognised by geriatricians and prevention stakeholders. The concept of frailty is characterised by increased vulnerability to stress factors (for example, an infection episode), which results from a diminution of physiological reserve. Frailty increases the risk of deterioration in health and increases dependency. GPs are encouraged to

screen their patients for frailty and to refer them if necessary to a consultant or a geriatric day hospital, where an assessment of the causes of frailty leads to a personalised care plan.

Among the possible treatments for frailty, it is recommended that the medicinal treatment of patients is adjusted and simplified (HAS, 2014) or,

in other words, that "polypharmacy" is reduced; this is what the World Health Organisation (WHO) defines as 'the simultaneous administration of many

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This article is part of research work carried out by IRDES on the frailty of elderly people and healthcare consumption (Sirven, 2016; 2014; and 2013). With the permission of Éditions Springer, the following is an overview of the article Herr et al. (2017). "Frailty, Polypharmacy, and Potentially Inappropriate Medications in Old People: Findings in a Representative Sample of the French Population", *European Journal of Clinical Pharmacology*, vol. 73, n° 9, 2017/09, 1165-1172.

medications or the excessive administration of medications' (Monégat et al., 2014). Epidemiological studies have in fact demonstrated that frail people are more likely to receive polypharmacy than those who are not frail (Herr et al., 2015). But polypharmacy exposes elderly people to various risks, in particular undesirable reactions to medications, falls, increased use of healthcare services, and mortality. Polypharmacy also increases the risk of being prescribed "potentially inappropriate medications" (PIM), that is to say medications that have a well-established risk of negative effects in elderly people or medications whose effectiveness has not been established. The first set of explicit criteria for PIMs was produced in 1991 by Beers et al. for use in nursing homes. Since then, it has been updated several times, extended to the noninstitutionalised aged population, and adapted in various countries.

In this context, the aim of this study was to analyse the relation between the use of medications and frailty, by taking into account the quantity of medications prescribed (polypharmacy) and the quality of the prescription (according to the French criteria of PIM) among elderly people aged 65 years and over living in a standard household. We used data from the Health, Health Care and Insurance Survey (Enquête Santé et Protection Sociale, ESPS), which was representative on the national level, addressing the themes of health and healthcare in France, and in which the data on frailty and medications were subject to in-depth analysis for the year 2012.

Identifying the frailty phenotype in the general population

The frailty phenotype is characterised by the presence of a critical number of alterations in physical strength, physical activity, nutrition, mobility, and energy (Fried et al., 2001). Epidemiological studies have demonstrated that frailty is associated with greater use of healthcare and that it foreshadows health problems such as the emergence or aggravation of functional limitations, falls, hospitalisations, and mortality.

Frailty, according to the Fried phenotype, was empirically developed as part of a survey into cardiovascular health in the United States and adapted to declarative data. The five characteristics of frailty were defined as follows:

- Exhaustion: physical fatigue or weakness, or a lack of energy signalled by the person.
- Unintentional 5% weight loss over the previous twelve months.
- Muscular weakness: difficulty in carrying a bag weighing 5 kg (excluding any difficulty in using one's hands or fingers), or difficulty in leaning over or kneeling without assistance.
- Reduced mobility: difficulty in walking 500 metres without assistance or difficulty in going up or down twelve steps unassisted.
- A low level of physical activity: no walking, cycling, or any other sport (jogging, fitness, swimming, cycling, etc.).

The IRDES report on the results of the 2012 Health, Health Care and

Insurance Survey, or ESPS, (Célant et al., 2014) provided additional details about the assessment of frailty (the exact phrasing of the questions and coding). Frail individuals were those cumulated at least three criteria, and pre-frail had only one or two criteria. Previous analyses from the same survey pointed to a concordance between this measurement and other measurements of the frailty phenotype in the general population, such as those used in the SHARE (Survey on Health, Ageing, and Retirement in Europe), which included objective measurements of grip strength. According to the Fried phenotype, frail persons accounted for 15% of the study population (people aged 65 years old and over living in a standard household in mainland France using survey weights), which was similar to the figures produced using SHARE (Santos-Eggiman et al., 2009).

The prevalence of polypharmacy and PIMs

Polypharmacy and PIMs were measured by combining the Health, Health Care and Insurance Survey (ESPS) with the French National Health System (Assurance Maladie) data, which contains exhaustive information about all the medications for which people had been reimbursed in 2012. The medications were coded using the Anatomical Therapeutic Chemical (ATC) system. The number of medications used during 2012 was estimated by calculating the average of the total number of medications used over three-month periods,

Definitions and measurements

Polypharmacy: the simultaneous administration of many medications, defined in this case as the average of the total number of different medications reimbursed over three-month periods based on reimbursement data for 2012 (polypharmacy if ≥ 5 different medications, and excessive polypharmacy if ≥ 10 different medications).

Potentially inappropriate prescriptions: prescriptions of a medication having a poor benefit/risk ratio in elderly patients, due to a clear risk of side effects or questionable effectiveness, in this case defined by the Laroche list complemented by indicators of prolonged use (≥ 3 reimbursements over a 4-month period).

Anticholinergic medications: medications likely to produce peripheral (dry mouth and constipation) and central side effects (falls, dizziness, and cognitive problems). Anticholinergic medications are found in many therapeutic classes (antidepressants, neuroleptics, hypnotics, antihistamines, etc.). Only a few medications are used for their anticholinergic properties (urinary antispasmodic drugs, for example).

SOURCES AND SAMPLE

The data used was provided by the 2012 transversal French Health, Health Care and Insurance Survey (ESPS) and combined with data provided by the French National Health Insurance System (Assurance Maladie). The survey, coordinated by IRDES, was designed to be representative of the French population (1 person included in the ESPS representing 2,231 persons on average in the general population). The source population comprised 599,544 individuals included in the Echantillon Généraliste des Bénéficiaires (EGB) in 2012, a representative permanent sample of the population covered by French National Health Insurance System (Assurance Maladie). A random subsample of inhabitants of the community was drawn from the EGB; these reference individuals along with members of their household were eligible for the survey. In total, 8,413 households, representing 23,047 French residents, took part in the 2012 survey. Of these, 14.2% were aged 65 or over (3,271 observations remaining). The respondents in the survey were then cross-referenced with the data from the French National Health Insurance System (in the EGB), resulting in 1,955 observations. The individuals who were not cross-referenced were members of a household whose public health insurance was independent of the health insurance of the reference person indicated in the permanent sample of health insurance beneficiaries (Echantillon Généraliste des Bénéficiaires, EGB). And 65 other persons, whose medications were not reimbursed in 2012, were removed from the analysis. The analysis sample ultimately comprised 1,890 individuals living in a standard household, aged 65 or over, 11% of whom were considered frail (frailty score $\geq 3/5$).

without taking into account combinations of drugs (a specific drug comprising two active ingredients counts as a single medication). Polypharmacy was defined as taking at least 5 medications and excessive polypharmacy as at least 10. These figures included medications taken regularly and occasionally. The PIMs were evaluated for the whole of 2012 using the Laroche list (Laroche et al., 2007), which results from a consensus of experts and takes into account medications marketed in France. Five criteria requiring information on the underlying conditions were excluded because it was not possible to evaluate them in this framework. The concomitant use of medications referred to cases where two medications were prescribed the same day. Based on current literature and the national recommendations,

inappropriate durations of treatment (≥ 3 reimbursements over a 4-month period) were also taken into account for certain a priori selected drug classes — non-steroidal antiinflammatory drugs (NSAIDs) and benzodiazepines —, particularly hypnotic drugs.

Polypharmacy and excessive polypharmacy were observed respectively in 43% and 27% of the study population, and 47% of the study population had received at least one PIM. The PIMs on the Laroche list concerned 37% of the study population. The most frequent medications were benzodiazepines, anticholinergic medications, NSAIDs, and cerebral vasodilators. The frequency of the PIMs increased to 47% when inappropriate durations of treatment were taken into account.

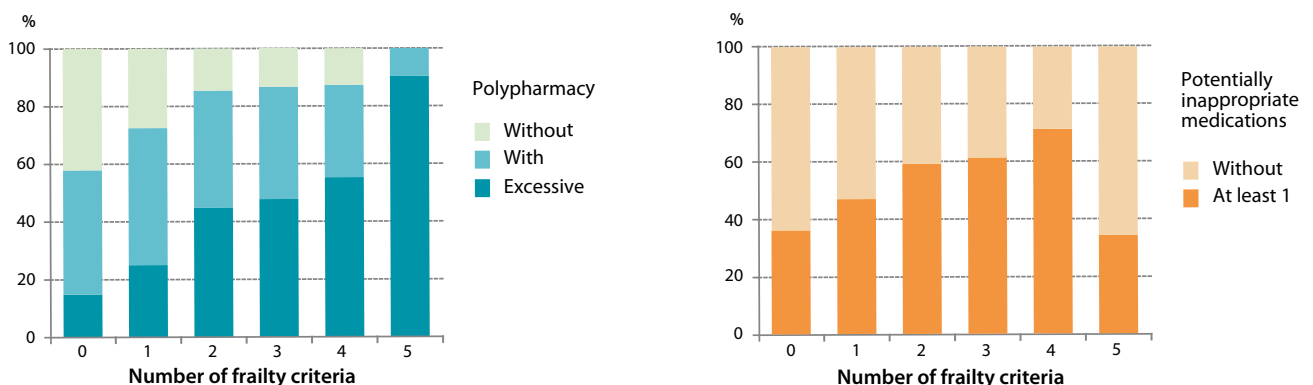
Our estimations of the prevalence of polypharmacy and PIMs were relatively high compared with previous estimations, which, given our methodology, was expected. Indeed, the prevalence of polypharmacy must be considered according to our definition, which encompasses all the prescribed medications over 3-month periods. As for PIMs, their prevalence was evaluated over a whole year and not at a given moment, which very probably increased the likelihood that a given person had received a PIM compared with a one-off evaluation. Furthermore, we added three criteria (corresponding to inappropriate durations of treatment) to those on the Laroche list, which resulted in an increase in the prevalence of PIMs by almost 10%. In consistence with a recent review of literature (Tommelein et al., 2015), we identified benzodiazepines and NSAIDs amongst the most observed PIMs. However, the inappropriate use of antidepressant drugs was limited in our study.

Untangling the links between frailty, polypharmacy and PIMs

The graph illustrates the gradual increase of the prevalence of polypharmacy and PIMs with the number of frailty criteria. The associations between frailty and polypharmacy, on the one hand, and frailty and PIMs, on the other, were analysed in detail in the table. They remain strong even when

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Prevalence of polypharmacy and PIMs in relation to the number of frailty criteria (N = 1,890)



Sources: ESPS, EGB 2012; INSEE, CNAM.
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Prescriptions of medications associated with frailty

Explained variables	Explained variable: Score (0 to 5) according to the Fried phenotype					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Polypharmacy						
5-9 versus 0-4 medications	1.587 ***		1.163 **		1.139 *	1.171 *
≥ 10 versus 0-4 medications	2.710 ***		1.451 ***		1.392 ***	1.501 ***
Potentially inappropriate medications (PIMs)						
At least one PIM from the Laroche list + other criteria		1.578 ***		1.180 ***	1.102 *	1.221 *
Anticholinergic medications		1.521 ***		1.192 **	1.169 **	1.337 **
Prolonged use of benzodiazepines		1.266 **		1.072	1.012	1.062
Anti-hypertensive drugs		1.384 **		0.967	0.958	1.018
Cerebral vasodilators		1.211 **		1.085	1.015	1.201
Concomitant distribution of psychotropic medications of the same class		1.454 **		1.110	1.093	1.093
Prolonged use of	hypnotic drugs (≥ 3 reimbursements over a 4-month period)	1.454 ***		1.095	1.007	1.190
	benzodiazepines (> 3 reimbursements over a 4-month period)	1.556 ***		1.112 **	1.034	1.201
	NSAIDs (> 3 reimbursements over a 4-month period)	1.165 *		1.166 **	1.106	0.807
Control variables	No	No	Yes	Yes	Yes	Yes
Notes: (1) Specification of the models: Model 1: number of frailty criteria ~ polypharmacy; Model 2: number of frailty criteria ~ PIM; Model 3: number of frailty criteria ~ polypharmacy + control variables; Model 4: number of frailty criteria ~ PIM + control variables; Model 5: number of frailty criteria ~ polypharmacy + PIM + control variables; and Model 6: number of frailty criteria ~ polypharmacy + PIM + interaction term + control variables. (2) The values are incidence rate ratios (IRR). (3) Control variables: age, gender, difficulties in carrying out everyday activities, perceived health, cardiovascular diseases, musculoskeletal diseases, diabetes, depression, and BMI. (4) Caption: *p < 0.1; **p < 0.05; ***p < 0.001.						
Reading: In model 1, individuals with excessive polypharmacy (≥10 medications) have a frailty level 2.7 times higher than individuals who do not take many medications (<5 medications). In model 6, once the effect of all the combined factors is taken into account, individuals involved with polypharmacy have a level of frailty 50% higher than those persons who do not take many medications.						
Sources: ESPS, EGB 2012; INSEE, CNAM.						
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comorbidities are taken into account in the model (models 3 and 4). If one considers the combined effect of polypharmacy and PIMs, only the first factor played a significant role in the model (model 5). Nevertheless, if one breaks down the effect of PIMs, while analysing polypharmacy and comorbidities, the prescription of anticholinergic medications (see the inset "Definitions and measurements") is associated with greater frailty.

The relation between PIMs and frailty observed at the outset in the non-adjusted or partly adjusted models became insignificant when polypharmacy was introduced to the multi-varied models. This result suggests that the association between PIMs and frailty reflects the association between PIMs and polypharmacy on the one hand, and between polypharmacy and frailty on the other. Nevertheless, this result should be considered with caution because the PIMs still tended to be associated with frailty in the adjusted model on polypharmacy, and a lack of ability to detect a significant association cannot be excluded. In addition, the PIM variable encompasses

various situations: certain medications are considered to be inappropriate due to their dubious safety profile, while others are deemed to be inappropriate on account of the uncertainty of their effectiveness. This is why the PIMs were considered as a whole and per criterion, particularly anticholinergic medications.

Strengths and limits of the study

The strength of this study lies in the use of a set of unique data that combines a health survey that is representative on the national level and data on the reimbursements of medications by the French National Health Insurance System (Assurance Maladie) from the individuals surveyed. Our results partly corroborate those established in the literature: excessive polypharmacy has been associated with a higher level of frailty, and the link between the prescription of anticholinergic medications and frailty has already been identified in France in the case of persons treated in day centres for their frailty (Moulis et al., 2015). Hence, this study con-

firms the previous conclusion (a link between polypharmacy and frailty) and gives it a more general application by extending its scope to the general population (a link between anticholinergic medications and frailty).

However, this study has its limits. Even if it is representative on the national level, the sample is restricted to elderly people aged 65 and over. With regard to the evaluation of frailty, the self-reported variables were used in the absence of objective measurements of grip strength and walking speed. Another limit is the absence, relating to 30% of the participants, of data on at least one frailty variable. Taking into account only individuals with complete information would have led to a selection bias and a loss of efficacy, which is why the missing the data was imputed based on available information. The results were comparable with regard to the estimated coefficients but slightly different with regard to the standard error of the estimations. Although highly reliable, the data on the use of medications only reflects the medications purchased by the persons

METHODS

The statistical analysis was conducted using individual sample weights (the inverse of the probability that the observation is included considering sampling design, age, gender, household size, and social security scheme) to provide representative estimates.

Missing data were imputed, regarding frailty criteria, for 29.7% of the survey respondents, who only partly completed the questions on this theme. The method used was an imputation at the average point, using age and gender (logit modelling and imputation of the variable as 1 when the probability was higher than 0.5 and 0 in the opposite case). The imputation of the frailty criteria conditional on age and gender helped improve the statistical impact without introducing bias in the estimates, because (i) age and gender are exogenous covariates (not determined by frailty or its determinants), and (ii) these two variables are included as covariates in the model, thus assigning the observations to the average individual. Ultimately, there was no difference in the proportion of frail persons between the original set of data and the set of imputed data (p -value = 0.11).

The independent and combined effects of polypharmacy and PIMs on the evolution of the frailty score of 0 to 5 were assessed by Poisson regres-

sion models with the number of frailty criteria as a dependent variable. Initially, the effect of polypharmacy and that of the PIMs were modelled separately. Then, the models were adjusted for confounders, corresponding to the variables associated with the number of frailty criteria with a value of $p < 0.20$ in bivariate analysis. The final adjustment was obtained by gradually removing variables associated with frailty with a $p > 0.10$. Then polypharmacy, PIMs, and confounders were entered in the model simultaneously. Lastly, an interaction term between polypharmacy and PIMs was added. The results are presented in the form of an incidence rate ratio (IRR and exponential function coefficient) with 95% confidence interval (CI 95%).

The analytical choices (imputation, use of sampling weights, Poisson modelling, and robust standard errors) aimed to maximise the statistical impact of the analysis, which is particularly important when introducing interaction terms in the models. Sensitivity analyses were carried out to test the influence of imputation on the frailty variables by repeating the analysis with the original variables.

and not those actually taken. In the event of concomitant use — defined as situations where two drugs of the same class were delivered on the same day — we miss cases where people buy their medications on different days and use medications they have left at home. Furthermore, no information was available about the use of over-the-counter products and medications received during hospitalisation. Lastly, the cross-sectional design of this study did not

reach any conclusions about the causality of the relationships between frailty, polypharmacy, and PIMs.

* * *

This study demonstrates how polypharmacy and the use of anticholinergic medications are independently associated with frailty in elderly people. This should raise awareness about the excessive use of medications in the elderly

and encourage doctors to abandon the prescription of medicaments with a low benefit/risk ratio for their patients, in particular anticholinergic medications. ♦

Overview based on: "Frailty, Polypharmacy, and Potentially Inappropriate Medications in Old People: Findings in a Representative Sample of the French Population". Herr M., Sirven N., Grondin H., Pichetti S., Sermet C., *European Journal of Clinical Pharmacology*, vol. 73, n° 9, 2017/09, 1165-1172. Published with the permission of Éditions Springer.

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