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## Polymédication chronique : description et risque

Jordan Guillot

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THÈSE PRÉSENTÉE  
POUR OBTENIR LE GRADE DE  
**DOCTEUR DE  
L'UNIVERSITÉ DE BORDEAUX**

École Doctorale, Sociétés, Politique, Santé Publique  
Pharmacologie option pharmaco-épidémiologie, pharmaco-vigilance

Par Jordan GUILLOT

Né le 11 avril 1991 à Beaumont

**Polymédication chronique : description et risque**

Sous la direction de : Julien BEZIN

Soutenue le 11 janvier 2021

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*A Yannick, Mémé Marguerite, Mamie Lucie*

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**Monsieur le Docteur Pierre Verger**

**Madame le Docteur Catherine Helmer**

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## Résumé : Polymédication chronique : description et risque

La polymédication est définie comme l'administration de nombreux médicaments de façon simultanée ou comme l'administration d'un nombre excessif de médicaments. L'objectif général de la thèse était de décrire la polymédication chronique et le risque associé à partir des bases de données médico-administratives.

Un indicateur de description de la polymédication chronique, défini par l'usage concomitant et chronique de 5 médicaments ou plus, a été développé pour décrire la prévalence et les médicaments impliqués. À partir des données de l'Assurance Maladie Française, nous avons estimé que la polymédication chronique concernait plus de 5 % des français de tout âge, et impliquait majoritairement les médicaments cardiovasculaires. Afin d'approfondir la caractérisation de la polymédication chronique, une description de la part potentiellement inappropriée a été conduite en utilisant les données de l'Assurance Maladie Française et de la *Veterans Health Administration* aux États-Unis. À partir de ces données nous avons estimé que la part inappropriée de la polymédication chronique était majeure puisque concernant, en France, 65 % des sujets âgés ( $\geq 65$  ans) et 46 % des sujets d'âge moyen (45-64 ans), et aux États-Unis, 67 % des vétérans. Les inhibiteurs de la pompe à proton, les médicaments psychiatriques et les médicaments du diabète étaient les médicaments potentiellement inappropriés les plus fréquents. La polymédication, qu'elle soit appropriée ou non est un facteur de risque de mortalité. Chez les vétérans américains nous avons montré que la polymédication chronique et les médicaments potentiellement inappropriés augmentaient le risque de décès.

**Mots clés :** Polymédication ; Pharmaco-épidémiologie ; Base de données ; Etude d'utilisation ; Risque

## **Abstract: Chronic polypharmacy: description and risk**

Polypharmacy is defined as the administration of many drugs at the same time or as the administration of an excessive number of drugs. The main objective of this thesis was to describe chronic polypharmacy and the associated risk, from medico-administrative databases.

A specific indicator of chronic polypharmacy, defined by five or more concomitant and chronic drug uses, was developed to describe the prevalence and the involved drugs. Based on data from the National French Health Insurance, we estimated that chronic polypharmacy concerned more than 5% of all aged French individuals, and involved mainly cardiovascular drugs. To further describe chronic polypharmacy, a description of inappropriateness was carried out using data from the National French Health Insurance and the United States Veterans Health Administration. We estimated that the inappropriateness of chronic polypharmacy was major. It concerned 65% of French older adults ( $\geq 65$  years old), 46% of French middle-aged adults (45-64 years old) in France, and 67% of American veterans. Proton pump inhibitors, psychiatric drugs and diabetes drugs were the most common potentially inappropriate medications. Furthermore, we have shown that chronic polypharmacy, whether appropriate or not, is associated with increased mortality. In American veterans, chronic polypharmacy and potentially inappropriate medications both increased the risk of all-cause death.

**Keywords:** Polypharmacy; Pharmacoepidemiology; Database; Drug utilization study; risk



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## Liste des principales abréviations

AINS	Anti-Inflammatoires Non Stéroïdiens
AMM	Autorisation de Mise sur le Marché
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ATC	<i>Anatomical Therapeutic Chemical</i>
CCAM	Classification Commune des Actes Médicaux
CDW	<i>National Corporate Data Warehouse</i>
CIP	Codes d'Identification de la Présentation
CNAMTS	Caisse Nationale d'Assurance Maladie des Travailleurs Salariés
CNSA	Caisse Nationale de Solidarité pour l'Autonomie
DCIR	Datamart de Consommation Inter Régime
DRUGS-SAFE	Drugs Systematized Assessment in real-life Environment
EGB	Echantillon Généraliste de Bénéficiaire
EPPM	Etude Permanente sur la Prescription Médicale
HAD	Hospitalisation à Domicile
IPP	Inhibiteur de la Pompe à Proton
MAI	<i>Medication Appropriateness Index</i>
MCO	Médecine, Chirurgie, Obstétrique
MPI	Médicament Potentiellement Inapproprié
MSA	Mutuelle Sociale Agricole
OTC	<i>Over-The-Counter</i>
PMSI	Programme de Médicalisation des Systèmes d'Information
PROMPT	<i>Prescribing Optimally in Middle-aged People's Treatments</i>
RSI	Régime Social des Indépendants
SNDS	Système National des Données de Santé
SNIIRAM	Système National d'Information Inter-Régimes de l'Assurance Maladie
SSR	Soins de Suite et Réadaptation
START	<i>Screening Tool to Alert doctors to Right Treatment</i>
STOPP	<i>Screening Tool of Older Person's Prescriptions</i>
VA	<i>United States Department of Veterans Affairs</i>
VHA	<i>Veterans Health Administration</i>

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# I Introduction

## A La pharmaco-épidémiologie

Avant d'être commercialisé, les médicaments doivent avoir démontré leur efficacité et leur sécurité d'emploi. Un médicament en développement doit passer des études précliniques (in vitro, et chez l'animal) et cliniques. Les essais cliniques sont des études interventionnelles réalisées sur de courtes périodes, chez des sujets particulièrement sélectionnés et suivis dans des conditions strictes. Bien que ces études soient absolument nécessaires pour le développement d'un médicament, leurs conditions sont éloignées des pratiques d'utilisation des médicaments au sein des populations [1].

Face à ces limites, des méthodes de surveillance et d'étude de l'utilisation des médicaments après leur commercialisation (obtention d'une autorisation de mise sur le marché AMM) ont été développées et ont donné naissance notamment à la pharmaco-épidémiologie. Cette discipline utilise le raisonnement et les outils épidémiologiques tout en étant centrée sur le médicament. Elle permet ainsi l'étude du médicament sur de grandes populations et donc sur des personnes d'âges différents, avec des modes de vie différents et des pathologies différentes, multiples ou non [2]. Contrairement aux études interventionnelles, les études de pharmaco-épidémiologie sont observationnelles et s'appliquent à modifier le moins possible le cours naturel des choses et permettent ainsi de décrire la réalité de terrain. De part cette nature observationnelle, ces études sont d'avantages sujettes à différents types de biais mais les méthodologies développées permettent d'en limiter l'impact [3].

Suivant l'objectif, différentes études pharmaco-épidémiologiques peuvent être conduites. Les études d'utilisation du médicament sont des études descriptives. Leur but est de quantifier et qualifier l'utilisation des médicaments présents sur le marché. Ces études sont le plus souvent transversales afin de décrire la consommation des médicaments à un instant donné. Les études de risques et/ou d'efficacité sont des études quantitatives et permettent d'estimer la balance bénéfice-risque des médicaments. Ces études sont prospectives et suivent les patients dans le temps le plus souvent suivant un schéma de type étude de cohorte. Elles peuvent également être rétrospectives pour, à partir d'un événement donné, examiner le risque associé à une exposition antérieure et suivent le plus souvent un schéma de type cas-témoins.

Pour tous ces types d'études, le choix de la source des données est également primordial et on en distingue deux grandes catégories : les études de terrain et les études à partir de bases de données. Les études de terrain nécessitent de collecter des données qui serviront spécifiquement à répondre à la problématique de l'étude ; on parle alors de données *ad hoc*. Ces données peuvent concerner des médicaments, des conditions cliniques, le mode de vie ou d'autres facteurs sociodémographiques.

Elles peuvent être collectées par interrogations des médecins, pharmaciens, professionnels de santé ou des patients eux-mêmes. Collecter ces données nécessite de réaliser un sondage sous la forme d'auto-questionnaire ou de questionnaire rempli par les enquêteurs, qui sera distribué dans la population cible de l'étude. Les études de terrain ont pour avantage de permettre à l'investigateur de choisir les données qu'il souhaite collecter. Cependant, ces études sont souvent lourdes et chères à mettre en place et ne peuvent considérer qu'un échantillon restreint de personnes. De plus, elles sont particulièrement exposées aux biais de sélection et d'information. Pour toutes ces raisons, elles sont de plus en plus délaissées au profit d'études réalisées à partir des bases de données. Ces dernières, permettent la réalisation d'études sur de grands échantillons, voire même sur des populations nationales, en garantissant ainsi une puissance statistique suffisante et une bonne représentativité de la population dont elles sont issues. L'exploitation de ces données est souvent moins coûteuse que la réalisation d'une étude de terrain. Cependant, ces études ont également des limites tels que l'absence ou l'incertitude de certaines données cliniques, les exposant ainsi à certains biais de confusion.

## B Les bases de données en pharmaco-épidémiologie.

### B.1 Définition d'une base de données

Une base de données permet le stockage informatisé de grandes quantités d'informations de manière structurée et organisée. Les principaux types de bases de données utilisées en pharmaco-épidémiologie sont les bases de données médicales et les bases de données médico-administratives.

Les bases de données médico-administratives ont été conçues à l'origine à des fins purement administratives mais constituent néanmoins un outil précieux pour les chercheurs. Elles ont été développées pour que l'Etat ou les structures organisationnelles de soin puissent rembourser les consommations de soin à l'assureur ou au patient. Lorsqu'un patient se voit facturer un acte de soin tels qu'une consultation ambulatoire ou hospitalière, un examen en laboratoire ou une délivrance en pharmacie, des données sont recueillies et codées selon des classifications nationales ou internationales.

Les bases de données médicales ont été conçues dans le but d'enregistrer les dossiers médicaux des patients en format électronique. Elles intègrent les données individuelles de la prise en charge médicale, sans objectif de collecter des données financières. Ces données sont souvent collectées par des cliniciens qui renseignent les dossiers médicaux informatisés, selon des recommandations précises, lors de leur pratique médicale quotidienne. Les données sont intégrées dans une base de données commune et anonymisée. De par la nature des données collectées, ces bases ont l'avantage

de fournir une information exhaustive sur la prise en charge médicale, le mode de vie du patient et les résultats d'examen.

Idéalement pour répondre à l'ensemble des besoins, les données doivent être disponibles individuellement, fiables, valides, mises à jour et contrôlées régulièrement. Elles doivent être issues d'une population de grande taille et stable au cours du temps (de la date de naissance jusqu'à la date de décès de l'individu, avec un suivi continu en cas de changement de profession ou de couverture de santé). Enfin, la base de données idéale regrouperait les médicaments consommés (sur prescription ou en automédication), les caractéristiques médicales cliniques et/ou paracliniques (événement clinique, historique du patient), des informations sur le mode de vie et certains facteurs de risque (alcool, tabac, obésité, etc.), les caractéristiques socio-environnementales (zone de résidence, catégorie socio-professionnelle, etc.) et les coûts associés à chaque acte médical. À ce jour, il n'existe aucune base intégrant l'ensemble de ces caractéristiques. Les différentes bases médico-administratives dans le monde se rapprochent de cet idéal tout en possédant leur propres forces et lacunes.

## B.2 Les forces et limites des bases de données

L'avantage majeur des bases de données est l'accès à des données de soins pour des échantillons de très grandes tailles. L'exploitation de ces bases est souvent peu coûteuse par rapport à la taille de l'échantillon puisque que les données sont souvent issues d'un organisme administratif préexistant. Certaines bases de données sont exhaustives, c'est-à-dire qu'elles concernent l'intégralité des soins médicaux dispensés quelle que soit l'assurance ou la mutuelle complémentaire des patients. Dans certains cas comme aux Etats-Unis, elles sont spécifiques de l'assurance privée ou du système public de soins (Medicare, Medicaid, Vétérans) et exhaustives car regroupant l'ensemble des soins (médecins, pharmacie, etc.). Les bases de données médicales ont en plus l'avantage de contenir des informations sur les caractéristiques socio-environnementales qui sont d'importants facteurs de confusion. Elles peuvent également informer sur les indications des médicaments dispensés et les résultats des examens pratiqués. De par l'enregistrement des données, ces bases ont l'avantage de s'affranchir de possibles biais liés à l'enquêteur ou aux patients (biais de mémorisation). Chaque base de données peut également être enrichie par le croisement avec d'autres sources de données informatisées (registres de décès, de pathologies, données spécifiques hospitalières) permettant d'élargir le potentiel et le champ d'application de ces bases pour la recherche. Cependant le croisement de ces bases doit faire appel à l'utilisation d'éléments d'identification communs tel que le nom, la date de naissance ou des numéros d'identification spécifiques d'un individu (par exemple, le



numéro de sécurité sociale), et une définition standardisée du contenu sémantique de ces différentes sources de données.

Les principales limites des bases de données sont liées au fait que la validité des données de diagnostic reste incertaine tout particulièrement pour les bases de données administratives qui collectent des informations à des fins financières. Si possible, le dossier médical doit être confronté à ces bases afin d'évaluer la validité du diagnostic. Les informations concernant le mode de vie et les facteurs socio-économiques sont également absentes de certaines bases. Par exemple, les informations concernant la consommation de tabac ou d'alcool ne sont pas toujours disponibles mais s'avère pourtant primordiales lors d'analyses. Une autre limite majeure des bases, surtout celles administratives, est le fait que la population ne reste pas stable au cours du temps, soit du fait d'un changement de situation professionnel, de couverture médicale ou d'un déménagement. Si ces situations ne sont pas identifiées elles peuvent compromettre une étude longitudinale. Pour pallier cette information incomplète, l'investigateur peut réaliser une analyse de sensibilité en censurant les patients après une longue période d'inactivité dans la base. De plus, certaines bases sont limitées par le type de population couverte, ceci étant particulièrement vrai pour les bases américaines. Dans ce pays, l'absence d'un système de couverture médicale universelle est un frein au développement d'une base de données nationale.

### B.3 Les bases de données françaises du Système National des Données de Santé

Le Système National des Données de Santé (SNDS) a été créé par la loi de modernisation du système de santé français. Il vise à l'amélioration des connaissances sur la prise en charge médicale et l'élargissement du champ des recherches, des études et évaluations dans le domaine de la santé (Loi n°2016-41 du 26 janvier 2016, article 193).

Le SNDS, géré par la Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS) permet de chaîner différentes bases de données :

- La base SNIIRAM (Le Système National d'Information Inter-Régimes de l'Assurance Maladie) de l'Assurance Maladie
- Les données nationales des hôpitaux : le PMSI (Programme de Médicalisation des Systèmes d'Information)
- Les causes médicales de décès (Base CépiDC de l'Inserm)
- Les données relatives au handicap (données de la Caisse Nationale de Solidarité pour l'Autonomie (CNSA, en projet d'intégration)

- Des données provenant des organismes d'assurance santé complémentaire (mutuelles privées, en projet d'intégration)

Le SDNS est une base de données en évolution et l'ensemble de ces données n'a pas été chaîné dès sa création. Le chaînage entre le SNIIRAM et le PMSI ont constitué la première version. Les causes médicales de décès alimentent le SNDS depuis 2017, les données de la CNSA et les données des organismes complémentaires (en cours d'intégration).

En France, le système de protection de l'Assurance Maladie est composé de plusieurs régimes spécifiques qui couvrent l'ensemble de la population française. Le régime général (CNAMTS) couvre 86% de la population résidant en France. Les deux autres régimes important sont la caisse nationale d'assurance pour les salariés et les exploitant agricoles (Mutuelle Sociale Agricole, MSA) et le Régime Social des Indépendants (RSI) jusqu'à 2018, couvrant chacun 5% de la population. Le RSI est maintenant intégré à la CNAMTS et une douzaine de régimes supplémentaires, très minoritaires, couvre le reste de la population.

Le terme SNDS est apparu avec la nouvelle loi de modernisation du système de santé français mais le SNIIRAM est utilisé et mentionné depuis 1999. Depuis cette époque le SNIIRAM définissait implicitement la base résultant du chaînage entre le PMSI et les données de l'assurance maladie qui était nommé DCIR (Datamart de Consommation Inter Régime). Le SNDS inclut des données exhaustives et anonymes qui sont :

- les caractéristiques sociodémographiques : sexe, mois et année de naissance, régime d'affiliation (Régime Général, MSA, RSI, etc.), commune de résidence, affiliation à la Couverture Maladie Universelle complémentaire (CMU-c), le cas échéant, date et cause de décès (CépiDC) ;
- les données relatives à la reconnaissance des Affections de Longue Durée (ALD) avec les numéros et libellés correspondants ainsi que les codes associés de la Classification Internationale des Maladies, dixième révision (CIM-10), dates de début et de fin ;
- les données de remboursement individualisées par bénéficiaire comprenant les Codes d'Identification de la Présentation (CIP) et code *Anatomical Therapeutic Chemical* (ATC) des médicaments délivrés, des dispositifs médicaux (selon la Liste des Produits et Prestations, LPP), des actes médicaux techniques (selon la Classification Commune des Actes Médicaux, CCAM), des consultations, etc. ;
- les données hospitalières du PMSI à partir de 2005 (séjours en établissements publics et privés en médecine, chirurgie, obstétrique (MCO), odontologie, hospitalisations à domicile (HAD), séjours en soins de suite et de réadaptation (SSR), psychiatrie) avec les codes CIM-10 des diagnostics principaux, reliés et associés, dates d'hospitalisation et durées de séjour.

Face à la demande croissante des chercheurs d'avoir accès à une base de données adaptée à la conduite d'étude épidémiologique, un échantillon a été développé : l'EGB (Echantillon Généraliste de Bénéficiaire). C'est un échantillon permanent représentatif de la population protégée par l'Assurance Maladie Française. Il résulte d'un sondage au 1/97<sup>ème</sup> portant sur le numéro de sécurité sociale des bénéficiaires de l'Assurance Maladie Française, qu'ils aient ou non bénéficié de remboursements de soins. Il regroupe actuellement plus de 780 000 bénéficiaires majoritairement assurés du régime des travailleurs salariés (CNAMTS ; à l'exception des étudiants et des fonctionnaires) et doit, à terme, couvrir l'ensemble des régimes de Sécurité Sociale française sur une période de 20 ans. Les données sont conservées à partir de 2003 pour le régime général, à partir de 2011 pour le RSI et MSA. Sa répartition par âge et sexe est très proche de celle de la population exhaustive, de même que la dépense moyenne remboursée par consommant. Par les régimes qu'il intègre, il est représentatif de 94,5% de la population.

#### B.4 Les bases de données américaines : l'exemple de la base des vétérans.

A l'heure actuelle, il n'existe pas de système d'assurance santé universelle aux Etats-Unis. Le principe du remboursement des soins est celui d'un contrat passé entre un individu et un système d'assurance privé de son choix ou via l'entreprise pour laquelle il travaille. Ces entreprises peuvent être développées sur une base géographique (souvent un ou quelques états) ou corporatiste (profession, communauté universitaire, etc.). Les assurances se laissent le libre choix de définir les prestations remboursées ainsi que les professionnels de santé (*healthcare providers*) pris en charge. À titre d'exemple, citons « Kaiser Permanente », la plus grande assurance privée (non lucrative) des Etats-Unis qui prend en charge les soins dans 39 hôpitaux et 700 cabinets médicaux pour 12 millions de membres dans 8 états. On peut également citer « Yale Health » qui prend en charge les remboursements des étudiants et employés affiliés à l'Université de Yale.

Il existe des assurances de santé subventionnées par le gouvernement fédéral des Etats-Unis et les Etats. Les plus connus sont les programmes Medicaid et Medicare : le programme Medicaid assure le remboursement des soins des personnes les plus défavorisées et Medicare des personnes de plus de 65 ans. Mais il en existe d'autres, comme celui spécifiquement dédié aux vétérans.

Aux Etats-Unis, un vétéran est une personne qui a servi au sein des forces armées américaine au moins 24 mois, mais pas nécessairement sur une zone de combat. Il y a actuellement 21 millions de vétérans américains vivant aux Etats-Unis. Le *United States Department of Veterans Affairs* (VA) fournit aux vétérans une assurance ainsi que de nombreux autres services (éducation, finances, etc.). Les soins sont gérés et pris en charge par le *Veterans Health Administration* (VHA) qui possède ses propres

infrastructures partout aux Etats- Unis (827 cliniques ambulatoires, 151 centres médicaux et hôpitaux, 126 maisons de retraite). Les soins reçus sont gratuits pour toute maladie liée au service, sinon, le coût dépend du salaire actuel du vétéran. Actuellement, il y a plus de 9 millions de vétérans qui reçoivent ces services. Les données de tous les vétérans qui ont bénéficié du VA depuis 1997 (plus de 20 millions) sont accessibles via le *National Corporate Data Warehouse* (CDW).

Le CDW est une base de données médico-administrative qui rassemble:

- les données démographiques (âge, sexe, groupe ethnique) ;
- les diagnostics ambulatoires, d'hospitalisations ou de consultations (codés par la CIM 9 ou 10) ;
- les examens cliniques et biologiques (pression artérielle, poids, formule sanguine, etc.) ;
- les médicaments délivrés incluant la date, la durée de prescription et la dose ;
- le statut tabagique (depuis 1999) ;
- la consommation d'alcool (depuis 2007) ;
- des scores de douleurs et de dépressions.

## C La polymédication

### C.1 Définition du terme polymédication

Le terme polymédication est défini comme l'administration de nombreux médicaments de façon simultanée ou l'administration d'un nombre excessif de médicament [4,5]. Cette définition amène à la notion d'un surnombre de médicaments, cependant elle n'apporte pas de précision quant à un nombre seuil de médicaments et il n'existe, à l'heure actuelle, aucun consensus à ce sujet [6].

L'absence de consensus a conduit à l'utilisation de seuils différents pour définir la polymédication dans la littérature. Ils diffèrent en fonction des objectifs de l'étude, de l'âge des personnes concernées (adultes, personnes âgées, etc.) ou du mode de vie (domicile, maison de retraite, etc.) [6,7]. Le seuil le plus fréquemment utilisé est celui de 5 médicaments ou plus [4]. Certains auteurs utilisent également des seuils supplémentaires, le plus souvent à partir de 10 médicaments, définissant l'hyperpolymédication ou la polymédication excessive.

Les périodes, sur lesquelles on compte le nombre de médicaments, varient suivant les études [7]. Ces périodes, définies comme des fenêtres de temps, peuvent être regroupées en trois grandes catégories définissant trois types de polymédication :

- la polymédication simultanée se calcule à partir du nombre de médicaments en cours d'utilisation un jour donné, et l'évolution de ce nombre est suivi sur plusieurs jours consécutifs ou à intervalles réguliers ;
- la polymédication cumulative, aussi appelée multiple, correspond à la somme des différents médicaments administrés au cours d'une période définie ;
- la polymédication continue ne conserve que les médicaments présents sur deux périodes espacées d'un certain temps.

L'élaboration d'une définition spécifique de la polymédication continue a pour but l'étude des médicaments utilisés sur le long terme, sans tenir des comptes des médicaments pris de manière ponctuelle. Une telle distinction est justifiée par le fait que la durée du traitement est un facteur pouvant affecter la survenue des effets indésirables [8]. Il semble donc intéressant de spécifiquement distinguer ces médicaments afin de mieux comprendre l'impact globale de la polymédication (figure 1). Au vu des périodes considérées, la polymédication continue capture à la fois les traitements pris sur le long terme de façon continue et les traitements pris sur le court terme de façon récurrente. Par conséquent, elle ne permet pas une analyse dédiée de la polymédication des médicaments de longue durée, appelée polymédication chronique.



*Figure 1 La notion de polymédication inclue des traitements courts et des traitements longs. La durée des traitements pourrait affecter la survenue d'effets indésirables et l'impact de la polymédication*

La polymédication chronique découle du traitement des multimorbidités chroniques. Le terme de multimorbidités chroniques définit l'existence de plusieurs pathologies distinctes chez un même individu [9]. Leur prévalence est importante et en augmentation dans le monde notamment à cause du vieillissement de la population [10]. Par exemple, aux Etats-Unis 80 % des dépenses du système de soin Medicare est dédié à des patients ayant au moins quatre pathologies [11]. Entre 1992 et 2006 en Australie, presque deux tiers des personnes de 65 ans et plus étaient concernées par deux pathologies chroniques ou plus [12]. Par ailleurs, une revue de la littérature incluant 70 études a estimé que la prévalence de la multimorbidité (deux pathologies chroniques ou plus dans cette étude) chez les personnes de plus de 65 ans était d'environ un tiers [10].

L'augmentation de la polymédication chronique en réponse à l'augmentation de la multimorbidité chronique n'est pas sans conséquences. Il a été montré qu'une augmentation du nombre de médicaments, qu'ils soient sur prescription ou non, entraîne une augmentation du risque de recevoir un médicament potentiellement inapproprié (MPI) [13].

## C.2 Utilisation de médicaments potentiellement inappropriés

Une des notions capitales à l'évaluation de la bonne utilisation des médicaments est l'évaluation de la pertinence de son utilisation. On considère un médicament comme potentiellement inapproprié (MPI) si son utilisation, dans une situation donnée, engendre plus de risques potentiels que de bénéfices attendus [14].

L'identification des MPI peut se faire de manière implicite ou explicite. L'identification est dite implicite si elle repose sur le jugement du clinicien, pour une situation donnée. Le clinicien utilise les informations qu'il collecte sur le patient et le contexte clinique. Il identifie ensuite le ou les MPI présents grâce à ses connaissances et/ou grâce à une recherche personnalisée dans la littérature scientifique. Des outils, comme le *Medication Appropriateness Index* (MAI), peuvent permettre au clinicien d'établir un score pour chaque prescription afin de l'aider dans sa recherche de MPI [15]. C'est donc une démarche personnalisée qui se concentre sur le patient mais peu sur un type de médicament ou de pathologie. Elle est très sensible pour l'identification de MPI, notamment en pratique clinique, mais est chronophage et donc peu adaptée aux études pharmaco-épidémiologique [16]. L'identification est dite explicite si elle repose sur des critères élaborés par consensus d'experts et restitués sous forme de liste. Les listes sont applicables de façon générale aux patients en fonction de leur âge, ou de pathologies. Ces critères peuvent être utilisés en clinique ou lors d'entretiens pharmaceutiques afin d'aider le professionnel de santé à la prescription ou à la déprescription. Ils peuvent également être utilisés en recherche afin d'identifier les MPI en population [16,17].

Les listes définissant les MPI sont nombreuses, une revue de la littérature, réalisée en 2018, en a répertorié 36 [18]. Chez les patients âgés, en Amérique du nord, les critères de Beers, et les critères de Mcleod sont fréquemment utilisés [15,19,20]. En Europe, la liste de Laroche est une adaptation des critères de Beers aux spécificités des médicaments disponibles en France. La Norvège, le Royaume-Uni et l'Irlande ont également développé des critères spécifiques à leur pays [17]. Certains de ces critères comme les critères *Screening Tool of Older Person's Prescriptions* (STOPP) et *Screening Tool to Alert doctors to Right Treatment* (START) sont très précis pour l'identification de MPI et aident à la prescription ou la déprescription de médicaments. Cependant, les nombreuses informations cliniques nécessaires à leur utilisations les rendent plus difficilement applicables pour la recherche pharmaco-

épidémiologique sur base de données [21]. La plupart des listes de MPI concernent les patients âgés car le vieillissement s'accompagne de médicaments physiologique qui rend les personnes plus vulnérables aux effets indésirables médicamenteux. Cependant les médicaments peuvent présenter une balance bénéfico-risque défavorable chez des sujets plus jeunes. Les critères de PROMPT (*PRescribing Optimally in Middle-aged People's Treatments*) ont été développés spécifiquement pour être utilisés chez les personnes de 45 à 65 ans. A l'inverse des listes précédentes, ces critères ont aussi été développés pour être facilement applicables sur les bases de données médico-administratives, en limitant le nombre d'informations cliniques nécessaires [22,23]. Les MPI peuvent également être détectés d'après leur mécanisme pharmacologique. Par exemple, de nombreuses listes répertorient les médicaments anticholinergiques et les classant suivant leur potentiel anticholinergique sont utilisables en recherche [24].

Les MPI, qu'ils soient identifiés de manière implicite (MAI) ou explicite (Beers, STOPP/START) augmentent le risque de mortalité, d'hospitalisation et d'effet indésirable médicamenteux [25–30]. De même, les médicaments anticholinergiques sont souvent cités comme exposant les personnes âgées à un risque de démence, de déclin cognitif et de mortalité [31,32]. Les MPI sont donc une préoccupation majeure de santé publique et l'étude de la part qu'ils représentent au sein de la polymédication chronique est essentielle.

### C.3 La polymédication, une préoccupation de santé publique majeure

Au cours des dernières années, les études pour comprendre le lien entre polymédication et surmortalité se sont multipliées. Une revue systématique de la littérature a inclus 47 études réalisées en 1992 et 2016 et la méta-analyse a montré une association entre polymédication et surmortalité [33]. De plus, une autre étude menée à partir d'un registre a montré que, parmi différents facteurs (charge anticholinergique, MPI), seule la polymédication était associée à un risque de surmortalité et de réhospitalisation [34]. La polymédication pourrait donc être un indicateur direct de la qualité des traitements.

D'après une étude réalisée dans un hôpital du nord de Londres, la prévalence des patients en polymédication aux urgences est de 45%, et 39% de ces patients seraient concernés par une interaction médicamenteuse [35]. A l'hôpital, les personnes âgées ont un risque d'interaction médicamenteuse augmenté de 50 % avec une prise de 5 à 9 médicaments et de 100 % avec une prise de 10 médicaments ou plus. Les interactions médicamenteuses sont une cause importante de survenue d'effets indésirables médicamenteux évitables [36]. La polymédication serait également associée à d'autres

types d'interactions, notamment avec l'alcool, les drogues ou certains aliments, également associés à des risques d'évènement indésirables [37–39].

Qu'ils aient pour origine une interaction ou non, les effets indésirables médicamenteux sont fréquemment décrits en situation de polymédication. En effet, aux États-Unis, il a été reporté que les personnes en polymédication avaient un risque augmenté d'admission à l'hôpital pour cause d'effet indésirables médicamenteux [40,41]. De manière générale, chez les patients en polymédication, les médicaments les plus souvent responsables d'effets indésirables sont les médicaments cardiovasculaires, les AINS (Anti-Inflammatoires Non Stéroïdiens), les psychotropes ou encore les médicaments anticholinergiques [41,42].

Paradoxalement, la polymédication pourrait aussi être liée à une perte d'observance aux traitements. En effet, il a été montré que les patients prenant 4 médicaments ou plus avaient un taux de non adhérence aux traitements de 35 % [43]. Cela en fait un argument supplémentaire pour considérer la polymédication comme un indicateur de qualité des traitements. D'une manière similaire, la polymédication peut également être considérée comme un indicateur de qualité de vie ou d'autonomie. En effet, chez les personnes âgées, l'utilisation de 10 médicaments ou plus était associée à une diminution de la capacité à réaliser ses tâches quotidiennes [44]. Ceci pourrait être expliqué par le risque de déclin cognitif associé à la polymédication. Dans cette même étude finlandaise 33 % des patients âgés prenant 6 à 9 médicaments et 54 % des patients prenant plus de 10 médicaments serait atteint par des troubles cognitifs contre 22 % des patients prenant 5 médicaments ou moins [44].

En plus des conséquences en termes de santé, la polymédication pose également des problèmes économiques. A l'augmentation du coût lié au surnombre de médicaments s'ajoute le coût des complications associées à la polymédication, telles que les hospitalisations ou l'augmentation de la durée du séjour à l'hôpital [45].



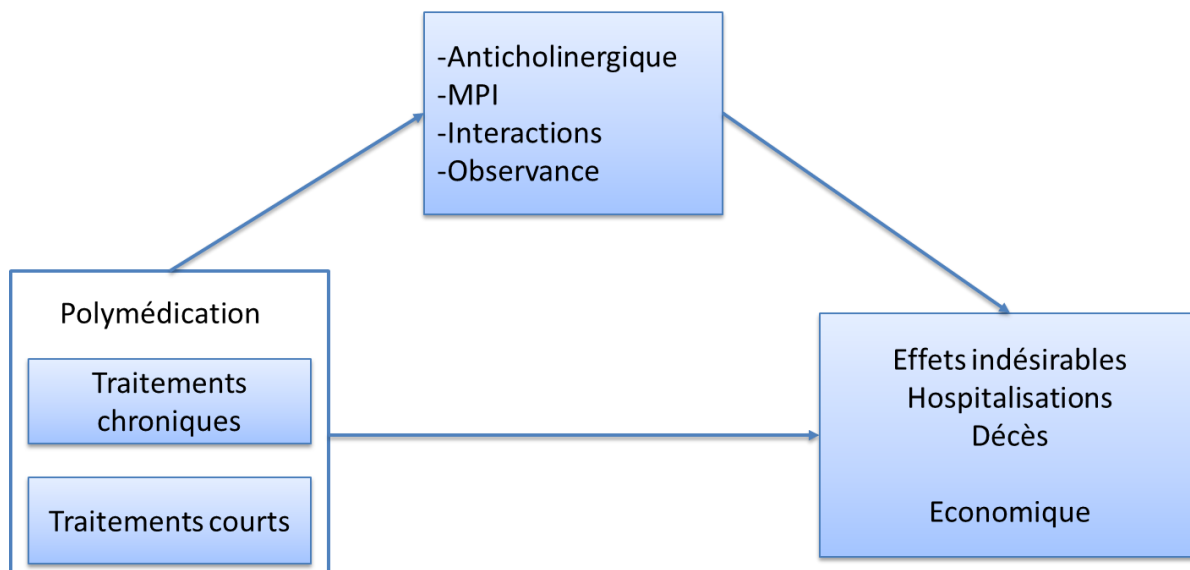


Figure 2 La polymédication est associée à un risque décès, hospitalisation, économique et à des facteurs eux même associés à ces même risques

#### C.4 Utilisation des bases de données pour étudier la polymédication

Le contexte de l'évaluation de la polymédication se caractérise par la diversité des médicaments, appropriés ou non, et des pathologies à étudier. Cette situation ne peut être étudiée expérimentalement, les essais cliniques ne considérant que des échantillons restreints de patients soigneusement sélectionnés pour une pathologie ou un traitement. De plus, en raison du vieillissement de la population et de l'augmentation de la prévalence des pathologies chroniques avec l'âge, la représentativité de l'échantillon d'étude semble être un critère majeur pour l'extrapolabilité des résultats, ce qui est difficilement compatible avec les conditions expérimentales. La pharmaco-épidémiologie semble donc être l'outil idéal pour l'étude de la polymédication car permettant l'étude de larges populations et en condition de vie réelle.

Des études de terrain *ad hoc* peuvent également être réalisées pour étudier la polymédication. Il est possible par exemple de mettre en place une enquête par questionnaire téléphonique chez des patients identifiés après une consultation en ambulatoire [46]. Cependant, la taille de l'échantillon reste forcément limitée et l'étude exposée aux biais classiques des études de terrain. La base de données est l'outil de choix pour la polymédication car elle permet l'étude du phénomène sur de grands échantillons, de tout âge et en vie réelle. De plus, l'exhaustivité des données permet généralement d'identifier les traitements chroniques et d'estimer s'ils sont inappropriés ou non. De nombreuses bases de données sont adaptées à l'étude de la polymédication, que ce soit des cohortes de populations, de registres ou de bases de données administratives [47–49]. Ces bases de données

concernent des populations différentes et présentent leur propres forces et limites. Utiliser plusieurs sources de données est donc d'intérêt majeur pour une étude globale de la polymédication.

## D Objectifs de la thèse

En raison de la nature variée des conséquences qui lui sont associées, la compréhension de la polymédication doit être considérée comme un enjeu de santé publique majeure. De même, les mécanismes conduisant le sujet en polymédication, à ces conséquences, notamment à long terme, restent encore à explorer. De par l'impact de la durée de traitement sur les conséquences à long terme, il a été fait le choix pour ces travaux de thèse de se centrer sur la polymédication chronique. Les bases de données médico-administratives, qui permettent la réalisation d'études sur de grands échantillons, de tout âge et en vie réelle, ont été choisies comme sources de données pour la réalisation de ces travaux.

L'objectif général de la thèse était ainsi de décrire la polymédication chronique et ses risques associés à partir des bases de données médico-administratives. Pour atteindre cet objectif, le projet a été divisé en trois étapes de recherche :

- Une revue générale des définitions et des déterminants de la polymédication a été réalisée afin de mieux comprendre notamment les problématiques de caractérisation et d'identification de la polymédication. Un indicateur a ensuite été spécifiquement développé pour identifier et décrire la polymédication chronique et a été appliqué dans les données de l'Assurance Maladie Française.
- Afin d'approfondir la caractérisation de la polymédication chronique, une description de la part potentiellement inappropriée des médicaments en polymédication chronique a été conduite. Cette description a été réalisée en utilisant deux sources de données complémentaires en termes de richesse d'information, notamment clinique, et de population concernée : les données de l'Assurance Maladie Française et les données du *Veterans Health Administration* aux États-Unis.
- Enfin, une étude de risque a été conduite afin d'explorer l'association entre polymédication chronique et mortalité. De par la richesse d'informations cliniques, biologiques ou sur le mode de vie, la base de données du *Veterans Health Administration* aux États-Unis a été utilisée pour ces analyses.

## II Revues des définitions et développement d'un indicateur de polymédication chronique.

### A Revue générale des définitions, descriptions et déterminants de la polymédication.

#### A.1 Problématique

Afin d'évaluer la polymédication chronique en population il était nécessaire de développer un indicateur adapté et applicable dans les bases de données médico-administratives. Toutefois avant de développer cet indicateur de polymédication chronique il était tout d'abord utile de décrire et appréhender les différentes notions qui définissent la polymédication.

#### A.2 Objectifs

L'objectif de ce travail était de réaliser une revue générale des définitions et des descriptions de la polymédication dans la littérature scientifique.

#### A.3 Considérations méthodologiques

Ce travail est une revue générale des définitions de la polymédication. La construction des définitions de la polymédication a été comparé entre les études fréquemment cités dans la littérature afin d'identifier les aspects principaux entrant dans la définition de polymédication. L'analyse de ces aspects a permis d'identifier les paramètres qui permettrait une description plus ou moins spécifique de la polymédication chronique.

La comparaison des différentes définitions a également amené à une comparaison des prévalences observés et des déterminants, c'est-à-dire des facteurs associés à une définition de la polymédication. Ces différences nous ont également renseigné sur les spécificités de chaque définition.

Cette revue était générale et non pas systématique. Elle n'avait pas pour objectif de présenter l'ensemble des prévalences retrouvés dans la littérature mais de permettre comprendre la construction d'une définition et son impact sur les résultats observés.

#### A.4 Résumé des travaux et principaux résultats

La polymédication, classiquement définit comme de l'administration de nombreux médicaments de façon simultanée, fait appel à différentes notions.

Le type de médicaments à considérer est une première notion qui diffèrent entre les études. Selon les modalités de prescription (médicaments en accès libre en pharmacie aussi appelés *Over-The-Counter* (OTC) contre les médicaments sur prescription) ou d'administration (médicaments topiques contre médicaments oraux ou systémiques) l'impact n'est pas le même. Les indications et caractéristiques pharmacologiques diffèrent entre ces médicaments et le choix de les considérer dans le compte de la polymédication doit être justifié par les objectifs de l'étude. Deuxièmement, le seuil de médicaments à partir duquel on peut considérer une situation de polymédication diffèrent et il n'existe, à l'heure actuelle, aucun consensus à ce sujet [6]. Bien que le seuil de 5 médicaments soit le plus utilisé, des seuils différents et parfois multiples existent [6,7]. Par ailleurs, la détermination de ce seuil est également impactée par l'unité considérée, soit en spécialité médicamenteuse ou en substance active. Enfin, différentes fenêtres de temps définissent la période durant laquelle les médicaments considérés sont dénombrés. Trois grandes catégories de fenêtre de temps sont souvent décrites dans la littérature, définissant respectivement trois types de polymédication : la polymédication simultanée, la polymédication cumulative et la polymédication continue [50]. Chacun de ces types de polymédication utilise des définitions différentes des médicaments à considérer en fonction de leur durée ou de leur fréquence amenant ainsi à des descriptions et des estimations variables de la polymédication. Cette notion de fenêtre de temps paraît ainsi essentielle à la définition de la polymédication chronique.

Dans la littérature, La prévalence de la polymédication varie entre 4 % et 57 %. La variabilité des résultats descriptifs peut être expliquée par les différences entre les définitions appliquées et les populations étudiées. En effet, au sein d'une même population, un changement dans la définition peut faire varier les estimations de la prévalence de la polymédication. Par exemple, parmi les vétérans américains, 13 % de sujets étaient concernés par la polymédication continue et 25 % par la polymédication cumulative [50]. D'autre part, la prévalence de la polymédication diffère également selon la population considérée notamment en fonction de l'âge. En effet, la polymédication semble augmenter avec l'âge de la population étudiée, atteignant son maximum chez les personnes de 80 ans [51–53]. C'est pour cette raison que la polymédication reste fréquemment étudiée chez les personnes âgées. Toutefois, cette situation n'apparaît pas rare chez les adultes d'âge moyen avec 15 % des sujets âgés de 35 à 75 ans en situation de polymédication [54].

Certaines études identifiées pour cette revue avaient pour objectif de décrire la polymédication chronique. Pour cet objectif, la définition de polymédication continue permet de quantifier les médicaments pris de manière régulière mais elle présente des limites puisqu'elle capture à la fois les traitements pris sur le long terme de façon continue et les traitements pris sur le court terme de façon récurrente [47,55,56]. Pour pallier à ces limites des chercheurs ont utilisés des variations des définitions de la polymédication simultanée et continue plus spécifique de la polymédication chronique. Par exemple, des chercheurs ont compté le nombre de mois où un patient recevait 5 médicaments ou plus. Si le patient était concerné par cette situation 6 ou 12 mois de suite, il était considéré en situation de polymédication chronique [57]. Dans ce cas les chercheurs identifiaient la persistance de la polymédication dans le temps, mais sans distinction entre traitement chronique et traitement court. Le deuxième indicateur identifiait une situation de polymédication chronique par l'utilisation de 5 traitements dispensés en même temps pour une durée de 3 mois, ou de 6 mois. Cette définition nécessitant l'initiation concomitante des traitements chroniques, elle n'identifie pas l'accumulation successive de traitements chroniques au cours du temps [58].

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## CLINICAL PHARMACOLOGY

# Polypharmacy: A general review of definitions, descriptions and determinants

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**Summary** Polypharmacy is considered as the administration of many drugs. It is a major public health concern, which is growing worldwide. The identification of polypharmacy relies on drug count on a given time window. Polypharmacy exists if this count exceeds a predefined threshold. Although there is no consensus among scientists, five is the most frequently used number. Depending on the time-windows, polypharmacy can be qualified as simultaneous, cumulative, or continuous. Drugs can be selected according to the duration or the recurrence of their use thereby introducing the concept of chronic polypharmacy. This general review aimed to compile data from the literature regarding descriptions and determinants of polypharmacy, according to used definitions and studied populations. The prevalence of polypharmacy varied according to the definition used (from 4% to 57%). It was high in elderly people but was also non negligible in younger subjects such as middle aged. Cardiovascular, digestive and metabolism drugs were among the most frequent drugs involved in polypharmacy. The determinants of polypharmacy included factors linked to the patient (sociodemographic parameters such as age, sex, income, and place of residence, ethnicity, behaviour), factors linked to the disease (certain diseases such as cardiovascular or metabolic disease, multiple comorbidity status), as well as factors linked to the healthcare system or to the physician. Finally, to date, little data is available regarding polypharmacy appropriateness, although these data are needed to have clinically important information beyond a quantitative estimation. Further research is warranted to fill this gap.

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## Abbreviations

ATC	anatomical therapeutic chemical
COPD	chronic obstructive pulmonary disease
NSAID	nonsteroidal anti-inflammatory drugs
OTC	over-the-counter
ROC	receiver operating characteristic
START	screening tool to alert to right treatment
STOPP	screening tool of older people's prescriptions
USA	United States of America
WHO	World Health Organisation

## Introduction

Polypharmacy is defined by the World Health Organisation (WHO) as the administration of many drugs at the same time alternatively, the administration of an excessive number of drugs [1]. It is common among the elderly — who often present with multiple comorbidities — and tends to become a major public health concern in high-income countries, because of ageing-related demographic changes, and the general increase in medication use [2–4]. For example, in the United States of America (USA), the prescription of five or more drugs increased in adults aged 20 or over from 8.2% in 1999–2000 to 15% in 2011–2012 [5].

While an elevated number of drugs may be justifiable in some specific cases such as patients with multiple comorbidities, sometimes polypharmacy stems from inappropriate drug prescriptions, which may be avoidable [3]. These medications are not only useless, they can also be harmful and even deleterious. On the one hand, increasing the amount of medications prescribed to elderly people could lead to a poor patient compliance and therefore to treatment failure [2,6]. Moreover, in certain situations, polypharmacy may be associated with adverse effects, which can cause outpatient and inpatient hospitalizations [7], drug interactions, falls, and mortality [3,8]. Polypharmacy is also a predictor of rehospitalization [9]. In addition, polypharmacy generates economic concerns, due to the increasing sum of costs induced by involved drugs, but also because of the cost of complications that lead to hospitalization or longer hospital stays [10].

Owing to the health and economic burden associated with polypharmacy, several studies have described polypharmacy in terms of the amount and implied medications, and investigated which factors were associated with this condition. However, these studies used different definitions of polypharmacy applied to various populations, leading to a wide range of results, and finally making this problem difficult to assess. The aim of this general review was to present the major definitions of polypharmacy and the way they are structured, and to compile descriptions and determinants of polypharmacy resulting from these definitions.

## Definitions of polypharmacy

The definitions of polypharmacy retrieved in the literature differ according to authors and studied populations or medical areas (see Masnoon et al. for a systematic review on this

scope [11]). They all use the WHO definition, in whole or in part, which defines polypharmacy as the administration of many drugs at the same time or the administration of an excessive number of drugs [1]. This definition appeals indeed two dimensions included in the concept of polypharmacy — thresholds and time windows — that are interpreted differently according to the authors, as it implies to define what is meant by “many” or by “excessive”, and which time window should be considered to measure drug exposure.

## Indicators of polypharmacy

### Drugs considered in the estimation of polypharmacy

Assessing polypharmacy involves in first place to determine which drugs to consider. This choice will mainly depend on the available data source. Most of studies found in the literature are based on claim databases, which store data relative to prescription drugs. Therefore, over-the-counter (OTC) drugs, although frequently used, are rarely considered in polypharmacy studies. This could imply an underestimation of polypharmacy using claim databases. Thus, it was found that 90% of community-dwelling elderly patients living in a rural area of Pennsylvania received at least one OTC drug, and that half of them had from two to four OTC drugs [12]. Moreover, Kaufman et al. found that OTC drugs represented six of the ten most frequently used drugs in the American adult population. However, these authors also found that the most commonly reported OTC drugs were paracetamol, ibuprofen and aspirin [13]. In some countries like France, these drugs are available as OTC drugs but can also be prescribed and reimbursed by healthcare insurances. Thus, at least the reimbursed part of these drugs will be included in polypharmacy estimation. Moreover, medications such as herbal medicines, vitamins, or topical drugs are often not considered. Most of the time, these medications are not used to assess the quality of a treatment because their clinical impact could not be considered as important as that of a systemic treatment [14]. Finally, the question of chronic versus acute use of drugs has also to be addressed when assessing polypharmacy. Inclusion of the former, the latter, or of both types will lead to different estimations and conclusions.

### Drug counting process and cut-off used for the number of drugs

Before choosing any cut-off regarding the number of drugs to consider, the number of active substances should be counted properly. The emergence of fixed drug combinations with two or more pharmacologically active substances, especially polypharmacy for cardiovascular diseases prevention, should be considered when determining the threshold. Taking into account the number of these active substances, instead of the number of drug packaging boxes, seems to be more biologically plausible to measure polypharmacy [15]. Patients' characteristics such as age or living conditions (home, nursing home, etc.) imply different thresholds of the number of drugs to consider polypharmacy as clinically significant [8]. Although there is no consensus, a cut-off of five distinct drugs seems to be the most commonly used to assess



polypharmacy among adults [11]. Furthermore, in some studies, a number of drugs exceeding ten defined polypharmacy as "excessive" or "hyperpolypharmacy". The second term should be preferred since it does not arbitrarily suggest that the negative impact increases with the number of drugs [11,16]. Moreover, instead of arbitrarily choosing a cut-off for the number of drugs to consider, receiver operating characteristic (ROC) curves have been used to estimate the most appropriate threshold for a specific risk detection. For instance this study showed that a cut-off of 4.5 drugs is optimal for a link between polypharmacy and mortality [17]. Nevertheless, defining ascending grades of polypharmacy could serve for considering linear increase of side effects risks with number of medications and drug consumption rising in recent years [2,3].

### Time window used for polypharmacy estimation

The WHO definition of polypharmacy also suggests a time notion [1]. Three major types of polypharmacy indicators can be defined according to the considered time window or period: cumulative polypharmacy, continuous polypharmacy, and simultaneous polypharmacy [2,18].

Cumulative polypharmacy corresponds to the sum of all different medications that were dispensed within a given time window. It takes into account of all medications, regardless of the duration of use [18]. In this case, estimated prevalence varies with the length of the time window, meaning that the longer the period, the higher the prevalence [19].

Continuous polypharmacy is similar to cumulative polypharmacy but requires at least two separate time windows. Medications should appear in both time windows to be considered in this estimation, as it would mean they are taken continuously in the overall period between these two time windows [18]. An alternative to this indicator consists in counting the number of repeated medication use in a time window (e.g. three uses per year could be considered as a repeated medication [20] or four uses a year [21]) This variation is one of the various definitions of chronic polypharmacy that exist in the literature.

Simultaneous polypharmacy is assessed by the sum of drugs used a given day. It can either correspond to the accurate number of drugs or to the mean number of drugs used over a period. Since this indicator can be applied each day of follow-up, it is possible to follow medication changes and identify transient influences that could have led a patient to polypharmacy status [18,22,23].

A variation of simultaneous polypharmacy consists in daily chronic polypharmacy: in some situations, counted drugs can be restrained to those used continuously over a defined period covering several months, which means counting only chronic medications. This indicator does not count short-term treatments, even if they are recurrent, which makes it different from the original definition of simultaneous polypharmacy. As an example, Nisthala et al. used this variation to describe temporal trends of chronic polypharmacy [16]. Wastesson et al. also described chronic polypharmacy with two indicators using a simultaneous definition with a month as time window. Contrary to daily chronic polypharmacy, they firstly define polypharmacy from

the number of drugs taken in a month, and then define polypharmacy as chronic if the number a drugs taken is above 5 during 6 or 12 month or if this situation represented 80% of the follow-up [24].

### Towards a clinically significant indicator

In addition to the notions of threshold for the drug number and time window, which refer to quantitative metrics, the definition of polypharmacy according to WHO also includes a qualitative dimension, represented by the concept of appropriateness. Although accumulating drugs on long-term periods is questionable in many cases, this may be required for patients with serious, chronic and/or multiple diseases to treat. Thus, polypharmacy, and even hyperpolypharmacy, do not necessarily reflect a worse status. An appropriate drug is optimised according to the best evidence and necessity to maintain a good quality of life, improve longevity and minimise harm. Polypharmacy can therefore include exclusively appropriate drugs, inappropriate or useless drugs, or a combination of both types. This inappropriateness may be objectified by the identification of (i) a hazardous combination of drugs because of interactions, (ii) an unacceptable demand of medicine taking for the patient, which decreases adherence of treatment, or (iii) a prescription of medications to treat side effects of other medications [3]. Some examples of this situation are the use of more drugs than are clinically indicated or too many inappropriate drugs, the use of two or more medications to treat the same condition, or the use of two or more drugs of the same therapeutic class [10,25,26]. Appropriateness is a major concept to define polypharmacy in terms of clinical conditions and potential drug interactions, and therefore should prevail over arbitrary thresholds, which not accurately identify patients receiving suboptimal treatment [27].

### Description of polypharmacy

Polypharmacy prevalence is used to describe the number of people who experienced polypharmacy during a time period [4,10]. Prevalence estimates of polypharmacy found in the literature ranged from 4% to 57% in a population of users and non-users of drugs, which include both studies regarding all aged population and studies regarding elderly only (Table 1). In addition, a study including people with at least one dispensed drug found a higher prevalence of 64.3% [28]. The variations observed in these estimates that were sometimes calculated within the same population can be explained by different choices made to define either polypharmacy itself or the length of studied time window. For example, the prevalence of patients taking more than five medications ranged from 13% for continuous polypharmacy to 25% for cumulative polypharmacy [18]. Also, prevalence of simultaneous polypharmacy was lower than prevalence of continuous polypharmacy among people aged 75 and over (14% vs. 39%) [2]. Aside polypharmacy prevalence, incidence corresponds to the number of individuals who had a first episode of polypharmacy with no history of polypharmacy in a defined previous period [22]. Estimates of polypharmacy incidence that are reported in the literature varied with the definition and the time window but also with the wash out

**Table 1** Prevalence of polypharmacy in the literature and most frequent drugs contributing to polypharmacy.

	Authors	Country	Year	Population	Population size (n)	Chronicity	Time-window	PP prevalence ( $\geq 5^a$ ), %	Most frequent drugs involved in PP	References
Simultaneous	Abolhassani et al.	Switzerland	2012	35–75 y-o	6733	No	1 day	15.3	Cardiovascular system (lipid-lowering drugs, statins)	[32]
	Bjerrum et al.	Denmark	1994	All	46,657	No	1 day	5.1	NA	[30]
	Bjerrum et al.	Denmark	1994	$\geq 16$ y-o	466,567	No	1 day	5.1	Cardiovascular system (diuretics), analgesics	[22]
	Feng et al.	USA	2010	Medicaid c 18–64 y-o	37,570	Yes (60 d)	1 day	44.6	Analgesics, antibiotics	[34]
	Kennerfalk et al.	United Kingdom	1996	65–90 y-o	5000	No	1 day	20.6	NA for PP	[56]
	Monégat et al.	France	2013	$\geq 75$ y-o ( $\geq 1$ prescription)	69,324	No	1 day	14	NA	[2]
	Morin et al.	Sweden	2018	$\geq 65$ y-o	1,742,336	No	1 month	44	NA	[29]
	Nishtala et al.	New-Zealand	2013	$\geq 65$ y-o	603,670	Yes (90 d)	1 day	29.5	Digestive, cardiovascular system	[16]
	Nishtala et al.	New-Zealand	2013	$\geq 65$ y-o	603,670	Yes (180 d)	1 day	22.5	Digestive, cardiovascular system	[16]
	Slabaugh et al.	Italy	2007	$\geq 65$ y-o	960,359	No	1 day	39.4	Antithrombotics, proton pump inhibitors, cardiovascular (ACE)	[23]
Cumulative	Wastesson et al.	Sweden	2013	$\geq 75$ y-o	822,619	No	1 day	45	Cardiovascular, analgesics, psychotropics	[36]
	Veehof et al.	The Netherlands	1997	$\geq 65$ y-o	1544	Yes (60 d)	1 day	4	NA	[53]
	Bjerrum et al.	Denmark	1994	All	46,657	No	3 first months	4.6	NA	[30]

Table 1 (Continued)

Authors	Country	Year	Population	Population size (n)	Chronicity	Time-window	PP prevalence ( $\geq 5^a$ ), %	Most frequent drugs involved in PP	References
Kaufman et al.	USA	1998–1999	$\geq 18$ y-o	2590	No	1 week	7	Analgesics, hormones, cardiovascular drugs	[13]
Kennerfalk et al.	United Kingdom	1996	65–90 y-o	5000	No	1 month	34.6	NA for PP	[56]
Haider et al.	Sweden	2005	75–89 y-o	626,258	No	3 months	57	Cardiovascular drug, antithrombotic	[47]
Hovstadius et al.	Sweden	2006	All	9,113,257	No	3 months 6 months 12 months	11.3 17.2 24.4	NA	[19]
Hovstadius et al.	Sweden	2008	All	9,219,637	No	3 months	11.1	NA	[57]
Jørgensen	Sweden	1994	$\geq 65$ y-o	4642	No	1 year	39	NA for PP	[33]
Kantor et al.	USA	2011–2012	$\geq 20$ y-o	5558	No	30 days	15	NA for PP	[5]
Nobili et al.	Italy	2005	$\geq 65$ y-o	1,767,239	No	365 days	46	NA for PP	[21]
Pereira et al.	Brazil	2010	$\geq 60$ y-o	1705	No	30 days	32	Cardiovascular, digestive, nervous system	[31]
Tatum	Ireland	2013	$\geq 45$ y-o ( $\geq 1$ prescription)	794,628	No	1 month	64.3	NA	[28]
Rawle	United Kingdom		69 y-o	2007	No	1 year	22.9	NA	[58]
Monégat et al.	France	2013	$\geq 75$ y-o ( $\geq 1$ prescription)	69,324	Yes	365 days	39	NA	[2]
Nobili et al.	Italy	2005	$\geq 65$ y-o	1,767,239	Yes	365 days	19.7	NA for PP	[21]
Grimmsman et al.	Germany	2007	All ( $\geq 1$ prescription)	136,521	Yes	3 <- 3months -> 3	10.5	Cardiovascular (renin-angiotensin system drugs)	[35]

d: days; NA: not available; PP: polypharmacy; y-o: years-old.

<sup>a</sup> Gives the estimates of polypharmacy prevalence considering 5 drugs or more.

period defining new polypharmacy. For instance, in 65 years old people, the incidence of simultaneous polypharmacy in Sweden was 19.9% per year considering a six months wash out period [29]. In a region of Italy, incidence rate of simultaneous polypharmacy was 1.3% per month considering a three months wash out period [23]. With the same last definition, the incidence estimate in people aged 16 years and over in Denmark was 0.2% per month [30].

Regardless of the definition of polypharmacy, prevalence may increase with age at least until 80 years old, which is consistent with the increased use of drugs in older people [13]. This is illustrated by results of different studies. In Brazil, Pereira et al. found that people aged 80 and over had a higher prevalence of cumulative polypharmacy than the overall population (42% vs 32%) [31]. In Denmark, Bjerrum et al. found that prevalence of simultaneous polypharmacy increased with age until 80–90 years and then decreased [22]. Consistently, Hovstadius et al. showed that prevalence of cumulative polypharmacy in the Swedish population increased with age and then was stable for people aged 80 and over [19]. Polypharmacy may also be noticeable in younger people. Thus, Abolhassani et al. found that 15.3% of 35–75 years old people had prevalent simultaneous polypharmacy [32].

Differences in polypharmacy estimates according to sex of patients are not well established. There actually may have been changes in the differences observed between men and women during the couple past decades. It appears that polypharmacy was globally more prevalent in women than in men until the 2010s. For example, Jørgensen et al. found that women used more drugs than men (average 4.8 vs. 3.8) in elderly people in Sweden in 1994 [33]. Moreover, for any ages, women were more concerned by polypharmacy than men (respectively 16% vs. 7% in 18–44 years old people, 43% vs. 26% in 45–64 and 57% vs. 44% in  $\geq 65$  years) in the United-States in 1998–1999 [13]. Pereira et al. (people aged 60 and over) and Feng et al. (aged 18–64, with limited income and resources) also found that women had a higher prevalence of polypharmacy than men [31,34]. However, the observed gap between men and women seems to have been reducing in recent years. Nishtala et al. (people aged 65 and over) also showed a higher prevalence in women in 2005 but showed that men and women reached similar prevalence in 2013 [16]. Moreover, Bjerrum et al. (age 16 and over), who found that polypharmacy increased with age faster in women than in men, reported no significant difference in prevalence after the age of 70 [22].

### Drugs contributing to polypharmacy

Many published studies have provided a list of top frequent drugs involved in polypharmacy (Table 1). As for prevalence estimates, the most encountered medications changed according to the used definition. Nishtala et al. found that the combination docusate sodium/sennosides, a drug for the treatment of occasional constipation, was the most frequent medication in chronic simultaneous polypharmacy. In this study, cardiovascular medications such as cilazapril, quinapril (both angiotensin-converting-enzyme inhibitors), isorbide mononitrate, amlodipine, the antiplatelet agents dabigatran and clopidogrel, and the proton-pump inhibitor

omeprazole, were also frequent. Furthermore, tramadol, which is an opioid analgesic, was the 10th most frequent drug in 2013 and was in the top 10 since two years [16]. Pereira et al., who classified the medication according to the pharmacological class or the chemical group (level 3) of the anatomical therapeutic chemical (ATC) classification system, cited cardiovascular, digestive and metabolism, and nervous system medications as the most frequent drugs involved when assessing cumulative polypharmacy [31]. Using the continuous polypharmacy indicator, Grimmsmann et al. counted six cardiovascular drugs among the ten most frequent medications. They also found analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) as frequent [35]. Moreover, Wastesson et al. found that paracetamol and aspirin were the two most frequent medications using cumulative polypharmacy not considering chronicity [36]. All these results highlighted that simultaneous definition without chronicity and continuous polypharmacy considered both long and short recurrent treatments. In addition, Monégat et al. also showed that simultaneous and cumulative polypharmacy considered long and short treatments compared with continuous polypharmacy, which included chronic and recurrent treatment [2]. Finally, the chronic variation of simultaneous polypharmacy, corresponding to chronic polypharmacy, only considered treatment, which are long-term medications [16].

### Appropriateness of polypharmacy

Only few studies have quantified or identified inappropriate polypharmacy, although the prevalence of inappropriate drugs regardless of polypharmacy condition has been extensively assessed in the elderly, and showed a high rate of this condition and the involvement of drug classes similar to those contributing to polypharmacy [9,10,37,38]. Only seven (6.4%) among the 110 articles reviewed recently by Masnoon et al. defined appropriate polypharmacy or distinguished appropriate and inappropriate polypharmacy [11]. Factors linked to the prescription or delivery of appropriate polypharmacy such as clinical pharmacy [39] or skills of the medical staff [40] were explored. Explicit criteria such as Beers criteria and adaptations [41,42], STOPP/START criteria [43] or medication appropriateness index [44] were often used to define inappropriate drugs, but this was rarely done in a context of polypharmacy. As an example of study, which explored appropriateness in polypharmacy patients, 9.3% of elderly South Carolinian were prescribed at least six drugs including at least one medication defined as inappropriate according to several explicit criteria [45]. Another study using Beers criteria showed that 21% of hospitalized cancer patients with polypharmacy had at least one inappropriate drugs [46]. Altogether, these elements highlight the need of data that quantify and describe inappropriate polypharmacy.

### Determinants of polypharmacy

The determinants of polypharmacy include patient-related factors, disease-related factors (i.e. clinical factors), prescribing-related factors, and healthcare accessibility factors (Table 2).

**Table 2** Determinants of polypharmacy.

Determinants	Characteristics	References
Patient-related factors	Older age	[16,23,31,47]
	Sex: men	[16,23]
	Sex: women	[22,31,34,47,48]
	Living location	[16,23,34,47]
	Ethnicity	[5,16]
	Smoking	[32]
	Obesity	[32]
	Living in couple	[32]
	Deprivation/low incomes	[16,34]
	Education: influence	[47]
Disease-related factors	Education: no influence	[31,32]
	Patients' behaviour	[51,52]
	Cardiovascular diseases	[22,32,53]
	Digestive or metabolism diseases	[32,53]
	Respiratory diseases	[22]
	Multiple comorbidities	[34,47]
	Drug misuse	[53]
Prescribing related factors	Frailty	[54]
	Physicians' behavior	[51,55]
Healthcare accessibility factors	Drugs without proper indications	[53]
	Consulting a physician	[4,31]
	Recent hospitalization	[31]
	Health insurance	[10]
	Multiple providers	[10]

### Patient-related factors

As presented above, age and sex were shown to be determinants of polypharmacy. Several studies found increased odds of polypharmacy with older age [16,23,31,47]. Moreover, age was independently associated with polypharmacy in two studies that found increased odds ratios in both unadjusted model and model adjusted for hospitalization [31] or adjusted for Charlson comorbidities index [47]. Sex remained a controversial determinant of polypharmacy with studies that found a higher risk in women [31,34,47,48] or at the opposite a higher risk in men [23]. As suggested above, the difference may disappear over time and especially in the elderly [16,22]. Other sociodemographic factors such as education or socioeconomic status may change the risk of polypharmacy entry. Nishtala et al. found for example that the risk of polypharmacy increased with deprivation [16]. Hence, in a study among Medicaid subjects (corresponding to low-income American individuals aged 18–64 years old), 44.6% of people presented with simultaneous

polypharmacy, and cash assistance was found to increase the risk of polypharmacy compared to other pathways [34]. Regarding education, a low educational status was either associated with polypharmacy or was not, depending on considered studies [31,32,34,47]. Moreover, smoking, obesity or living in couple also increased the odds of polypharmacy onset [32]. The living location may also be a determinant of polypharmacy; some studies found that living in urban areas increased the odds of polypharmacy, while others did not [23,34,47]. Hence, several studies showed differences in polypharmacy rates according to geographic, with a higher risk of polypharmacy in Southern areas of New Zealand or USA, considering the country in whole or in part [16,34,48]. Moreover, drug use and polypharmacy reach a high level in nursing homes. In 2001–2002, 51% of European elderly home care patients took six medications or more daily [49]. French institutionalized people had an average number of 6.9 ( $\pm$  3.3) drugs prescribed and the prevalence of hyperpolypharmacy was 21.1% [50]. In addition, a study showed that Swedish nursing home subjects received more medication than those living in the community (average 8.2 vs. 4.6), although they had a lower risk to be exposed to polypharmacy (OR = 0.80, 95% CI 0.78–0.82). Living in a nursing home was indeed associated with a reduced risk of polypharmacy incidence (HR = 0.79, 95% CI 0.77–0.82) when adjusted to control for education, multi-dose dispensing, and time-to-death. These results suggest that polypharmacy might be rather due to the burden of morbidity among institutionalized people than living in a nursing home [29].

Polypharmacy may also vary with ethnic origin. For instance, in New Zealand, the Maori population had the highest risks of polypharmacy and hyperpolypharmacy of all ethnic groups compared to New Zealand Europeans [16]. Kantor et al. showed that prevalence of polypharmacy increased in all ethnic groups in the USA (White, Black and Hispanic) from 1999–2000 to 2011–2012, but prevalence was higher for White or Black than for Hispanic people [5]. Furthermore, Cashion et al. found a higher risk of polypharmacy in White American than in African American people [48].

Polypharmacy has also been associated with psychosocio-demographic parameters. Behaviours of the patients may favour polypharmacy. Patients who refuse therapeutic changes such as de-prescription or ask for medication may influence their entry in polypharmacy. Furthermore, switching to another physician or doctor shopping may induce failure to re-evaluate previous diagnoses, leading to inappropriate prescriptions [51,52].

### Disease-related factors

The clinical condition was also shown to be related to polypharmacy status. Several studies found that cardiovascular diseases, such as coronary ischaemic diseases or heart failure, and hypertension were associated with polypharmacy [22,32,53]. Among metabolic diseases, diabetes [32,53], and dyslipidemia [32] were associated with polypharmacy. Diseases of oesophagus and stomach were also linked to polypharmacy [53]. Furthermore, Bjerrum et al. found that anaemia and respiratory diseases were other predictors of polypharmacy [22]. In this study, it has also been found that chronic kidney disease and congestive heart failure are among the conditions with the highest

prevalence of polypharmacy, which is 85% for both, versus 69% of patients with a chronic obstructive pulmonary disease (COPD) [22]. Multiple chronic conditions may be also linked to polypharmacy. An increase in the number of chronic conditions and in the Charlson comorbidity index were reported to be associated with polypharmacy [34,47]. Moreover, frailty, a geriatric concept that refers to a higher vulnerability to stressors, was associated with polypharmacy [54].

### Prescribing-related factors

Several behaviours of physicians may also encourage polypharmacy. Thus, lack of communication between specialists and general practitioners, prescription refill request, preferences, personal beliefs, multiple sources of guidelines and information, and lack of proper continuous education can be factors which favour polypharmacy [51,55].

The use of drugs without a proper indication, which concerns mainly sedatives/hypnotics, laxatives, antidepressants and analgesics, were also predictors of polypharmacy [53]. These different factors may lead subjects to appropriate or inappropriate polypharmacy according to the appropriateness of the medication use.

### Healthcare accessibility factors

Finally, health-care system access is another category of polypharmacy determinant. People who consulted a physician in the last three months, or who have been hospitalized in the last six months were at higher risk of polypharmacy [31]. Furthermore, it was highlighted that visiting a primary care physician at least five times a year increased the risk of polypharmacy by fifteen [4], and that multiple providers or supplemental insurances are a marker of polypharmacy [10].

### Conclusion

Multiple definitions exist in the literature to describe polypharmacy. The quantitative dimension of polypharmacy has been better explored than its qualitative aspect so far. Quantitative polypharmacy indicators differ by their way of considering drug exposure. On the one hand, cumulative definition seems to be less specific by considering all medications over a given period. This indicator may serve to study polypharmacy defined by all treatments regardless of the duration or the recurrence of use. On the other hand, continuous treatment considers mainly long-term and recurrent treatments. This definition may describe polypharmacy induced by drugs to which the patient is often exposed, continuously or recurrently over defined periods. Finally, simultaneous polypharmacy can either include all drugs used on a given day, or be restricted to chronic drugs.

According to this review, prevalence of polypharmacy ranged from 4% to 57% but differed greatly according to definitions of polypharmacy and determinants relative to sociodemographic parameters, diseases, etc. Regardless of definition used, prevalence of polypharmacy is higher in elderly people compared to younger people, which has led to explore this condition almost exclusively in the elderly.

The main drugs involved in polypharmacy are cardiovascular, digestive and metabolism drugs, which can be explained by the prevalence of these pathologies and treatment patterns that combines multiple pharmacological pathways.

Most of the studies published so far only considered the quantitative dimension of polypharmacy. Only a few studies distinguished and estimated the amount of appropriate and inappropriate polypharmacy. Potentially inappropriate drugs may represent a major part of polypharmacy since their use is common in the population. Owing to this, appropriateness should be quantified and described in future studies. This information will be necessary to better understand risks associated with polypharmacy and assess its clinical impact.

### Disclosure of interest

J.G. declares that he has no competing interest.

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## A.6 Discussion des principaux résultats

Bien qu'ils existent des différences de seuils, la polymédication est définie le plus souvent par 5 médicaments ou plus. Bien que ce nombre ne fasse pas consensus, il permet de comparer les résultats facilement entre les études qui l'utilisent.

La notion de fenêtre de temps, la période durant laquelle les médicaments sont comptabilisés permet de définir trois types de polymédication majoritairement étudiées dans la littérature.

- La polymédication simultanée, nombre de médicaments en cours d'utilisation à un moment donné, par exemple un jour donné.
- la polymédication cumulative c'est le nombre de médicament qui ont été délivrés ou administrés au cours d'une période.
- la polymédication continue c'est le nombre de médicaments qui ont été délivrés en même temps au cours de plusieurs périodes.

Ce dernier indicateur est parfois utilisé par étudier la polymédication chronique. Cependant cela présente des limites, cette définition capturant à la fois les traitements sur le long terme qui nous intéressent mais aussi les traitement courts et récurrents. Certains auteurs combinent les définitions de polymédication simultanée et continue, mais cela présente les mêmes limites.

Bien que certaines études cherchent à distinguer la polymédication chronique de la polymédication globale, cette approche reste le plus souvent rare et incomplète. Pour la suite de ces travaux il était donc nécessaire de développer un indicateur identifiant spécifiquement la polymédication chronique.

## B Méthodes pour l'identification de la polymédication chronique dans les bases de données de santé

### B.1 Problématique

A partir de la revue générale précédente, un indicateur de polymédication chronique a été développé pour être appliqué dans une base de données médico-administrative. La polymédication étant rarement étudiée dans une population autre que les personnes âgées et pour laquelle la prévalence des multimorbidités n'est pas négligeable [10,59]. Cet indicateur a été appliqué dans les données populationnelles de l'Assurance Maladie Française et comparé avec les autres indicateurs identifiés dans la revue générale.

Dans la littérature, les descriptions de la polymédication identifient à la fois les traitements à long terme et les traitements à court terme [47,55–57]. Certains chercheurs proposent des variations de définitions identifiant plus spécifiquement des traitements à long terme afin d'étudier la polymédication chronique [58]. Cependant ces définitions présentent certaines limites, ne permettant pas une parfaite distinction entre traitement chronique et traitement court ou n'identifiant pas l'accumulation de traitements chroniques au cours du temps.

### B.2 Objectifs

Les objectifs de ces travaux étaient de développer un indicateur de polymédication chronique afin d'en décrire la prévalence et les médicaments impliqués dans la population française, en fonction de l'âge.

### B.3 Considérations méthodologiques

#### Source de données et médicaments considérés

Nous avons réalisé une étude descriptive transversale à partir de l'EGB sur les données 2014 et 2015.

Les médicaments, quelle que soit leur voie d'administration (systémique ou non systémique), ont été identifiés grâce à leur code ATC de niveau 5 et à leur code CIP. Les médicaments associant plusieurs substances actives ont été identifiés à partir du répertoire des spécialités de l'ANSM (<http://agence-prd.ansm.sante.fr/php/ecodex/index.php>). Ils ont été considérés comme autant de médicaments différents que de substances actives. Les médicaments administrés par voie locale contenant une combinaison de substances actives n'ont pas été subdivisés et ont compté pour un seul médicament.

#### Durée de traitement

Pour chaque délivrance d'un médicament, la période de traitement a été estimée à partir de la date de délivrance. La durée de traitement associée a été estimée à partir des durées moyennes de prescription des données EPPM (Etude Permanente sur la Prescription Médicale menée par la société IMS Health auprès de 1 190 médecins volontaires, représentatifs des médecins généralistes ou spécialistes exerçant en France métropolitaine). La polymédication concerne une grande variété de médicaments avec des schémas posologiques variables, et il était donc compliqué d'estimer ces durées de traitement à partir du nombre d'unités par boîte délivrée comme il peut être classiquement fait lors d'étude sur l'EGB.

De plus, les conditionnements trimestriels délivrés pour une durée de 3 mois ont été identifiés à partir de la liste réglementaire du 20 juin 2012 ; ([http://solidarites-sante.gouv.fr/IMG/pdf/ctrim\\_200612\\_pour\\_publication\\_site.pdf](http://solidarites-sante.gouv.fr/IMG/pdf/ctrim_200612_pour_publication_site.pdf)). A ces durées de traitement, a été ajoutée une période de grâce de 20 % afin de tenir compte de l'éventuel délai entre la dispensation et la prise du médicament et/ou des défauts d'observance du patient [60].

#### Définitions de l'exposition chronique

Plusieurs définitions de l'exposition chronique à un médicament ont été appliquées (Figure 3) :

- Exposition chronique journalière : Un patient a été considéré comme exposé de façon chronique à un médicament dès lors qu'il avait cumulé plus de 183 jours consécutifs de traitement (6 mois), incluant la période de grâce de la dernière délivrance.
- Exposition chronique de récurrence : Un patient était considéré comme exposé de façon chronique à un traitement dès lors qu'il avait reçu deux délivrances d'un médicament au cours d'une période de six mois. L'exposition chronique était maintenue jusqu'à ce que le délai entre deux délivrances soit supérieur à 6 mois.
- Exposition chronique continue : l'exposition a été définie comme chronique si le patient recevait trois délivrances d'un même médicament sur une année. C'est une des définitions utilisée de façon classique dans la littérature pour étudier la polymédication continue [4,61].

Les indicateurs d'exposition chronique de récurrence et continue sont les indicateurs les plus proches des indicateurs fréquemment retrouvés dans la littérature. Nous les avons définis afin de pouvoir comparer nos résultats à ceux de la littérature. Néanmoins, leur utilisation est limitée du fait qu'ils identifient à la fois les traitements longs et les traitements courts récurrents. Nous avons développé l'indicateur de polymédication chronique journalière car il identifie de manière spécifique les traitements pris sur le long terme et permet donc une description spécifique de la polymédication chronique. Pour les indicateurs journalier et de récurrence, la période de 6 mois a été retenue afin

d'éviter qu'une seule délivrance d'un conditionnement trimestriel soit identifier comme un traitement chronique.

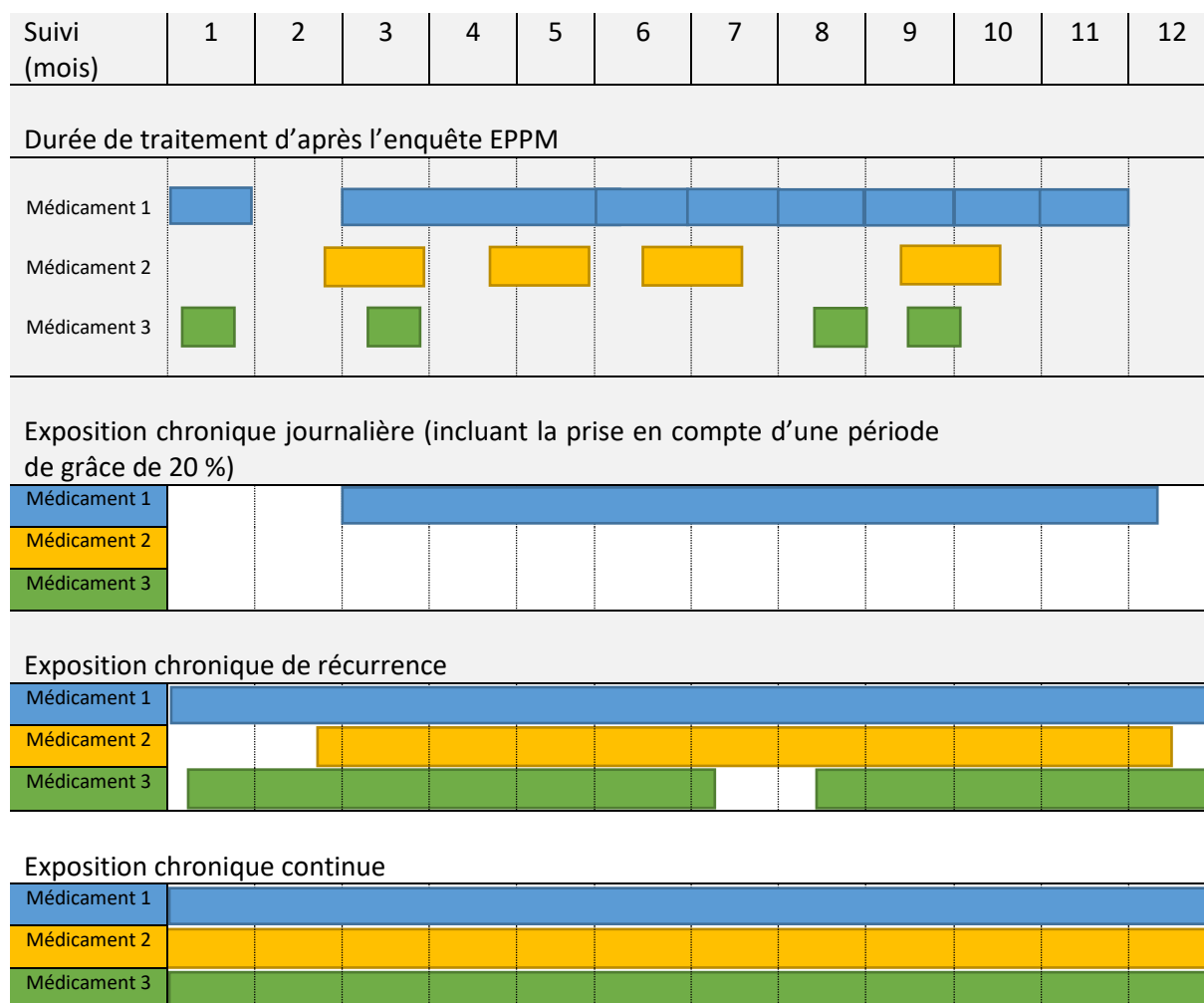


Figure 3 Définitions des périodes d'exposition chronique

### Définitions de la polymédication chronique

Le seuil de cinq médicaments ou plus est le plus fréquemment utilisé [4]. Certains auteurs proposent également des seuils supplémentaires afin de prendre en compte une hyperpolymédication, parfois appelée polymédication excessive. Cette notion de seuils multiples permet de prendre en compte la croissance linéaire du risque d'effets indésirables avec le nombre de médicaments [4]. Afin de pouvoir facilement nous comparer aux études publiées, nous avons fait le choix d'utiliser des seuils classiques et fréquemment utilisés dans la littérature. Dans la présente étude, les deux niveaux de polymédication considérés étaient :

- la polymédication chronique, pour une exposition concomitante (*i.e.* le même jour) à au moins cinq médicaments chroniques ;

- l'hyperpolymédication chronique, pour une exposition concomitante à au moins 10 médicaments chroniques.

### Analyses descriptives

La prévalence de la polymédication chronique a été définie par le nombre de sujets ayant au moins un jour de polymédication chronique sur l'année 2015. L'incidence de la polymédication chronique a été définie par le nombre de patients ayant au moins un jour de polymédication chronique sur l'année 2015, sans aucun jour de polymédication chronique en 2014.

Les médicaments chroniques rencontrés en polymédication chronique en 2015 ont été décrits selon la classification ATC et les résultats présentés en densité d'exposition exprimé en patient-année. Un patient-année est une unité représentant l'utilisation d'un médicament chronique par un patient durant un an. L'exposition pour l'ensemble des sujets en situation de polymédication chronique, rapportée au total de l'exposition à l'ensemble des médicaments utilisés en situation de polymédication chronique permet d'exprimer le part de la polymédication chronique représenté par chaque médicament.

Les analyses descriptives ont été stratifiées selon le sexe et selon l'âge des patients (en deux catégories de classes d'âge : personnes âgées (75 ans ou plus) et personnes non âgées (moins de 75 ans) ; [0-3[, [3-10[, [10-18[, [18-40[, [40-60[, [60-70[, [70-80[, [80-90[, et ≥ 90 ans).

#### B.4 Résumé des travaux et principaux résultats :

Le nombre de sujets identifiés dans l'EGB, affiliés à l'Assurance Maladie en 2015 et sur l'intégralité de l'année 2014 était de 584 862 personnes. La moyenne d'âge était de 42,2 ans (e-t 23,6 ans), le sex-ratio était proche de 1 et la mortalité toute-cause en 2015 était de 0,8 %.

La prévalence de la polymédication variait en fonction de la définition considérée (de 5,6 % ( $\pm 0,1$ ) pour la polymédication chronique journalière à 28,8 % ( $\pm 0,1$ ) pour la polymédication chronique de récurrence) ; il en était de même pour l'incidence (de 1,1 % ( $\pm 0,0$ ) pour la polymédication chronique journalière à 5,2% ( $\pm 0,1$ ) pour la polymédication chronique de récurrence). Quelle que soit la définition, le groupe anatomique de médicaments contribuant le plus fréquemment à la polymédication chronique était celui des médicaments cardiovasculaires. L'importance des classes médicamenteuses dans la polymédication variait en fonction du type de polymédication considéré : les inhibiteurs de l'HMG-Coa réductase étaient les médicaments les plus représentés dans la polymédication chronique journalière, et les anilides (une classe d'analgésiques) dans les polymédications dites de récurrence et continue.

La polymédication chronique concernait aussi bien les hommes que les femmes ; des différences étaient observées en fonction de l'âge des patients, avec des prévalences de polymédication plus élevée chez les patients âgés de 75 ans et plus. La polymédication chronique journalière, spécifique des traitements longs, augmentait de 0,2 % chez les sujets de 18 à 40 ans jusqu'à un maximum de 29,2 % chez les personnes âgées 80 à 90 ans, avant de redescendre à 23,6 % chez les sujets de 90 ans ou plus. Il existait des différences d'exposition suivant l'âge qui concernaient les médicaments cardiovasculaires (respectivement, 43,5 % de l'exposition chez les sujets de moins de 75 ans vs. 45,7 % chez les sujets de 75 ans et plus) et les médicaments du système nerveux (respectivement 13,7 % vs. 11,5 % de l'exposition).

En résumé, l'exposition chronique journalière était spécifique des médicaments chroniques pris tous les jours, sur une longue période. Les deux autres définitions considéraient à la fois ces médicaments et ceux dont les délivrances étaient répétées de façon plus espacée. L'exposition chronique journalière permet donc une description spécifique de la polymédication chronique. La polymédication chronique est importante dans la population française et sa prévalence augmente avec l'âge. On observe également une évolution avec l'âge des médicaments chroniques impliqués.

La description des différents indicateurs de la polymédication chronique a donné lieu à un rapport d'étude destiné à l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) réalisé dans le cadre de l'activité de la plateforme nationale de pharmaco-épidémiologie DRUGS-SAFE (Drugs Systematized Assessment in real-liFe Environment). L'application spécifique de l'indicateur de polymédication chronique journalière a donné lieu à un article scientifique soumis à la revue internationale *Fundamental & Clinical Pharmacology*.

Les résultats mis en évidence dans cette première partie ne présument cependant pas d'un usage approprié ou inapproprié de médicaments. La description de la polymédication chronique doit ainsi être complétée par la définition et la description de sa part inappropriée.

B.5 Article soumis : Chronic polypharmacy: a population-based study regardless of age

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# Chronic polypharmacy: a population-based study regardless of age

*Chronic polypharmacy according to age*

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## Abstract

Polypharmacy is a growing concern although often described only in elderly by cumulating all drug taken. We aimed to describe chronic polypharmacy in France, regardless of age.

A cross sectional descriptive study was performed using the 1/97<sup>th</sup> representative sample of the French health insurance nationwide database (EGB). All subjects alive on January 1<sup>st</sup>, 2015 and covered by the French healthcare insurance were included, and their information collected until December 31<sup>st</sup>, 2015 or date of death. Drug exposures were estimated from drug dispensing dates and treatment durations. Chronic uses of drug were defined as drugs used daily for more than 6 months. Chronic polypharmacy corresponded to the exposure to five chronic uses of drug or more.

In 2015, information of 584,862 subjects were collected (mean age: 42.2 years). Prevalence of chronic polypharmacy was 5.6% and incidence 1.1%. Prevalence of chronic polypharmacy increased noticeably from 0.2% for subjects aged 18 to 40 years to a maximum of 29.2% for subjects aged 80 to 90 years, and then decreased to 23.6% for subjects aged 90 years and more. Lipid modifying agents were the most frequent drugs involved in chronic polypharmacy (10% of exposure). According to age, the most important differences between the younger and the elderly were found for cardiovascular drugs (43.5% vs. 45.7% of exposure, respectively) and nervous system drugs (13.7% vs. 11.5% of exposure, respectively).

This population-based study showed increasing of chronic polypharmacy and evolution of chronic drug patterns with age.

Abstract word count: 240/250

**KEYWORDS** (6/6): polypharmacy, observational study, pharmacoepidemiology, drug utilization, aged, middle-aged

## **Introduction**

Polypharmacy is the use of many drugs or an excessive number of drugs at the same time. Although there is no consensus on the threshold for the number of drugs, it is often defined by the use of five drugs or more, and excessive polypharmacy or hyperpolypharmacy by the use of ten drugs or more [1]. This situation of drug pattern is associated with an increased risk of adverse drug reactions, hospitalizations and death [2–9]. In addition to the major public health concern, polypharmacy also poses economic issues related to the costs of using many drugs and associated complications [10,11].

In the United States, the prevalence of polypharmacy increased from 8.2% to 15% between 1999-2000 and 2011-2012[12]. However, this prevalence represents all drugs delivered regardless of their duration. Several indicators have been developed to describe polypharmacy such as cumulative, continuous and simultaneous polypharmacy [9,13]. Although these indicators capture different drug patterns, none of them distinguish especially long-term treatments for chronic diseases that could have a particular impact in the context of polypharmacy. Furthermore, polypharmacy is rarely studied in population other than the elderly, population for which prevalence of multiple diseases is high [14,15].

In this context, we aimed to study chronic polypharmacy in the French population regardless of age.

## **Methods**

### **Study design**

We performed a cross-sectional descriptive study using data from the French National Insurance databases.

### **Data source**

EGB (*Echantillon Généraliste de Bénéficiaires*) is a 1/97<sup>th</sup> permanent random sample of the nationwide databases of the French Health Care Insurance System, which covers 98.8% of the French population [16]. It is representative for age, gender and medical expenses. It includes individual, anonymous data related to demographics and long-term diseases. It also provides comprehensive data on outpatient medical reimbursements (including, for drugs, date of dispensing, number of units per pack, and number of packs delivered), and hospitalizations with dates and medical diagnoses recorded during the stay. Dispensed drugs are encoded using ATC (Anatomic, Therapeutic, Chemical) classification.

### **Study population**

Data of subjects alive on January 1<sup>st</sup>, 2015 and covered by the French healthcare insurance since at least January 1<sup>st</sup>, 2014 were collected until December 31<sup>st</sup>, 2015. Subjects who died in 2015 were not excluded to take into account end of life polypharmacy and potential mortality risk.

## **Drugs of interest**

Drugs were considered regardless of route of administration (systemic or not) and identified using their ATC codes. Specific therapeutic classes (not used chronically or without pharmacological systemic effects) were excluded: homeopathy, vaccines (ATC : J07), anesthetics (N01), blood substitutes and perfusion solutions (B05), immune sera and immunoglobulins (J06), diagnostic drugs or radiopharmaceuticals (S01J, V04 and V09), contrast media (V08), antidotes (V03AB), medical gases (V03AN) insecticides and repellents (P03B), antiseptics and disinfectants (D08), medicated dressings (D09), surgical dressings (V20), tissue adhesives (V03AK) and all other non-therapeutic products (V07).

Information on drugs dispensed during hospitalization is not available in EGB; these were assumed to be similar to those used on the day before admission. Fixed-dose combinations were split into active ingredients. Each ingredient was assigned its corresponding ATC code (if different codes could be assigned, the code reflecting more the indication of the original combination was chosen). Ingredients without any ATC code were assigned the ATC code of the combination. Topical combinations were not split and were assigned the ATC code of the combination.

## **Exposure**

Treatments were assumed to start on the date of dispensing [17]. Periods of drug use were estimated using mean durations of drug prescriptions coming from a survey including 1,190 French physicians, representative of practices of general practitioners (GP) and specialists [18]. A 20% grace period was added to each period of treatment to consider compliance issues.

Chronic use was defined as an uninterrupted daily use lasting at least 183 days (i.e. 6 months). Chronic polypharmacy was defined by the chronic use of five drugs or more, and chronic hyperpolypharmacy by the chronic use of ten drugs or more (Figure S1).

## **Statistical analyses**

All data management and analyses were performed using SAS software version 9.4 (*SAS Institute, North Carolina, USA*).

Prevalence in 2015 was defined as the number of subjects who had at least one day of chronic polypharmacy in 2015 and in 2014. Incidence was defined as the number of subjects who had at least one day of chronic polypharmacy in 2015 but not in 2014.

Chronic drug uses encountered in chronic polypharmacy in 2015 were described according to ATC classification. Results were presented in density of exposure expressed in drug-years and percent of the total exposure to polypharmacy. One drug-year represented a chronic drug use in a patient in polypharmacy during one year. For the analysis exposure was regarded daily in every patient and then cumulated. An interactive Sunburst diagram and treemap diagrams were used to represent these drugs according to the ATC levels.

All analyses were stratified on age (younger people: < 75 years old; elderly people:  $\geq$  75 years old [19]; age classes [0-3[, [3-10[, [10-18[, [18-40[, [40-60[, [60-70[, [70-80[, [80-90[,  $\geq$  90).

Sensitivity analyses were performed. First, drugs dispensed during hospitalization were not estimated from treatments before admission. Moreover, since 29% of nursing homes have no care reimbursement data identifiable in the EGB database, a sensitivity analysis aiming to exclude all people who might be in a nursing home was performed by excluding people aged 60 (minimum legal age for admission) and over with no reimbursement of care [20].

## **Results**

### **Description of the study population**

Information on 584,862 people were collected. Mean age was 42.2 years (standard deviation 23.6 years). Sex-ratio was close to 1 and all-cause mortality in 2015 was 0.8% (Table I).

### **Prevalence and incidence**

In 2015, prevalence of chronic polypharmacy was 5.6% (95% confidence interval:  $\pm$  0.1) in the French population. Incidence of chronic polypharmacy was 1.1% ( $\pm$  0.0) (Table I).

Prevalence were higher in elderly ( $\geq$ 75 years old) than in younger subjects (<75 years old) for chronic polypharmacy (respectively 26.7%  $\pm$  0.4 vs. 3.3%  $\pm$  0.0) and chronic hyperpolypharmacy (4.6%  $\pm$  0.2 vs. 0.7%  $\pm$  0.0). In more detail, prevalence of chronic polypharmacy increased noticeably from 0.2% for subjects aged 18 to 40 years to a maximum of 29.2% for subjects aged 80 to 90 years, and then decreased to 23.6% for subjects aged 90 years and more (Figure 1, Tables S-I).

### **Drugs involved in chronic polypharmacy**

Description of all drugs involved in chronic polypharmacy is available in an interactive sunburst diagram (Figure 2, interactive html file in supplementary materials), which provide global data visualization from first to fifth level of the ATC classification.

In chronic polypharmacy, the cardiovascular group was the most contributing group (Level 1 of ATC C, 44.6% of the exposure to chronic drug uses); the two other most contributing groups were alimentary tract and metabolism (A; 19.1 %) and nervous system groups (N; 12.6%) (Figure 2 Table II). When considering therapeutic subgroups (level 2 of ATC), lipid modifying agents (C10) and agents acting on the renin-angiotensin system (C09) were the most frequent drugs (10.0% and 9.8% of the exposure, respectively) (Table S-II, Figure 2).

According to age, the biggest differences between the younger and the elderly were found for cardiovascular and nervous system anatomical subgroups (43.5% vs. 45.7% and 13.7% vs. 11.5%, Figure 3, Table II). Considering the therapeutic class, some drugs represented a more important part of exposure in younger such as drugs used in diabetes (A10, 10.0% in younger people vs. 5.5% in elderly), lipid modifying agents (C10, 10.9 % vs. 9.1%) and psycholpeptics (N05, 5.9% vs. 4.1). Conversely, diuretics (C03, 7.7% vs. 9.5%) and cardiac therapy (C01, 1.6% vs. 3.1%) represented a more important part in elderly (Figure 3, Tables S-II).

The drug exposure densities described using level 4 and 5 of ATC classification are available in supplementary material (Tables S-III and S-IV). The most frequent chemical subgroups were HMG CoA reductase inhibitors (C10AA, 8.0% of exposure, Table S-III). Acetylsalicylic acid (B01AC06) and hydrochlorothiazide (C03AA03) were the most frequent molecules involved chronic polypharmacy (5.3% and 3.5% of exposure, respectively) (Table S-IV).

### **Sensitivity analysis**

All performed sensitivity analyses showed similar results regarding prevalence and incidence rates and drugs involved in polypharmacy (Tables S-V to S-IX).

## **Discussion**

In 2015 in France, prevalence of chronic polypharmacy concerned 5.6% of the population, and incidence 1.1%. Chronic polypharmacy increased with age to reach a maximum at the age of 80-90 years. However, younger people were also concerned with a prevalence of 2.8% of among 40-60 years old. Cardiovascular drugs were the most frequent drugs in polypharmacy. Some differences were observed according to age: diuretics representing a bigger part in elderly than in younger people and drugs used in diabetes represented a twice bigger part of chronic polypharmacy in younger people than in elderly.

While the wide majority of the literature focus on elderly people, several studies showed that polypharmacy can be observed in middle aged people. In the US population, polypharmacy concerned 15% of people aged 40 to 64 years [12]. Another study showed that polypharmacy concerned 20.3% of middle aged people in Northern Ireland and 46.7% in Republic of Ireland [21]. Although these studies did not focus only on chronic drugs, the high prevalence found highlighted that chronic polypharmacy is becoming a major concern in middle-aged people. Our results concerning incidence also highlighted that, even if the highest incidence concerned elderly, incidence of chronic polypharmacy was noticeable in people aged 40 – 70 years. Contrary to the different definitions of polypharmacy used in the literature [13], the definition we hereby propose identifies drugs used each day for long term, and thus considers the effective situations of chronic polypharmacy. Two published studies conducted in the elderly used a definition of polypharmacy close to ours [22,23]. Nishtala *et al.*'s definition defined chronic drug uses when drugs were used more than 90 days, or 180 days in a sensitivity analysis and identified polypharmacy according to those drugs only [23]. They found a prevalence of polypharmacy among 65 years old New-Zealanders of 29.5% in their main analysis and 22.5% in their sensitivity analysis, this latter result being similar to ours in the same age class. Conversely, Veehof *et al.* found a lower prevalence of chronic polypharmacy among 65 years old subjects from Netherlands (4%). This difference was probably due in part to the methodological choice of chronicity requirements which were prescriptions of at least 60 days per quarter per year. This study was also carried out over the period 1994 – 1997 and the consumption of drugs has probably changed nowadays [22]. In the literature, the large range of definitions, which count drugs used continuously but also recurrently over a period, differs between studies, leading to a large range of prevalence [24]. However, regardless of methodological choices, polypharmacy increased with age [25–28].

Frequent medications seemed to be similar between studies considering elderly people and those conducted regardless of age [24]. In population including elderly and younger people, cardiovascular drugs were shown to be the most encountered drugs in polypharmacy in Switzerland [29], Denmark [27] and the United-States [30]. We also observed cardiovascular drugs were the most frequent regardless of age, but differences existed in pharmacological classes according to age. Furthermore, we also observed difference were amongst digestive and metabolism drugs such as drugs in diabetes or pump-proton inhibitors and nervous system drugs such as analgesics, which were more important in younger people. These drugs were also shown to be frequent in polypharmacy in older people, for instance in New-Zealand [23], Italy [31], Sweden [32]. Our results suggested

than different types of polypharmacy could exist according to age, which was not highlighted in studies regarding only elderly. Since the most frequent drugs in younger people are also found in elderly, it suggested that polypharmacy is driven by multimorbidities which changes with age. For instance, 12 million people aged 40 to 74 years in the United States had prediabetes conditions in 2000 [33]. These medications that represented a major proportion of polypharmacy in younger seemed to persist in elderly. However, their proportion remained smaller due to the introduction of treatment for new pathology (mainly cardiovascular drugs), which become the bigger part of the chronic polypharmacy.

Strengths and limits of this study are mainly linked to the quality of the data used. Since EGB is representative of the French population, this description of polypharmacy can be extrapolated in all classes of age. Moreover, EGB contains all reimbursements of outpatient treatments including most of all treatment of chronic diseases [16]. Reimbursement data can estimate chronic drugs use and treatment duration [17]. Accuracy of EGB data also allowed us to identify separately each agent of fixed combinations to consider each pharmacological effect [34]. However, the present study has certain limitations. Durations of prescriptions are not available in EGB; however, they were estimated from a representative survey of medical prescriptions in France to be as close and representative as possible of drug use practices in France. We also added a grace period which maintained the chronicity of a drug if a small gap of delivery occurred. Switch between medications used chronically were not identified but they would not have a major impact on prevalence on polypharmacy since the exposure is considered daily over one year. The database does not include over-the-counter (OTC) drugs which are not reimbursed. This may have a negligible impact as it seems unusual or unlikely that these drugs were used daily by patients for more than 6 months. Furthermore, some OTC drugs such as analgesics or laxative can also be reimbursed and then their data would then be integrated in the EGB database. Finally, the lack of information on drug use during hospitalization or nursing home stays could underestimate chronic polypharmacy. However, sensitivity analyses performed here showed no major differences for prevalence or drug descriptions encountered in polypharmacy, suggesting that the absence of these data had minimal impact on our results.

## **Conclusion**

Polypharmacy is a public health concern, especially as polypharmacy of drugs chronically used is high. This population-based study showed increasing of chronic polypharmacy and evolution of chronic drug patterns with age. The continuation of multiple drug prescribing from the middle age to old age

should encourage changing practices and considering all prescriptions as a whole in order to optimize patient treatment. Evaluation of chronic polypharmacy should be completed with the identification of potentially inappropriate drugs that could be deprescribed.

## **Acknowledgments**

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## **Conflict of interest**

The authors declare that they have no conflict of interest.

## **Ethics approval**

Neither committee approval nor informed consent required because only anonymous data were used according to French Data Protection Supervisory Authority (CNIL) agreement.

## **Authors' contributions**

AP conceived and designed the study. JG, SMR and JB performed the research. JG analysed the data. JG, SMR and JB wrote the paper.

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## Tables

**TABLE I** Description of the population of the EGB in 2015 according to age

	EGB Population n = 584,862	< 75 years old n = 526,494	≥ 75 years old n = 58,368
Age, Mean (sd)	42.2 (23.6)	37.6 (20.2)	83.1 (6.1)
Men, n (%)	288,839 (49.4)	266,151 (50.6)	22,688 (38.9)
Women, n (%)	296,023 (50.6)	260,343 (49.4)	35,680 (61.1)
Died in 2015, n (%)	4,604 (0.8)	1,551 (0.3)	3,053 (5.2)
Polypharmacy			
Prevalent - n (% ± 95CI)	32,723 (5.6 ± 0.1)	17,146 (3.3 ± 0.0)	15,577 (26.7 ± 0.4)
Incident - n (% ± 95CI)	6,217 (1.1 ± 0.0)	3,527 (0.7 ± 0.0)	2,690 (4.6 ± 0.2)
Hyperpolypharmacy			
Prevalent - n (% ± 95CI)	3,020 (0.5 ± 0.0)	1,572 (0.3 ± 0.0)	1,448 (2.5 ± 0.1)
Incident - n (% ± 95CI)	903 (0.2 ± 0.0)	443 (0.1 ± 0.0)	460 (0.8 ± 0.1)

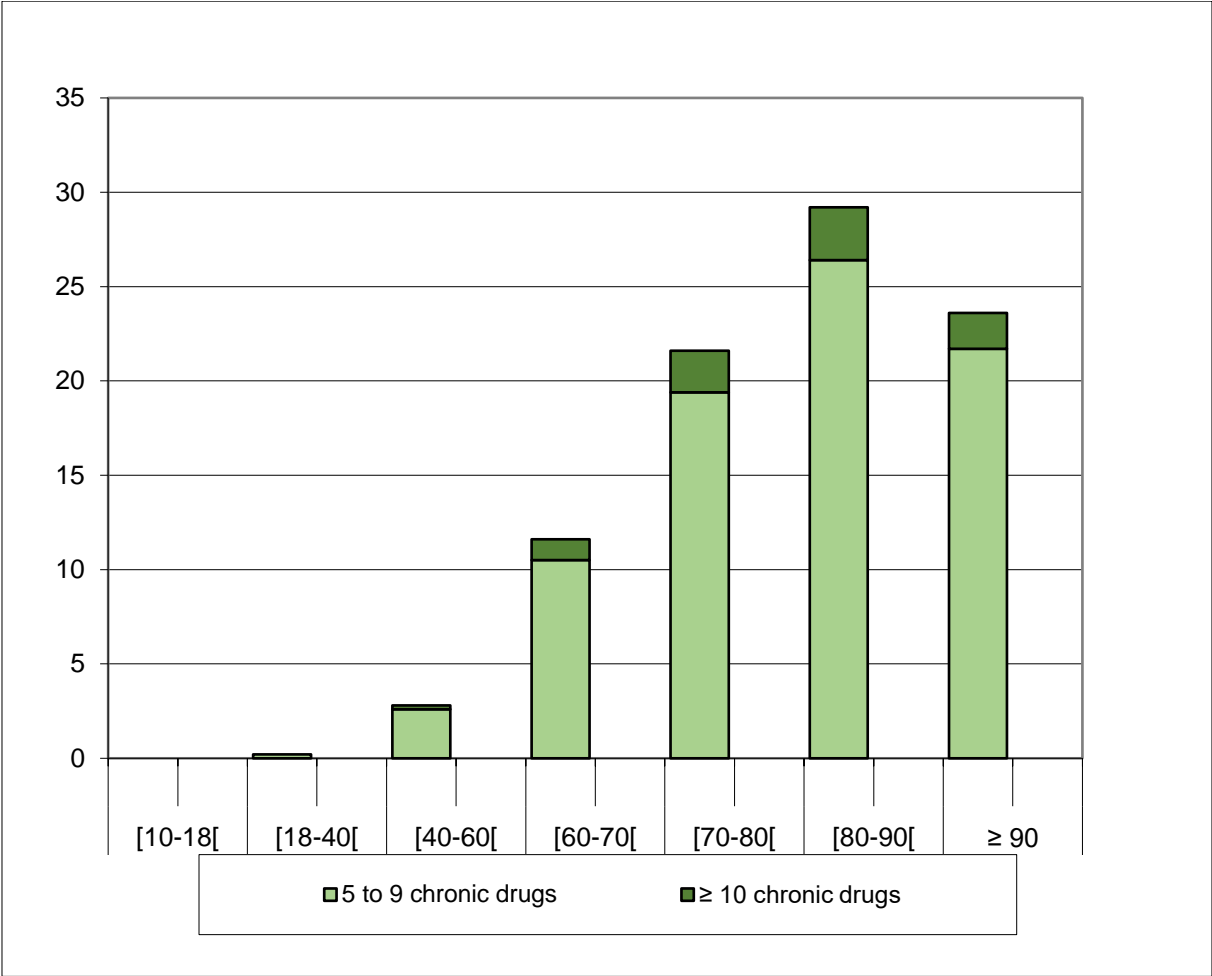
n: sample; sd: standard deviation; 95CI: 95% confidence interval

**TABLE II** Drug exposure in chronic polypharmacy according to the level 1 of ATC in the population according to age

Level 1 of ATC	EGB		< 75 y-o		≥ 75 y-o		Difference <sup>a</sup>	
	Population							
	Drug-years	%	Drug-years	%	Drug-years	%		
A - Alimentary tract and metabolism	25,795	19.1	14,118	20.1	11,677	18.1	2.0	
B - Blood and blood forming organs	12,388	9.2	5,968	8.5	6,420	10.0	-1.5	
C - Cardiovascular system	60,077	44.6	30,638	43.5	29,439	45.7	-2.2	
D - Dermatologicals	476	0.4	271	0.4	205	0.3	0.1	
G - Genito urinary system and sex hormones	3,583	2.7	1,572	2.2	2,011	3.1	-0.9	
H - Systemic hormonal preparations, excluding sex hormones and insulins	3,089	2.3	1,479	2.1	1,610	2.5	-0.4	
J – Anti-infectives for systemic use	427	0.3	378	0.5	49	< 0.1	0.5	
L - Antineoplastic and immunomodulating agents	709	0.5	469	0.7	240	0.4	0.3	
M - Musculo-skeletal system	3,752	2.8	1,813	2.6	1,939	3.0	-0.4	
N - Nervous system	17,023	12.6	9,615	13.7	7,408	11.5	2.2	
P - Antiparasitic products, insecticides and repellents	59	< 0.1	41	< 0.1	17	< 0.1	0.0	
R - Respiratory system	5,337	4.0	3,174	4.5	2,164	3.4	1.1	
S - Sensory organs	2,048	1.5	799	1.1	1,248	1.9	-0.8	
V - Various	97	< 0.1	55	< 0.1	42	< 0.1	0.0	

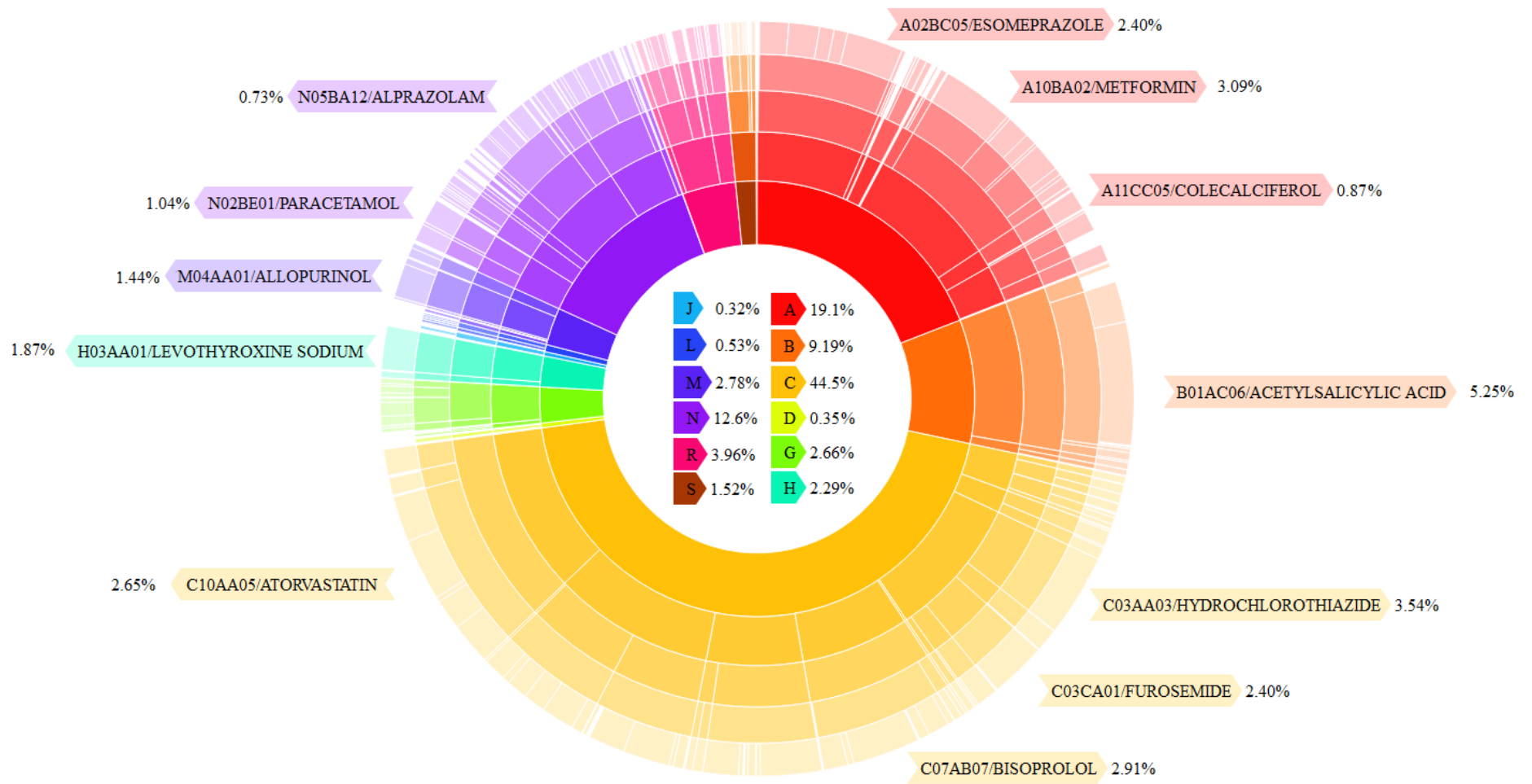
ATC: Anatomic, therapeutic, chemical; y-o: years old; <sup>a</sup> : difference, for a given ATC code between density of exposure in younger people (< 75 years old) and the one in elderly ( $\geq 75$  years old) in percent points, difference >0 means that density of exposure is higher in younger people than in the elderly and vice versa, a null difference means no difference of density of exposure between younger people and elderly.

# Figures



**FIGURE 1** Prevalence of chronic polypharmacy in 2015 according to age classes in the population (%)





**FIGURE 2** Density of exposure to chronic drugs in chronic polypharmacy according to the five levels of ATC (Anatomic, Therapeutic, Chemical) in the population



## Figures legends

**FIGURE 1** Prevalence of chronic polypharmacy in 2015 according to age classes in the population (%)

The prevalence of polypharmacy refers to the number of patients taking more than five drugs (i.e. the sum of patients taking 5 to 9 drugs and those taking 10 or more drugs). The prevalence of hyperpolypharmacy is the number of patients taking 10 or more drugs.

**FIGURE 2** Density of exposure to chronic drugs in chronic polypharmacy according to the five levels of ATC (Anatomic, Therapeutic, Chemical) in the population

Each color represents one class of a level 1 of ATC, as displayed in the center of the sunburst. The five concentric circles represent the five levels of ATC (from level 1 in the center to level 5). The size of each piece is proportional to the density of exposure.

**FIGURE 3** Density of exposure to drugs in chronic polypharmacy according to the first and second levels of ATC (Anatomic, Therapeutic, Chemical)

The size of the rectangles is proportional to the density of exposure and the percentages represent the density of exposure of a therapeutic subgroup. ATC level 1 are represented by the different colors (yellow: C ; red: A; purple: N; orange: B; Pink: R; Indigo : M ; Green : G ; Turquoise : H ; Brown : S ; Others : D, J, L, P, V) and ATC level 2 by the rectangles containing the class label.

## B.6 Discussion des principaux résultats

L'indicateur de polymédication chronique journalière capture spécifiquement l'utilisation concomitante un jour données de 5 médicaments dont la durée de traitement est d'au moins 6 mois. Contrairement aux définitions retrouvées dans la littérature, cette définition ne capture pas les traitements courts et récurrents. Cet indicateur permet donc d'étudier spécifiquement la polymédication des traitements chroniques. La période de 6 mois est adaptée aux pratiques de délivrance en pharmacie en France. Dans la littérature un traitement peut être considéré comme chronique à partir de 3 mois [62]. Cependant notre définition considérant 6 mois de traitement, permettait d'éviter que la délivrance d'un seul conditionnement trimestriel soit considérée comme un traitement chronique. Ce choix reste arbitraire et pourrait être réadapté en fonction des données et des pratiques de soins associés à chaque base. De même, bien que le seuil de 5 médicaments ait été choisi de façon arbitraire, le choix de garder des seuils classiquement utilisés dans la littérature a été fait dans le but de pouvoir comparer les résultats obtenus par notre indicateur avec ceux de la littérature.

L'utilisation de notre définition, plus sélective que celles utilisées dans la littérature, a montré que la polymédication chronique est un phénomène fréquent dans la population générale en France. Bien qu'elle soit plus fréquente chez les personnes âgées, elle était non négligeable chez les adultes d'âge moyen. Notre étude suggérait donc que l'étude de la polymédication doivent se poursuivre chez les sujets d'âge moyen et les personnes âgées. Certains médicaments se démarquaient par la part importante qu'ils représentaient. Cependant l'ensemble de ces résultats ne présument pas d'un mésusage de médicaments. Il était donc justifié d'approfondir la description dans ce sens.

### III Description des médicaments potentiellement inappropriés de la polymédication chronique.

#### A Part inappropriée de la polymédication en France.

##### A.1 Problématique

La prévalence de la polymédication chronique commence chez l'adulte d'âge moyen et augmente avec l'âge. Il a été montré qu'une augmentation du nombre de médicaments augmente le risque de présence de MPI [63]. Tout comme la polymédication, les MPI sont associés à un risque de survenue d'effets indésirables [26,29,30,64–67]. Afin de mieux comprendre les enjeux et problèmes liés à la polymédication chronique il était nécessaire de décrire et de quantifier la part inappropriée.

L'identification de MPI dans la population française à partir des données de l'Assurance Maladie est possible grâce à l'application de critères explicites tels que les listes Beers, Laroche ou PROMPT [23,68,69].

##### A.2 Objectifs

L'objectif de cette étude était d'évaluer la part potentiellement inappropriée de la polymédication chronique en France.

##### A.3 Considérations méthodologiques

Une étude transversale a été réalisée à partir des données de l'EGB sur l'année 2016. Les adultes de 45 ans et plus, vivant au 1<sup>er</sup> Janvier 2016 et affiliés à la sécurité sociale au moins depuis le 1<sup>er</sup> Janvier 2015 ont été inclus dans l'étude et leur informations collectées jusqu'au 31 décembre 2016. Les sujets ont été classés en deux sous-groupes : les adultes d'âge moyen (âgés de 45 à 64 ans à l'inclusion) et les sujets âgés (âgés de 65 ans ou plus à l'inclusion). Les médicaments chroniques ont été définis suivant l'indicateur d'exposition chronique journalière développé précédemment, c'est à dire une exposition d'au moins 183 jours consécutifs. La polymédication/hyperpolymédication chronique a été définie par l'utilisation concomitante d'au moins 5/10 médicaments chroniques.

Les MPI ont été identifiés par les critères de Beers, la liste Laroche spécifiquement développés pour les personnes âgées et par les critères de PROMPT spécifiquement développés pour les adultes d'âge moyen. Les critères de Beers sont parmi les premières listes de MPI inventées. Ils incluent des MPI chez les personnes âgées en général et des MPI avec certaines pathologies. Les critères de la listes

Laroche sont des critères inspirés par Beers pour le marché français. On a choisi de combiner les critères Beers et la liste Laroche parce que les deux listes se basent sur des arguments pharmacologiques, et pas uniquement sur ce qui est disponible sur le marché dans le pays. Les critères de PROMPT ont été développés pour deux raisons spécifiques : (i) être applicables spécifiquement aux personnes de 45 – 64 ans, là où la plupart des listes ciblent les personnes âgées, et (ii) être applicables sur des bases de données dans lequel les informations cliniques sont absentes. Ce dernier point était particulièrement intéressant pour une application dans l'EGB.

Les critères de Beers et la liste Laroche ont été, suivant leur applicabilité à l'EGB, classés en critères applicables, critères partiellement applicables, ou non applicables. Les critères de PROMPT étaient soit applicables, soit non applicables à l'EGB. La part des MPI a été exprimée, dans chacun des sous-groupes, par la prévalence des MPI chroniques chez les sujets en polymédication/hyperpolymédication chronique et par la densité d'exposition aux MPI chronique en polymédication chronique.

#### A.4 Résumé des travaux et principaux résultats

En 2016, Parmi les 159 243 adultes d'âge moyen inclus, 8 666 (5,4 %) étaient en polymédication chronique et 760 (0,5 %) en hyperpolymédication chronique. Parmi les 117 545 sujets âgés inclus, 27 834 (23,7 %) étaient en polymédication chronique et 2 868 (2,4 %) en hyperpolymédication chronique. Parmi les sujets en polymédication chronique, 4 009 (46,2 %) des adultes d'âge moyen et 18 036 (64,8 %) sujets âgés étaient concernés par un MPI chronique. En hyperpolymédication, ces prévalences étaient respectivement 570 (75,0 %) et 2 544 (88,7 %). Les MPI les plus fréquents étaient les inhibiteurs des pompes à proton (43,4 % des sujets âgés en polymédication), les benzodiazépines à demie vie courte (16,1 % des adultes d'âge moyen en polymédication ; 13,7 % des sujets âgés) et les sulfamides hypoglycémiantes (12,3 % et 3,9%).

Cette étude a fait l'objet d'un article publié dans *Journal of Clinical Medicine (JCM)*.

A.5 Article publié : The burden of potentially inappropriate medications in chronic polypharmacy

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Article

# The Burden of Potentially Inappropriate Medications in Chronic Polypharmacy

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**Abstract:** We aimed to describe the burden represented by potentially inappropriate medications (PIMs) in chronic polypharmacy in France. We conducted a nationwide cross-sectional study using data from the French National Insurance databases. The study period was from 1 January 2016 to 31 December 2016. Chronic drug use was defined as uninterrupted daily use lasting  $\geq 6$  months. Chronic polypharmacy was defined as the chronic use of  $\geq 5$  medications, and chronic hyperpolypharmacy as the chronic use of  $\geq 10$  medications. For individuals aged  $\geq 65$  (older adults), PIMs were defined according to the Beers and Laroche lists, and for individuals aged 45–64 years (middle-aged) PIMs were defined according to the PROMPT (Prescribing Optimally in Middle-aged People's Treatments) list. Among individuals with chronic polypharmacy, 4009 (46.2%) middle-aged and 18,036 (64.8%) older adults had at least one chronic PIM. Among individuals with chronic hyperpolypharmacy, these figures were, respectively, 570 (75.0%) and 2544 (88.7%). The most frequent chronic PIM were proton pump inhibitors (43.4% of older adults with chronic polypharmacy), short-acting benzodiazepines (older adults: 13.7%; middle-aged: 16.1%), hypnotics (6.1%; 7.4%), and long-acting sulfonylureas (3.9%; 12.3%). The burden of chronic PIM appeared to be very high in our study, concerning almost half of middle-aged adults and two-thirds of older adults with chronic polypharmacy. Deprescribing interventions in polypharmacy should primarily target proton pump inhibitors and hypnotics.

**Keywords:** polypharmacy; appropriateness; potentially inappropriate medication; drug utilization study; observational study

## 1. Introduction

Multimorbidity is, nowadays, common and increases with age [1]. Polypharmacy, defined as the simultaneous use of many drugs, is linked to multimorbidity and is thus consistently rising, especially in the elderly [2–4]. While less studied, multimorbidities and their accompanying polypharmacy are already highly prevalent in middle-aged individuals [5]. Though potentially motivated by the therapeutic management of coexisting diseases, polypharmacy, which is usually defined as the concomitant use of five drugs or more [4,6], is associated with harmful events such as hospitalizations, falls, and even death [7]. Ensuring that polypharmacy is limited to what is needed for patients' best care is thus an important challenge. Limiting its inflation could indeed be of important matter in terms of public health, as inappropriate prescribing seems to increase with the number of chronic drugs [8].



Potentially inappropriate medications (PIMs) are defined as drugs for which the risks outweigh the potential benefits, especially when more efficient alternatives are available [9]. The use of PIMs in the population has been extensively studied, in particular in the elderly, where the prevalence of their use is high, as is the risk of related adverse events [10–16]. Conversely, the literature is scarce concerning its assessment in middle-aged adults, and especially in the context of polypharmacy. Yet, the prevalence of multimorbidity in the middle-aged attracts study in this population [1], especially in that those with polypharmacy should be the more likely to have PIMs [8].

The aim of this study was to evaluate, according to age, the burden of chronic potentially inappropriate medications in adults with chronic polypharmacy in the French population.

## 2. Methods

### 2.1. Study Design

We conducted a nationwide cross-sectional study using data from the French National Insurance databases.

### 2.2. Data Source

The EGB (Echantillon Généraliste de Bénéficiaires) is a nationwide permanent 1/97th random sample of the databases of the French Health Care Insurance System which covers 98.8% of the French population. It is representative of the general population in terms of age, gender, and medical expenses. It contains individual anonymous information on all outpatient reimbursed healthcare expenditures; the registration status for a list of 30 specifically individualized chronic diseases; and hospital discharge data, including diagnosis (coded with the International Classification of Diseases 10th revision, ICD-10). Dispensed drugs are encoded using the Anatomic, Therapeutic, Chemical (ATC) classification [17].

### 2.3. Study Population

The study period for the cross-sectional analysis was the year 2016. Individuals from the EGB were considered eligible for the analysis providing that they were covered by French healthcare insurance from 1 January 2015, and that they were alive and aged 45 or older on 1 January 2016. Individuals who died in 2016 were not excluded in order to take into account end of life polypharmacy. The included individuals were classified according to age on 1 January 2016, as older adults (65 and over at that date) or middle-aged adults (45 to 64 years old at that date).

### 2.4. Drugs of Interest

For our study of chronic polypharmacy, all drugs but those belonging to the following classes were considered: homeopathy, vaccines (ATC: J07), anesthetics (N01), blood substitutes and perfusion solutions (B05), immune sera and immunoglobulins (J06), diagnostic drugs or radiopharmaceuticals (S01J, V04, and V09), contrast media (V08), antidotes (V03AB), medical gases (V03AN), insecticides and repellents (P03B), antiseptics and disinfectants (D08), medicated dressings (D09), surgical dressings (V20), tissue adhesives (V03AK), and all other non-therapeutic products (V07). Drugs were identified using their ATC codes; information on fixed-dose combinations was split to allow taking into account, independently, the use of each of the combined active ingredients.

### 2.5. Exposure

Chronic drug use was defined as uninterrupted daily use lasting at least 183 days. Chronic polypharmacy was defined as the chronic use of five drugs or more, and chronic hyperpolypharmacy as the chronic use of ten drugs or more. The identification of chronic drug use and polypharmacy for each subject was based upon information regarding the drug prescriptions they had during the year 2016 and 2015.

For each identified prescription, treatment use was assumed to start on the date of prescription. From this date, the length of treatment episodes was computed using estimates of the mean durations of drug prescriptions in France [18]. A 20% grace period was added to each theoretical duration of prescription to take into account potential compliance issues [19].

As information on drugs prescribed during hospitalization was not available in EGB; these were assumed to be similar to those used on the day before admission [20].

### 2.6. Potentially Inappropriate Medications

PIM lists, originally aimed at helping clinicians, can also be used for research purposes [21–24]. These lists were created by panels of experts and are key indicators of medication prescribing quality. They list specific drugs that should not be prescribed for general treatment or in patients with several conditions.

In this study, PIM were identified using two tools specifically developed to assess PIM in older adults ( $\geq 65$  years old): the Beers criteria list and its adaptation to the French setting, the Laroche list, and one developed for the assessment of PIM in middle-aged adults (45 to 64 years old), the PROMPT (Prescribing Optimally in Middle-aged People's Treatments) criteria list [25–27]. For individuals who turned 65 in 2016, the Beers and Laroche lists were used throughout the 2016 period.

As the EGB database included limited medical information and does not include information on lab results, not all criteria listed in those tools could be used and some were only partially applicable. The used criteria, their requirements, their applicability, and the ATC codes considered for the identification of the corresponding drugs are listed in the Supplementary Material (Table S1 presents the combined Beers and Laroche criteria; Table S2 presents the PROMPT criteria; Table S3 presents the overlaps of Tables S1 and S2). Two levels of PIM were thus defined: PIM-narrow, considering only fully applicable criteria, and PIM-broad, considering both fully and partially applicable criteria.

### 2.7. Descriptive Analyses

The prevalence of chronic polypharmacy was defined as the proportion of individuals who had at least one day of chronic polypharmacy in 2016; the prevalence of chronic hyperpolypharmacy was defined similarly. In individuals with chronic polypharmacy/hyperpolypharmacy, the prevalence of chronic PIM was defined as the proportion of individuals with at least one day with any chronic PIM use in 2016. Estimations were carried out considering the two defined levels of PIMs—PIM-narrow and PIM-broad. The most frequent PIMs were defined as chronic PIMs contributing to polypharmacy/hyperpolypharmacy in at least 1% of individuals with such. Cumulated exposure to chronic PIM within polypharmacy/hyperpolypharmacy was defined as the proportion of days of exposure to PIM over the number of days of exposure to all drugs contributing to any individual's period of chronic polypharmacy/hyperpolypharmacy for the year 2016.

All the analyses were stratified according to chronic polypharmacy (polypharmacy vs. hyperpolypharmacy) and according to age (older adults vs. middle-aged).

All the data management and analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Neither committee approval nor informed consent was required because only anonymous data were used under the French Data Protection Supervisory Authority (CNIL) agreement.

## 3. Results

### 3.1. Description of the Study Population

Within the EGB, we identified 276,788 individuals who met the eligibility criteria. The sex ratio was close to 1; the mortality in 2016 was 1.5% (Table 1). A total of 117,545 were older adults ( $\geq 65$  years old) and 159,243 were middle-aged adults (45–65 years old). In 2016, the prevalence of chronic polypharmacy and hyperpolypharmacy increased with age, from 5.4% and 0.5% in middle-aged adults

to 23.7% and 2.4% in older adults. Diabetes mellitus was the most frequent long-term disease in both older adults (14.5%) and middle-aged adults (6.0%) (Table 1, Table S4 and S5).

**Table 1.** Description of demographic characteristics, chronic polypharmacy, and chronic diseases at baseline according to age.

	Cohort <i>n</i> = 276,788	Middle-Aged <sup>1</sup> <i>n</i> = 159,243	Older Adults <sup>2</sup> <i>n</i> = 117,545
Age, mean (sd)	63.5 (10.2)	54.1 (5.7)	76.2 (14.2)
Sex, <i>n</i> (%)			
Men	131,275 (47.4)	79,920 (50.2)	51,355 (43.7)
Women	145,513 (52.6)	79,323 (49.8)	66,190 (56.3)
Dead in 2016, <i>n</i> (%)	4239 (1.5)	663 (0.4)	3576 (3.0)
Chronic polypharmacy <i>n</i> (% ± 95CI)	36,500 (13.2 ± 0.2)	8666 (5.4 ± 0.1)	27,834 (23.7 ± 0.2)
Chronic hyperpolypharmacy <i>n</i> (% ± 95CI)	3628 (1.3 ± 0.0)	760 (0.5 ± 0.0)	2868 (2.4 ± 0.0)
Most frequent chronic diseases <sup>3</sup>			
Diabetes (type 1 or type 2)	26,622 (9.6)	9602 (6.0)	17,020 (14.5)
Cancer or leukemia	21,991 (8.0)	6914 (4.3)	15,077 (12.8)
Coronary artery disease	13,248 (4.8)	3566 (2.2)	9682 (8.2)
Heart failure, arrhythmia or valvular heart disease	12,437 (4.5)	1908 (1.2)	10,529 (9.0)
Psychiatric diseases	10,108 (3.7)	6301 (4.0)	3807 (3.2)

<sup>1</sup> 45–65 years old; <sup>2</sup> ≥65 years old; <sup>3</sup> defined as presenting with a prevalence >3% in the population; sd: standard deviation; 95CI: 95% confidence interval.

### 3.2. Potentially Inappropriate Medications in Chronic Polypharmacy

In 2016, among older adults with chronic polypharmacy 18,036 (64.8%) had at least one chronic PIM, as defined by the Beers/Laroche criteria. Among older adults with chronic hyperpolypharmacy, 2544 (88.7%) had at least one chronic PIM. Overall, chronic PIMs represented 13.5% of the total exposure to drugs involved in chronic polypharmacy. Pump proton inhibitors (PPIs) used without any concomitant use of chronic nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids were the most frequent chronic PIMs (43.4% of older adults with chronic polypharmacy; 67.1% of older adults with chronic hyperpolypharmacy; 6.3% of total exposure to chronic drugs). These were followed by short- and intermediate-acting benzodiazepines (13.7% of older adults with chronic polypharmacy; 23.0% of older adults with chronic hyperpolypharmacy; 2.0% of total exposure) and hypnotics (6.1% of older adults with chronic polypharmacy; 13.3% of older adults with chronic hyperpolypharmacy; 0.8% of total exposure) (Table 2. Full results are available in Table S6, descriptions of criteria are presented in Table S1).

In 2016, among middle-aged adults with chronic polypharmacy 4009 (46.2%) had at least one chronic PIM, as defined by the PROMPT criteria. Among middle-aged adults with chronic hyperpolypharmacy, 570 (75.0%) had at least one chronic PIM. Overall, chronic PIMs represented 10.4% of the total exposure to drugs involved in chronic polypharmacy. Short- and intermediate-acting benzodiazepines were the most frequent PIMs (16.1% of middle-aged adults with chronic polypharmacy; 30.5% of adults with chronic hyperpolypharmacy; 2.7% of total exposure to chronic drugs). They were followed by long-acting sulfonylureas (12.3% of middle-aged adults with chronic polypharmacy; 23.4% of middle-aged adults with chronic hyperpolypharmacy; 1.9% of total exposure) and long-acting benzodiazepines (10.1% of middle-aged adults with chronic polypharmacy; 18.2% of middle-aged adults with chronic hyperpolypharmacy; 1.5% of total exposure) (Table 3. Full results are available in Table S7, description of criteria are in Table S2).

**Table 2.** Prevalence and exposure to the most frequent potentially inappropriate medications in older adults with chronic polypharmacy according to the Beers criteria and Laroche list.

	Older Adults with Chronic Polypharmacy <i>n</i> = 27,834	Older Adults with Chronic Hyperpolypharmacy <i>n</i> = 2868	Cumulated Exposure to PIMs in Older Adults with Chronic Polypharmacy (%)
Potentially inappropriate medications-broad <sup>1</sup>	18,036 (64.8)	2544 (88.7)	13.5
Potentially inappropriate medications-narrow <sup>2</sup>	10,220 (36.7)	1730 (60.3)	6.7
Proton pump inhibitors (PPIs) without chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids <sup>1</sup>	12,073 (43.4)	1924 (67.1)	6.3
Benzodiazepines—short- and intermediate-acting	3807 (13.7)	660 (23.0)	2.0
Hypnotics (z-drugs)	1688 (6.1)	382 (13.3)	0.8
Central alpha-agonists	1404 (5.0)	308 (10.7)	0.8
Antidepressants (Tricyclic antidepressants (TCAs)/Paroxetine)	1324 (4.8)	228 (8.0)	0.7
Benzodiazepines—long-acting	1271 (4.6)	286 (10.0)	0.6
Sulfonylureas—long-acting	1071 (3.9)	201 (7.0)	0.6
First-generation antihistamines	659 (2.4)	159 (5.5)	0.5
Anticholinergic antispasmodics	626 (2.3)	119 (4.2)	0.3
Antidepressants (TCA, Selective serotonin reuptake inhibitors (SSRIs), or Serotonin–norepinephrine reuptake inhibitors (SNRIs)) with history of falls or fractures <sup>1</sup>	420 (1.5)	73 (2.6)	0.2
Non-cyclooxygenase-selective NSAIDs, oral without PPI <sup>1</sup>	418 (1.5)	65 (2.3)	0.2
Ergoloid mesylates	380 (1.4)	71 (2.5)	0.2

PPIs: proton pump inhibitors; NSAIDs: nonsteroidal anti-inflammatory drugs; TCAs: Tricyclic antidepressants; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin–norepinephrine reuptake inhibitors. Data are expressed as n (%);<sup>1</sup> considering both fully and partially applicable criteria;<sup>2</sup> considering only fully applicable criteria;<sup>1,2</sup> more details are provided in Table S1.

**Table 3.** Prevalence and exposure to the most frequent potentially inappropriate medications in middle-aged adults with chronic polypharmacy according to the PROMPT criteria.

	Middle-Aged Adults with Chronic Polypharmacy <i>n</i> = 8666	Middle-Aged Adults with Chronic Hyperpolypharmacy <i>n</i> = 760	Cumulated Exposure to PIM in Middle-Aged Adults with Chronic Polypharmacy (%)
Potentially inappropriate medications	4009 (46.2)	570 (75.0)	10.4
Benzodiazepines—short- and intermediate-acting	1395 (16.1)	232 (30.5)	2.7
Sulfonylureas—long- acting	1069 (12.3)	178 (23.4)	1.9
Benzodiazepines—long- acting	879 (10.1)	138 (18.2)	1.5
Opioid (use without laxative)	639 (7.4)	143 (18.8)	1.1
Hypnotics (z-drugs)	637 (7.4)	115 (15.1)	1.0
First generation antihistamines	450 (5.2)	90 (11.8)	0.7
Association of esomeprazole/omeprazole and clopidogrel <sup>1</sup>	251 (2.9)	59 (7.8)	0.8
Oral corticoid (without use of bisphosphonate)	176 (2.0)	38 (5.0)	0.3
Tricyclic antidepressants in first-line treatment	107 (1.2)	16 (2.1)	0.2
Chronic NSAIDs	80 (0.9)	14 (1.8)	0.1

NSAIDs: nonsteroidal anti-inflammatory drug; PIM: potentially inappropriate medications; PROMPT: Prescribing Optimally in Middle-aged People’s Treatments; Data are expressed as n (%).<sup>1</sup> These criteria considered both drugs (esomeprazole or omeprazole and clopidogrel) as potentially inappropriate, so the density (0.8%) of exposure is twice the exposure of each drug individually (0.4% each).

#### 4. Discussion

In this study, we found that the prevalence of PIM in older adults, defined according to the Beers and Laroche criteria, was substantial and increased with the number of medications involved in chronic polypharmacy (64.8% of older adults with chronic polypharmacy and 88.7% with chronic hyperpolypharmacy). We also observed this trend with the PROMPT criteria in middle-aged individuals (46.2% of middle-aged individuals with chronic polypharmacy and 75.0% with chronic hyperpolypharmacy). The most frequent PIM were PPIs, benzodiazepines and derivatives, long-acting sulfonyleureas, opioids, central alpha-agonists, and antidepressants.

In the literature, an increase in the prevalence of PIM with polypharmacy has already been observed in both inpatients and ambulatory patients [28,29], especially in the elderly [30,31]. Similarly, PPIs, benzodiazepines, and sulfonyleureas are frequent PIMs reported.

PPIs were the most frequent PIM in a recent study based on the Beers criteria, which found that gastrointestinal medications—referring to metoclopramide, mineral oil, or PPIs—were the most frequent PIMs (35.6% of adults) [28]. In Ireland, PPIs above maintenance dosage for greater than 8 weeks were the second most frequent PIM, according to the PROMPT criteria [32]. We could not assess inappropriate PPIs in middle-aged adults because the PROMPT criteria required the maintenance dose, and this information was not available from the EGB. However, a previous study showed that almost a quarter (16 million people) of the French population had a prescription of PPIs in 2015. Among them, half started the treatment to prevent adverse gastrointestinal events. However, 80% did not need this type of prevention according to the guidelines [33]. In 2012, PPIs were among the highest-selling classes of drugs in the United States, and esomeprazole was the top selling of all drugs [34]. Our study showed that PPIs are often prescribed chronically and inappropriately to patients who are already using many chronic treatments. PPIs can be associated with various adverse drug reactions such as fractures or infections, even if these occurrences are rare [35,36]. Altogether, these results highlight the need for a more rational use of PPIs. Targeting PPIs in polypharmacy could be an efficient first step to reduce their use, as these are the most prevalent among patients.

Benzodiazepines and derivatives are also psychotropic drugs often reported to be overwhelmingly used. France is, for instance, the country with the second highest level of benzodiazepine use in Europe, with an overall prevalence of long-term use estimated at 15% in new users [37,38]. This number is preoccupying especially because it could involve patients with multiple comorbidities and increase the risk of adverse drug reactions [39,40]. Although these drugs are frequently prescribed at the end of life, the low all-cause mortality in 2016 and our definition of chronic drug use highlighted the fact that benzodiazepines mainly concern healthy people.

Long-acting sulfonyleureas also constitute a major concern. A population-based study in the United Kingdom showed that sulfonyleureas, even as a second-line treatment, were associated with an increased risk of myocardial infarction, all-cause mortality, and severe hypoglycemia, compared with metformin monotherapy [41]. In older adults, the Beers criteria defined anticholinergic antidepressants, such as tricyclic antidepressants or paroxetine, as also of concern, especially because other selective serotonin reuptake inhibitors (SSRIs) or classes of antidepressants might be appropriate [25]. These two classes (i.e., long-acting sulfonyleureas and anticholinergic antidepressants) were examples of classes for which interventions aiming to reduce PIM should lead to treatment switches, which would result in improving the appropriateness of patients' treatment without lowering the importance of chronic polypharmacy.

Our study used the Beers, Laroche, and PROMPT criteria, but researchers can use many other tools to identify PIMs. A meta-analysis on this topic has referenced 36 different PIM lists, and many were derived from the Beers criteria [24]. The Beers and Laroche criteria defined drugs that are potentially inappropriate but not definitely inappropriate. This means that these drugs should be avoided in most individuals, according to the recommendations and statements listed, but some exceptions could exist [42]. Although PIMs could be appropriate in particular and rare situations, the high prevalence of the main PIMs found in our study seemed incompatible with only appropriate use in clinical conditions.

This study was completed with some strengths and limitations that are mainly related to the nature of the database used. The EGB database provided an exhaustive recording of outpatient medical reimbursements, hospitalization diagnosis codes, and lengths of stay, which allowed us to consider all of the drug reimbursements of each subject in 2016, enabling us estimate chronic polypharmacy and potentially inappropriate medication. In addition, the EGB database is highly representative of the French population [17]. Conversely, the durations of prescriptions were not available from the EGB. However, this information existed owing to a repeated dedicated survey focusing on prescription lengths performed from a representative sample of French physicians, the results of which were used to estimate treatment durations in our study [18]. The EGB did not include over-the-counter (OTC) drugs, as they are not reimbursed, which was a limitation in the complete identification of drug treatments. If this was of theoretical importance, this might have had a negligible impact in our study that focused on chronically used drugs—i.e., drugs used continuously for at least six months. Finally, the most important limitation was that the existing PIM lists did not allow for the identification of all inappropriate situations. Indeed, a study evaluating the performance of the Beers criteria showed that clinicians and pharmacists would prescribe inappropriate drugs twice more than the Beers criteria recommended [43]. Consequently, we combined the Beers list with the Laroche list, which reflects the opinion of different experts with a strong knowledge of French clinical practice, and used a pharmacological evaluation for the selection of PIM [26]. However, using data from the EGB, we could only partially apply the PIM criteria because not all the required information (clinical, lab, maintenance dosage) was available from the EGB. In this aspect, our estimate of the prevalence of chronic PIM within individuals with polypharmacy is likely to constitute an underestimation. The awareness of deprescribing has been rising recently. However, the major PIMs we identified in 2016 will continue to be a major concern in 2020 since their use and prescription may also be due to high patient demands. Longitudinal studies quantifying PIMs over the last few years are required. This study was reported using the observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE; Table S8) [44].

## 5. Conclusions

Our results provided us with two important types of information. First, chronic polypharmacy, and chronic PIM within it, was highlighted as an important concern already in middle-aged adults, showing that interventions aiming to reduce the burden of PIM should not be limited to older adults. Second, it helped in identify the drugs most involved in chronic PIM use both in middle-aged and older adults and that should be primarily targeted by such interventions. From this perspective, PPIs and benzodiazepine appeared once again as a major feature in drug overuse, extending to patients with an already high drug intake burden.

**Supplementary Materials:** The following are available online at <http://www.mdpi.com/2077-0383/9/11/3728/s1>, Table S1: Description of each Beers/Laroche inappropriate criteria, Table S2: Description of each PROMPT inappropriate criteria, Table S3: Overlaps in combined Beers/Laroche list and PROMPT list, Table S4: Prevalences of long term diseases according to chronic polypharmacy in 2016 in older adults, Table S5: Prevalences of long term diseases according to polypharmacy in 2016 in middle-aged adults, Table S6: Prevalence and exposure to potentially inappropriate medications in older adults with chronic polypharmacy according to Beers criteria, Laroche list, Table S7: Prevalence and exposure to potentially inappropriate medications and interactions in middle-aged adults with chronic polypharmacy according to PROMPT criteria, Table S8: The RECORD statement for pharmacoepidemiology (RECORD-PE) checklist of items, extended from the STROBE and RECORD statements, which should be reported in non-interventional pharmacoepidemiological studies using routinely collected health data.

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## A.6 Discussion des principaux résultats

En France, la part potentiellement inappropriée de la polymédication chronique est importante, représentant deux tiers des personnes âgées et presque la moitié des adultes d'âge moyen. Elle est d'autant plus importante que le nombre de médicaments chroniques augmente. Ces résultats mettent en lumière le fait que la polymédication inappropriée existe aussi bien chez le sujet âgé que chez le sujet adulte d'âge moyen. Les interventions d'optimisation de prescription et de déprescription ne devraient donc pas cibler uniquement les sujets âgés.

Les MPI les plus fréquents sont des médicaments déjà connus comme étant utilisés de façon excessive dans la population française, notamment les benzodiazépines et les inhibiteurs de la pompe à proton. D'autres comme les sulfamides hypoglycémifiants possèdent des alternatives avec une meilleure balance bénéfice-risque. Les MPI les plus fréquents devraient être les premiers médicaments visés par des interventions de déprescription, notamment chez les patients en polymédication qui sont déjà concernés par une lourde exposition médicamenteuse.

Cependant l'application des critères de Beers, de la liste de Laroche, des critères de PROMPT était limitée dans l'EGB notamment en raison de l'impossibilité d'identifier certaines conditions cliniques justifiant l'aspect inapproprié d'un médicament.

## B Part inappropriée de la polymédication au sein d'une population de vétérans aux Etats-Unis

### B.1 Problématique

L'identification de MPI dans la population française à partir des données de l'Assurance Maladie était possible grâce à l'application de critères explicites tels que les listes Beers, Laroche ou PROMPT [23,68,69] mais pourrait s'avérer incomplète en raison de données peu disponibles concernant les informations cliniques ou biologiques pour l'identification de MPI. En raison du caractère international de la polymédication et des limites inhérentes aux bases de données Françaises, une étude de la polymédication chronique et de sa part inappropriée à partir d'une base de données étrangère s'avérait pertinente. La base de données des vétérans américains, riche en données cliniques et biologiques, a donc été choisie afin de compléter la description réalisée à partir des données de l'Assurance Maladie Française [50].

### B.2 Objectifs

La base de données des vétérans est riche en données cliniques et permet une application optimale des critères explicites d'identification des MPI afin de compléter la description issue de la population française. De plus cette population est particulièrement vulnérable à la polymédication en raison du mode de vie et de la prévalence des multimorbidités. L'objectif était d'étudier la prévalence des MPI chez les vétérans en fonction de la polymédication chronique.

### B.3 Considérations méthodologiques

Une étude transversale a été réalisée à partir des données de la base médico-administrative des vétérans américains (VA). Les vétérans nés entre 1945 et 1965 étaient inclus dans une cohorte appelée *Birth cohort* et ces données étaient disponibles immédiatement pour les analyses. De plus, cette cohorte était représentative de l'ensemble des vétérans américains et incluait des individus âgés de moins de 65 ans et des individus âgés de plus de 65 ans. A partir des informations de cette cohorte, les individus affiliés au VA depuis le 1<sup>er</sup> octobre 2014, vivant au 1<sup>er</sup> octobre 2015 ont été inclus dans l'étude et leurs informations collectées jusqu'au 30 septembre 2016. Un médicament chronique a été défini suivant l'indicateur d'exposition chronique journalière défini précédemment, c'est à dire une exposition d'au moins 183 jours consécutifs. La polymédication et l'hyperpolymédication chronique ont été définis par l'utilisation concomitante d'au moins, respectivement, 5 et 10 médicaments chroniques.

Les MPI ont été identifiés par les critères de Beers et la liste Laroche combinés. Suivant leur applicabilité dans la base VA, ils ont été classés en critères applicables ou non applicables. La prévalence des MPI a été décrite chez l'ensemble des vétérans, chez les vétérans en polymédication chronique et chez les vétérans en hyperpolymédication chronique. Ces critères ont été utilisés aussi bien chez les moins de 65 ans que chez les plus de 65 ans, notamment parce qu'ils sont basés sur des arguments pharmacologiques qui peuvent concerner tout âge. Nous n'avons pas utilisé les critères de PROMPT car la base VA nous paraissait suffisamment riche en données cliniques.

#### B.4 Résumé des travaux et principaux résultats

Ont été inclus dans l'étude 2 748 705 vétérans âgés de 49 à 70 ans, avec une majorité d'hommes (93,3 %). Les pathologies chroniques les plus fréquentes étaient les hyperlipidémies (66,0 %) et l'hypertension (64,8 %). Le nombre de sujets en polymédication et hyperpolymédication chronique étaient respectivement 834 436 (30,4 %) et 201 375 (7,3 %). La prévalence d'utilisation d'au moins un MPI était de 30,5 % et augmentait chez les vétérans en polymédication chronique (67,0 %) et d'autant plus chez ceux en hyperpolymédication chronique (84,3 %). Les MPI les plus fréquents étaient les IPP (12,9 % de l'ensemble des vétérans ; 27,9 % des vétérans en polymédication chronique ; 33,8 % des vétérans en hyperpolymédication chronique), les sulfamides hypoglycémiantes (6,2 % ; 16,2 % ; 22,5 %), les AINS (4,8 % ; 10,1 % ; 12,6 %), les laxatifs stimulants (3,0 % ; 8,7 % ; 19,9 %), l'usage d'insuline rapide sans traitement par insuline lente (2,7%, 7,0%, 11,6%), les antidépresseurs à effet anticholinergique (2,1% ; 5,1 % ; 8,4%) et les benzodiazépines (1,7%, 4,3%, 7,7%).

Cette étude a fait l'objet d'un article soumis à *International Journal of Epidemiology (IJE)*.

B.5 Article soumis : The burden of potentially inappropriate medications in United States veterans aged 49-70 years increases with chronic polypharmacy

*Guillot J, Rentsch CT, Gordon KS, Justice AC, Bezin J. The burden of potentially inappropriate medications in United States veterans aged 49-70 years increases with chronic polypharmacy. Int J Epidemiol. (1<sup>ère</sup> soumission).*

# The burden of potentially inappropriate medications in United States veterans aged 49-70 years increases with chronic polypharmacy

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## Abstract

**Background:** United States (US) veterans are at increased risk of polypharmacy because of their multimorbidities and lifestyle. The study objective was to describe the prevalence of potentially inappropriate medications (PIMs) according to polypharmacy in US veterans born 1945 – 1965.

**Methods:** We conducted a cross-sectional study using electronic health records available through the US Department of Veterans Affairs national corporate data warehouse. Data on all veterans born 1945 – 1965, accessing care from October 1<sup>st</sup>, 2014 to October 1<sup>st</sup>, 2015 were extracted. Data on veterans alive on October 1<sup>st</sup>, 2015 were collected through September 30, 2016. Chronic drug use was defined as an uninterrupted daily use lasting at least 6 months. Chronic polypharmacy was defined by five chronic drug uses or more, and chronic hyperpolypharmacy was ten chronic drug uses or more. PIMs were defined by Beers and Laroche lists.

**Results:** Among veterans aged 49-70 years (n=2 748 705), prevalence of chronic polypharmacy and hyperpolypharmacy were 30.4% and 7.3%, respectively. Prevalence of PIMs was 30.5% and increased with polypharmacy (67.0%) and hyperpolypharmacy (84.3%). The most frequent PIMs among all veterans, those with polypharmacy, and those with hyperpolypharmacy were: proton pump inhibitor (12.9%; 27.9%; 33.8%, respectively), sulfonylureas (6.2%; 16.2%; 22.5%), Nonsteroidal anti-inflammatory drugs (4.8%; 10.1%; 12.6%), stimulant laxatives (3.0%; 8.7%; 19.9%), Insulin sliding scale (2.7%, 7.0%, 11.6%), antidepressants (2.1%; 5.1%; 8.4%), benzodiazepines (1.7%, 4.3%, 7.7%) and first generation antihistamines (1.6%; 4.2%; 8.6%).

### Conclusion:

The prevalence of PIMs increased with polypharmacy and hyperpolypharmacy. The most frequent PIMs should be targeted and prioritized for deprescribing.

**Keywords:** Polypharmacy; Appropriateness; Potentially inappropriate medications; Drug utilisation study; observational study; Veterans

### **Key messages:**

- Chronic polypharmacy is a concern in nearly one third of veterans and hyperpolypharmacy nearly one in ten.
- Potentially inappropriate medications (PIMs) more than doubled in veterans with polypharmacy and almost tripled in veterans with hyperpolypharmacy.
- Most frequent PIMs were proton pump inhibitors (PPIs), sulfonylureas and nonsteroidal anti-inflammatory drugs (NSAIDs).
- Given that both polypharmacy and PIMs are risk factors of adverse drug events. Interventions to reduce PIMs in polypharmacy in veterans are urgently needed.

## **Introduction**

In 2019, 9% of the worldwide population was aged 65 or over and it is estimated to increase to 16% by 2050, representing one in six people in the world [1]. Polypharmacy, usually defined as the use of five or more medications at the same time [2,3], is common with increasing age [4]. In the United States, polypharmacy rates increased from 8.2% to 15% between 1999 and 2012 among middle-aged and older people [5]. It is potentially motivated by the therapeutic management of coexisting diseases that are prevalent in the United States (80% of Medicare expenses concerned patients with at least 4 diseases) [6]. However, polypharmacy is associated with adverse drug events [7], drug-drug interactions [8], non-adherence [9], cognitive impairment [10], falls [11], hospitalisations [12] and mortality [13].

In addition, an increasing number of medications is associated with an increasing risk of having potentially inappropriate medications (PIMs), defined as drugs for which risks outweigh potential benefits [14]. In recent years, development of tools aimed at detecting PIMs have intensified, particularly PIMs lists [15]. PIMs are mostly studied in older adults because of their higher prevalence and risks of adverse events [16]. However, the prevalence of polypharmacy before older age suggests that it is also important to consider PIMs and polypharmacy in middle-aged people [17]. Identifying



PIMs in order to deprescribe has also been considered in veterans in old age [18,19] or with multiple conditions [20]; polypharmacy, due to multiple comorbidities and lifestyle, have been well established in United States (US) Veterans [21]. However, it remains unclear how the prevalence of PIMs varies in this population according to polypharmacy. In this context, the aim of this study was to describe PIMs according to polypharmacy among veterans aged 49 to 70 years.

## **Methods**

We conducted a cross sectional study using data from electronic health records available through the United States Department of Veterans Affairs (VA) national Corporate Data Warehouse (CDW).

The VA provides healthcare benefits to more than 9 million veterans yearly through the Veteran Health Administration. The CDW record is nationwide since 1997 and includes all pharmacy utilisation, inpatient and outpatient diagnosis indicated by International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9) codes, demographics and vital status. From this data was created the Birth Cohort that includes more than 4.5 million veterans born from 1945-1965. Data on veterans from the Birth Cohort who were alive on October 1<sup>st</sup>, 2015 were collected through September 30, 2016 or date of death whichever occurred first. Those who did not utilise the VA healthcare system between October 1<sup>st</sup>, 2014 and September 30, 2015 were excluded.

All drugs were considered regardless of route of administration (systemic or not). Specific therapeutic classes were excluded: antiseptics, soap, deodorants, keratolytics, diagnosis agents, vaccines, immunoglobulins, contact lens, eye washes, dental agents, devices. Fixed dose combinations were split into active ingredients for systemic and oral drugs. Topical combinations were not split and counted as one medication. They include dermatological, nasal, optical and otic agents. Chronic drug use was defined as an uninterrupted daily use lasting at least 183 days, allowing for a grace period between fills and after the last fill of 20% the prescription duration. Chronic polypharmacy was defined by the chronic use of five drugs or more on a same day during the study period; chronic hyperpolypharmacy was defined by the chronic use of ten drugs or more.

PIMs were defined among chronic medications by both Beers and Laroche lists [22,23]. Among the Beers criteria, updated in 2019, medications that are potentially inappropriate in most older adults, and those that should be avoided in older adults with certain conditions were used in this study. We also considered PIMs contraindicated with chronic seizure or epilepsy who were omitted from the 2019 update because they apply to both elderly and young people (present in the 2015 Beers version) [24]. The Laroche criteria published in 2007 list drugs that could either be inappropriate most of the time or with certain clinical conditions. This list can be used to identify PIMs that are not listed in Beers list. If a medication was mentioned differently on the lists but one of them demands specific dosage or condition to be applied, the less demanding list applied. Some of criteria were not applicable in the CDW data because they should be avoided only with a not identifiable disease (e.g benign prostatic hyperplasia), in a specific context in a disease (e.g PIMs with heart failure were identifiable but not PIMs with heart failure with reduced ejection fraction) or a specific indication (e.g aspirin not considered because it can be used as an antiplatelet or an analgesic). List of used criteria and their requirement are listed in supplementary material (Table S1 and S2). PIMs were considered as any drug identified as potentially inappropriate by at least one applicable criterion of Beers and/or Laroche lists regardless of age.

Prevalence of chronic polypharmacy/hyperpolypharmacy was defined as the number of subjects who had at least one day of chronic polypharmacy/hyperpolypharmacy from October 1<sup>st</sup>, 2015 to September 30, 2016. Prevalence of PIMs was defined as the number of veterans with at least one day with any chronic PIMs. All analyses were stratified on age and inappropriateness analysis were also stratified by polypharmacy and hyperpolypharmacy. Age classes were defined as older adults ( $\geq$  65 years old) and younger adults (< 65 years old) [25]. All data management and analyses were performed using SAS software version 9.4 (SAS Institute, North Carolina, USA).

## Results

Information concerning 2 748 705 veterans were analysed. They were mostly male (93.3%) and 45.4% of veterans were aged 65 and over. In the birth cohort, the most frequent chronic conditions were hyperlipidemia (66.0%), hypertension (64.8%), depression (34.3%) and diabetes (30.1%; Table 1). From October 1<sup>st</sup>, 2015 to September 30, 2016, prevalence of chronic polypharmacy was 30.4% and prevalence of chronic hyperpolypharmacy was 7.3%. Prevalences were higher in men than in women (respectively 30.8% vs. 24.9% for chronic polypharmacy and 7.4% vs. 5.9% for chronic hyperpolypharmacy) and higher in veterans aged 65 and over than in younger veterans (respectively 36.1% vs. 25.6% for chronic polypharmacy and 9.1% vs. 5.8% for chronic hyperpolypharmacy; Table 2).

According to Beers and Laroche criteria, 30.5% of veterans had at least one day with any chronic PIMs. This prevalence increased with chronic polypharmacy (67.0%) and chronic hyperpolypharmacy (84.3%). Proton pump inhibitors (PPIs) without any indication (chronic nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin or corticoid use, esophagitis, hypersecretory conditions or helicobacter pylori) were the most frequent PIMs in veterans (12.9% received inappropriate PPIs in 2016) and this prevalence increased among veterans with chronic polypharmacy (27.9%) and chronic hyperpolypharmacy (33.8%). Other most common PIMs included: sulfonylureas (6.2% overall; 16.2% of veterans with chronic polypharmacy and 22.5% with chronic hyperpolypharmacy) including mostly glipizide (5.7%; 14.9%; 20.6%), NSAIDs use without concurrent use of PPIs (4.8%; 25.9%; 34.7%), stimulant laxatives (3.0%; 8.7%; 19.9%), insulin sliding scale (2.7%; 7.0%; 11.6%), antidepressants (TCA and paroxetine; 2.1%; 5.1%; 8.4%); benzodiazepines (1.7%; 4.3%; 7.7%) including mostly long acting benzodiazepines (1.2%, 3.0%, 5.4%), first generation antihistamine (1.6%; 4.2%; 8.6%), skeletal muscle relaxants (1.6%; 4.3%; 8.7%) and nonbenzodiazepine hypnotics (Z-drugs; 1.2%, 3.0, 5.1%). All prevalences of PIMs increased in veterans with chronic polypharmacy and hyperpolypharmacy (most frequent PIMs presented in Table 3, all PIMs are presented in Table S3).

## Discussion

We describe in this study that PIMs concerned almost one third of veterans and that this prevalence increased among veterans with polypharmacy (more than two third) and hyperpolypharmacy (more than 8 in 10). Inappropriate use of PPIs, sulfonylureas and NSAIDs represented the biggest part of PIMs.

The high prevalence of polypharmacy and PIMs are not specific to US veterans. Among noninstitutionalized US adults, polypharmacy concerned 15% of the population in 2011 and 40% of people aged 65 and over [5]. In New-Zealand in 2013, chronic polypharmacy concerned 29.5% of people aged 65 years and over [26]. PIMs are also prevalent in most population representing for instance 18.0% of community dwelling people in Italy and 17.0% in the USA [27,28]. As in US veterans, prevalence of PIMs is often higher in people with polypharmacy than in population, whether hospitalized or not (Table 4).

Polypharmacy and PIMs are a major concern especially since both are risk factors for harmful adverse events. In the Southeast United States, 14.3% of patients with PIMs had a drug adverse event in the 30 days following the prescription, compared to 4.3% for patients without PIMs, and were also twice as likely to be hospitalized [31]. Additionally, polypharmacy is known to increase the risk of various adverse events such as hospitalizations, falls and even death [13]. Potentially, combining the prescription of PIMs in patients with polypharmacy could also synergistically increase this risk of adverse events [14]. Even if this is not the case, the risk associated with the use of PIMs in polypharmacy or not requires the identification of drugs potentially eligible for deprescribing.

PPIs were the most common PIMs in our study and several prior studies. In ambulatory patients in Saudi Arabia, gastrointestinal PIMs (including metoclopramide, mineral oil or PPIs) were the most frequent PIMs (35.6% of adults) [30]. Furthermore, inappropriate use of PPIs concerned 6.9% middle-aged adults in Northern Ireland and 17.7% in Republic of Ireland, being respectively the second and first most potentially inappropriate medications [32]. PPIs could be associated with various adverse

events in older adults such as *Clostridium difficile* infections, kidney toxicity or osteoporotic fractures [33]. In addition, in US veterans, PPIs use was shown to be associated with mortality due to cardiovascular disease, chronic kidney disease and upper gastrointestinal cancer [34]. The high prevalence of PPIs use also represents an important cost for the health care system. In 2012, PPI were among the highest-selling classes of drugs in the United States; esomeprazole being the top-selling of all marketed drugs [35]. Appropriate short-term PPIs prescriptions becoming potentially inappropriate at long-term, monitoring prescription of PPIs for deprescribing could thus be a source of reducing costs and avoidable events [36].

According to Beers list, chronic NSAIDs and PPIs are both appropriate as long as they are used at the same time, PPIs preventing NSAIDs gastrointestinal adverse effects [22,37]. In addition to PPIs, inappropriate NSAIDs were common in US veterans. These treatments are often initiated at the same time [38]. It would appear that one or the other drug was stopped without appropriate attention to the entire medication list. These two treatments represent a major proportion of the entire burden of PIMs in US veterans.

Unlike in prior studies, especially in Europe or in China, benzodiazepines were not the most frequent psychiatric PIMs in US veterans [39–41]. The high prevalence of post-traumatic stress disorder (PTSD) in veterans can explain chronic anxiety and justify the use of short acting benzodiazepine according to Beers criteria. However, chronic use of long acting benzodiazepine or hypnotics which are never indicated remained frequent and of concern. Antidepressants (TCA and paroxetine) and first generation antihistamines are classified as PIMs because of their anticholinergic properties. These two classes represented the most frequent psychiatric PIMs in US veterans. Frequent PIMs presenting anticholinergic effects are not only psychiatric; For instance, chronic skeletal muscle relaxants were frequent in veterans despite the risk of adverse events associated [42]. Since multiple medications has anticholinergic properties, cumulative anticholinergic effect was frequently described in polypharmacy and was associated with mortality and harmful events such as

cardiovascular events and admissions for falls/fractures and dementia/delirium [43]. Complementary to PIMs lists identifying anticholinergic drugs, index summarizing total burden of anticholinergic drugs were developed and could be used to identify high-risk patients who could benefit from anticholinergic drug deprescribing [44,45].

A limit of our study is that we used only the Beers and Laroche lists to identify PIMs. Beers is one of the most widely known list and was developed for the United States but there are many other lists, each developed for specific circumstances and countries, suggesting the burden of PIMs among veterans could be even more substantial than we have estimated [15]. One limit of the Beers list is that it was created to help clinician to identify PIMs in older adults but it cannot identify all inappropriate drugs [46]. Consequently, we combined Beers and Laroche lists since both reflect the opinion of experts and used a pharmacological evaluation for the selection of PIMs. [23]. For Instance, the Beers criteria identified only long-acting sulfonylureas as PIMs. In contrast, the Laroche list included glizipine, an intermediate-acting sulfonylurea with a prevalence ten times higher than all the long-acting sulfonylureas in our study. All sulfonylureas are associated with an increased risk of myocardial infarction, all-cause mortality, and severe hypoglycemia [47]. Although prescription of these drugs decreased in the US from 2009 to 2015, some are still a major concern for veterans for whom metformin monotherapy would be a safer alternative [48]. According to Laroche criteria, insulin is an alternative. However, the use of rapid-acting insulin without concurrent use of long-acting insulin (Insulin sliding scale) is inappropriate according to Beers, and was common in veterans. Using both lists, we found that a major part of PIMs are due to an inappropriate treatment of diabetes, which is among the most frequent diseases in veterans. The 2015 version of Beers was updated in 2019 and PIMs that were not specifically inappropriate for older adults were removed. For instance, we elected to retain PIMs such as those that in patients with chronic seizure or epilepsy (they can lower the seizure threshold at any age) [22,24]. Stimulant laxatives are another example. They were considered inappropriate in the 2003 Beers version except in the presence of opiate analgesic use, but removed in the 2012 version [49]. The Laroche list defined them as PIMs and

allowed us to highlight their high prevalence in veterans whereas osmotic laxative would be a safer alternative [23]. Together, these PIMs added a major and unnecessary burden to several major diseases among veterans.

Our study has other limits, the VA eliminates insurance-associated barriers to care and medication acquisition. Therefore, our results may not be generalizable to a system where cost and insurance are paramount determinants of healthcare utilization. Furthermore, the VA population is predominantly male and our analysis only focused on veterans born in the 1945-1965 period. However, this range covers both middle aged and elderly providing people with prevalent chronic diseases. Lastly, our data does not include over-the-counter (OTC) drugs if they are not purchased at the VA which is a limitation for the complete identification of drug treatments. This might have had a negligible impact in our study that focused on chronically used drugs. VA data also have several strengths. The VA health system is America's largest integrated health care system providing comprehensive services to over 9 million Veterans each year via approximately 1,200 sites of care [50] and represents a large proportion of racial and ethnic minority patients. The accuracy and exhaustiveness of pharmacy data and diagnosis allowed us to apply Beers and Laroche criteria accurately even when specific clinical conditions were needed.

## **Conclusion**

Prevalence of PIMs was high in the US veteran population and increased gradually in the context of polypharmacy and hyperpolypharmacy. Our results helped identifying most involved chronic PIMs for which interventions aiming to reduce their use should be implemented in priority. PPIs, NSAIDs, sulfonylureas, insulin or anticholinergic drugs could thus represent priority targets for drug monitoring considering the possibility of switching to alternatives or the possibility of deprescribing.

## **Additional sections**

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**Data availability statement:** Due to US Department of Veterans Affairs (VA) regulations and our ethics agreements, the analytic data sets used for this study are not permitted to leave the VA firewall without a Data Use Agreement. This limitation is consistent with other studies based on VA data. However, VA data are made freely available to researchers with an approved VA study protocol.

**Ethic Statement:** This study was approved by the institutional review boards of VA Connecticut Healthcare System and Yale University. It has been granted a waiver of informed consent and is Health Insurance Portability and Accountability Act compliant.

**Conflict of interest statement:** None declared



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Table 1 Characteristics of veterans aged 49-70 years in 2016 according to polypharmacy

	Birth cohort		Chronic polypharmacy		Chronic Hyperpolypharmacy	
	2 748 705		834 436		201 375	
Age – mean(sd)	62	(5.8)	63	(5.3)	64	(5.1)
Age – (≥ 65) – n(%)	1 249 119	(45.4)	451 201	(54.1)	114 172	(56.7)
Sex – male - n(%)	2 563 239	(93.3)	788 335	(94.5)	190 397	(94.5)
Race/Ethnicity – n(%)						
White	1 888 697	(68.7)	603 571	(72.3)	150 084	(74.5)
Black	558 521	(20.3)	154 715	(18.5)	33 830	(16.8)
Hispanic	164 378	(6.0)	47 705	(5.7)	11 007	(5.5)
Other	137 109	(5.0)	28 445	(3.4)	6454	(3.2)
Chronic diseases <sup>1</sup> – n(%)						
Hyperlipidemia	1 813 447	(66.0)	704 626	(84.4)	180 298	(89.5)
Hypertension	1 780 446	(64.8)	732 390	(87.8)	186 816	(92.8)
Other depression (formerly mild depression)	942 054	(34.3)	405 048	(48.5)	120 910	(60.0)
Diabetes	826 715	(30.1)	438 752	(52.6)	132 637	(65.9)
Pulmonary disorder	611 315	(22.2)	294 975	(35.4)	97 771	(48.6)
OLD (asthma and COPD codes combined)	589 441	(21.4)	284 826	(34.1)	94 805	(47.1)
PTSD	560 230	(20.4)	264 035	(31.6)	83 195	(41.3)
Alcohol Abuse	552 995	(20.1)	198 928	(23.8)	51 392	(25.5)
MI/CAD	517 395	(18.8)	281 136	(33.7)	90 184	(44.8)
Anxiety	517 012	(18.8)	224 151	(26.9)	68 318	(33.9)
COPD	489 461	(17.8)	247 688	(29.7)	84 587	(42.0)
Major depression	433 809	(15.8)	202 475	(24.3)	65 195	(32.4)

<sup>1</sup>The twelve most frequent chronic disease identified in the birth cohort are listed. OLD: Obstructive Lung Disease. COPD: Chronic obstructive pulmonary disease. PTSD: Post-traumatic stress disorder. MI/CAD: Myocardial infarction/Acute coronary disease

Table 2 Prevalence of chronic polypharmacy in the veterans aged 49-70 years according to sex and age in 2016

	Birth cohort 2 748 705		Men 2 563 239		Woman 185 466		< 65 years old 1 499 586		≥ 65 years old 1 249 119	
Chronic Polypharmacy	834 436	(30.4)	788 335	(30.8)	46 101	(24.9)	383 235	(25.6)	451 201	(36.1)
Chronic Hyperpolypharmacy	201 375	(7.3)	190 397	(7.4)	10 978	(5.9)	87 203	(5.8)	114 172	(9.1)

Table 3 Prevalence of potentially inappropriate medications (PIMs) defined by Beers and Laroche criteria in veterans aged 49-70 years according to polypharmacy in 2016

	Birth cohort 2 748 705		Chronic polypharmacy 834 436		Chronic Hyperpolypharmacy 201 375	
Potentially inappropriate medications - Overall – n(%)	837 031	(30.5)	559 341	(67.0)	169 842	(84.3)
Pump Proton Inhibitors (Beers31) – n(%)	353 572	(12.9)	232 363	(27.9)	68 155	(33.8)
Sulfonylureas – n(%)	169 007	(6.2)	135 500	(16.2)	45385	(22.5)
Glipizide(LarocheB28) – n(%)	155 316	(5.7)	124 307	(14.9)	41 545	(20.6)
Others (Beers28) – n(%)	14 856	(0.5)	12 263	(1.5)	4279	(2.1)
Nonsteroidal anti-inflammatory drugs (Beers33) – n(%)	131 150	(4.8)	83 944	(10.1)	25 277	(12.6)
Stimulant Laxatives (Laroche17) – n(%)	81 579	(3.0)	72 164	(8.7)	39 982	(19.9)
Insulin sliding scale (Beers26) – n(%)	74 824	(2.7)	58 455	(7.0)	23 431	(11.6)
Antidepressants (Beers14) – n(%)	57 385	(2.1)	42 232	(5.1)	16 878	(8.4)
Benzodiazepines	47 313	(1.7)	35 619	(4.3)	15 560	(7.7)
Short/intermediate acting (Beers17) – n(%)	15 027	(0.6)	11 355	(1.4)	4835	(2.4)
Long acting (Beers18) – n(%)	32 689	(1.2)	24 616	(3.0)	10 902	(5.4)
First-generation antihistamines (Beers1) – n(%)	44 156	(1.6)	35 368	(4.2)	17 231	(8.6)
Skeletal muscle relaxants (Beers35) – n(%)	43 731	(1.6)	36 006	(4.3)	17 513	(8.7)
Nonbenzodiazepine hypnotics (Z-drugs; Beers20) – n(%)	33 186	(1.2)	24 643	(3.0)	10 236	(5.1)

Table 4 Prevalences of PIMs defined by Beers and Laroche criteria according to polypharmacy in our study compared to PIMs defined by Beers criteria in the literature

Authors	years	country	Type of patient	Prevalence PIM	PIM in polypharmacy (nb of drugs <sup>1</sup> )	PIM in hyperpolypharmacy (nb of drugs <sup>1</sup> )	reference
Guillot et al.	2015	USA	Veterans	30.5%	67.0% (≥5)	84.3% (≥10)	
Hudhra et al.	2012	Spain	Hospitalized	22.9%	27.1% (≥6)	32.6% (≥10)	[29]
Alhawassi et al.	2016	Saudi Arabia	ambulatory	57.5%	66.7 (≥5)	NA	[30]
Maio et al.	2001	Italy	community-dwelling with one prescription	18.0%	30.5 (≥6)	37.5 (≥10)	[28]
Lau et al.	2005-2007	USA	community-dwelling with and without dementia	17.0%	23.9% (≥5)	33.6 (≥9)	[27]

<sup>1</sup>Between brackets is indicated the number of drugs which define polypharmacy/hyperpolypharmacy in the corresponding study



## B.6 Discussion des principaux résultats

La prévalence des MPI était élevée chez les vétérans américains avec environ un tiers des vétérans concernés. Cette prévalence augmentait graduellement avec le nombre de médicaments chroniques. Deux tiers des vétérans en polymédication chronique étaient concernés par l'utilisation d'un MPI, et 85 % des vétérans en hyperpolymédication.

Nos résultats ont permis d'identifier les médicaments les plus impliqués dans l'utilisation chronique des MPI pour lesquels des interventions visant à réduire leur utilisation devraient être mises en œuvre en priorité au sein des vétérans. Les IPP, les AINS, les sulfamides hypoglycémifiants, les insulines et les médicaments anticholinergiques pourraient représenter, compte tenu de la possibilité d'alternatives ou de déprescription, des cibles prioritaires pour des mesures de promotion du bon usage des médicaments.

Cette étude apporte des éléments essentiels à la compréhension de la polymédication et de sa part inappropriée chez les vétérans américains. De plus, la comparaison des caractéristiques de la polymédication inappropriée chez les vétérans à ceux de la population française pourrait permettre de mieux comprendre la problématique des MPI en polymédication de façon générale.

## C Comparaisons entre les vétérans américains et la population française

Bien que la population française et celle des vétérans américains soient structurellement différentes, la part de la polymédication chronique inappropriée au sein de ces deux populations est importante. Le but de ce chapitre est de mettre en regard les résultats obtenus à partir de la base française EGB et ceux obtenus à partir de la base des vétérans américains (VA). Nous avons ainsi comparé les résultats des deux études précédentes : les prévalences de la polymédication/hyperpolymédication chronique ont été comparées entre les français de 45 ans et plus (les adultes d'âge moyen de 45 à 64 ans et les personnes âgées de 65 ans et plus) issus de l'EGB et les vétérans américains de 49 à 70 ans. La part inappropriée de la polymédication a été comparé entre les vétérans de 49 à 70 ans et les adultes âgés de 65 ans et plus issus de l'EGB.

Les vétérans américains étaient plus concernés par la polymédication chronique que les français, notamment les adultes d'âge moyen. La polymédication chronique était cinq fois plus importante chez les vétérans de 49 – 64 ans que dans la population française de 45 à 64 ans (25,6 % vs. 5,4 %). Chez les sujets âgés de 65 et plus, la polymédication chronique était également plus importante chez les vétérans (âgés au maximum de 70 ans) que dans la population française (36,1 % vs. 23,7 %).

La prévalence des MPI était similaire chez les vétérans et dans la population française de 65 ans et plus, que ce soit en situation de polymédication chronique (67,0 % vs. 64,8 %, respectivement) ou en situation d'hyperpolymédication chronique (84,3 % vs. 88,7 %) (Tableau 1).

Les IPP étaient majoritaires aussi bien chez les vétérans que dans la population française, la prévalence en France était cependant supérieure à celle chez les vétérans (43,4 % vs. 27,9 %). L'identification des IPP présentait des forces et limites dans les deux bases de données. La base VA, riche en données cliniques permettait d'identifier certaines conditions justifiant l'usage chronique d'un IPP (certaines œsophagites, *Helicobacter pylori*). Cependant, il n'était pas possible de déterminer l'indication de l'aspirine chronique dans la base VA. Les IPP chroniques pris avec de l'aspirine faible dose en tant qu'antiagrégant ont été considéré comme appropriés amenant à une possible sous-estimation des MPI. La prévalence des IPP reste néanmoins élevée chez les vétérans malgré une meilleure identification du contexte clinique. En France, la prévalence a pu être surestimée par l'absence des diagnostics cliniques. Cependant, il est peu probable que cette surestimation soit égale à la différence de plus de 15 % observée par rapport aux vétérans. Les IPP représenteraient donc la majorité de la part inappropriée de la polymédication, avec une surconsommation plus importante en France.

Dans les deux études, les IPP étaient considérés comme appropriés si utilisés de manière concomitante avec un AINS chronique et vice versa. Les IPP et les AINS sont connus pour être souvent initiés en même temps, souvent sans suivre les recommandations. En effet, l'ajout d'IPP à un traitement par AINS sans facteur de risque, ni indication, représenterait 80 % des initiations en France, et serait aussi largement répandu chez les vétérans. Une fois l'arrêt soit des IPP soit des AINS, le traitement ne serait que rarement réévalué, ce qui conduirait à l'usage chronique et inapproprié de l'un des deux traitements [70,71]. Si en France, la prise chronique d'AINS chronique semble s'avérer plutôt rare (1,5 % des sujets en polymédication), cela semble être un problème majeur chez les vétérans (10,1 %). Ces mésusages fréquents des AINS ont déjà été reportés dans cette population, avec notamment le non-respect des posologies journalières [72].

Les données VA permettaient d'identifier les vétérans atteints d'anxiété chronique, condition pour laquelle l'usage de benzodiazépines de demi-vie courte est approprié d'après Beers [68]. Même si l'absence de ces données dans l'EGB a pu mener à une surestimation du mésusage des benzodiazépines de demi-vie courte, il est peu probable que la prévalence des troubles anxieux généralisés en France justifie la prévalence élevée retrouvée dans l'EGB (13,7 % contre 1,4 % chez les vétérans). De plus, la prévalence inappropriée des benzodiazépines de demi-vie longue et des hypnotiques apparentés aux benzodiazépines en polymédication chronique était également plus élevée dans la population française que chez les vétérans (respectivement 4,6 % vs. 3,0 % et 6,1 % vs. 3,0 %). Des études menées chez les vétérans américains soulignent le risque d'effets indésirables et appellent à la prudence dans leur utilisation [73,74]. Ceci pourrait expliquer la plus faible prévalence chez les vétérans. Au contraire, les benzodiazépines sont connues pour être excessivement utilisées en France, malgré les risques d'effets indésirables associés [75–78].

D'autres médicaments étaient identifiés comme MPI fréquents dans les deux populations : les sulfamides hypoglycémifiants, les antidépresseurs, les antihistaminiques et les antispasmodiques à effet anticholinergique. Des interventions de déprescription doivent également cibler ces traitements d'autant plus que des alternatives existent [68,79]. D'autres MPI étaient fréquents dans une seule des deux populations étudiées : par exemple les agonistes alpha centraux en France ou l'insuline rapide chez les vétérans. Certains problèmes spécifiques à un système de santé donné pourraient avoir un impact sur ces différences entre populations. Par exemple les traitements par insuline rapide en complément d'un traitement de fond par insuline lente, totalement pris en charge en France, sont des traitements coûteux aux États-Unis, même pour les vétérans, ceux qui limiteraient leur utilisation [80].

Tableau 1 Médicaments potentiellement inappropriés (MPI) les plus fréquents, définis par les critères combinés de Beers et Laroche, les plus fréquents chez sujets de 65 ans et plus issus de l'EGB et chez les vétérans américains de 49 à 70 ans, en polymédication chronique

	EGB ; sujets de ≥ 65 ans en polymédication chronique		VA ; sujets de 49-70 ans en polymédication chronique	
	27,834		834 436	
Prévalence de MPI – n(%)	18 036	(64,8)	640 201	(67,0)
Inhibiteur pompe à proton – n(%)	12 073	(43,4)	232 363	(27,9)
Antidépresseurs (tricycliques/paroxétine) – n(%)	1 324	(4,8)	42 232	(5,1)
Hypnotiques – n(%)	1 688	(6,1)	24 643	(3,0)
Benzodiazépines à demi-vie longue – n(%)	1 271	(4,6)	24 616	(3,0)
Sulfamides hypoglycémisants – n(%)	1,071	(3,9)	135 500	(16,2)
Antihistaminique de première génération – n(%)	659	(2,4)	35 368	(4,2)
Benzodiazépines à demi-vie courte – n(%)	3 807	(13,7)	11 355	(1,4)
Alpha agonistes centraux – n(%)	1,405	(5,0)	17 564	(2,1)
Antispasmodique anticholinergique – n(%)	626	(2,3)	3433	(0,4)
Anti-inflammatoire non stéroïdiens – n(%)	418	(1,5)	216 351	(10,1)
MPI avec antécédents de chute (tricyclique, IRSS, IRSNa) – n(%)	420	(1,5)	13 629	(1,6)
Laxatifs stimulant – n(%)	1	(0,0)	72 164	(8,7)
Insuline rapide sans traitement par insuline lente – n(%)	108	(0,4)	58 455	(7,0)
Myorelaxants – n(%)	0	(0,0)	36 006	(4,3)

MPI : Médicaments potentiellement inappropriés ; IRSS : Inhibiteur de recapture spécifique de la sérotonine ; IRSNa : Inhibiteur de la recapture de la sérotonine et de la noradrénaline

La comparaison entre la polymédication chronique des vétérans et des français permet de mieux comprendre les caractéristiques de la part inappropriée. De façon générale, les IPP, les médicaments anticholinergiques et les sulfamides hypoglycémiantes représentaient la part inappropriée majeure de la polymédication chronique. D'autres MPI, bien qu'également majeurs, étaient plus spécifiques d'une population ou d'un système de soin comme les benzodiazépines et les AINS. Les futures stratégies d'intervention, comme la déprescription, devront donc s'appliquer à l'ensemble des médicaments que nous avons identifiés, tout en tenant compte des spécificités de chaque population.

## IV Risque de mortalité de la polymédication chronique et des MPI.

### A Problématique

Comme nous l'avons démontré précédemment, la polymédication chronique reste fréquente en France et aux Etats-Unis. Dans les deux cas, elle semble majoritairement inappropriée. D'une manière générale, la littérature montre que la polymédication et les MPI sont indépendamment associés à un risque de survenue d'effet indésirable médicamenteux [27,40], d'hospitalisation [26,35,41] et de décès [6,81–83]. Cependant, les risques de la polymédication restent encore peu explorés concernant les médicaments chroniques et leur part inappropriée.

La base de données des vétérans, riche en données cliniques et biologiques, permet une estimation précise de l'état de santé des individus et ainsi une bonne évaluation de la pertinence des médicaments. De plus, la profondeur historique des données exploitables de plus de 10 ans paraissait en adéquation avec un objectif d'estimation des risques au long cours. C'est pourquoi, nous avons choisi d'utiliser cette base de données pour la réalisation d'une étude d'estimation du risque dépendant du temps afin de déterminer le risque de mortalité associé à la polymédication chronique et à sa part inappropriée.

### B Objectifs

L'objectif de cette étude était d'estimer le risque de décès toutes causes associé à l'usage chronique de médicaments et à l'usage de MPI, indépendamment, chez les vétérans américains nés entre 1945 et 1965.

### C Considérations méthodologiques

Nous avons réalisé une étude de cohorte avec une exposition dépendante du temps incluant des patients initiant une utilisation de médicament chronique entre le 1er octobre 2008 et le 30 septembre 2017. Les individus ont été exclus s'ils avaient  $\geq 5$  utilisations de médicaments chroniques ou un MPI au cours des 12 premiers mois suivant leur inclusion définissant la période de référence. Après cette période, les individus ont été suivis jusqu'à la date de leur décès ou jusqu'au 30 septembre 2019.

Il nous faut rappeler qu'une des raisons de la présence de nombreux médicaments chronique est la multimorbidité. La multimorbidité est également à risque de décès, donc facteur de confusion, et il faut en tenir compte lors de l'étude de la polymédication (Figure 4).

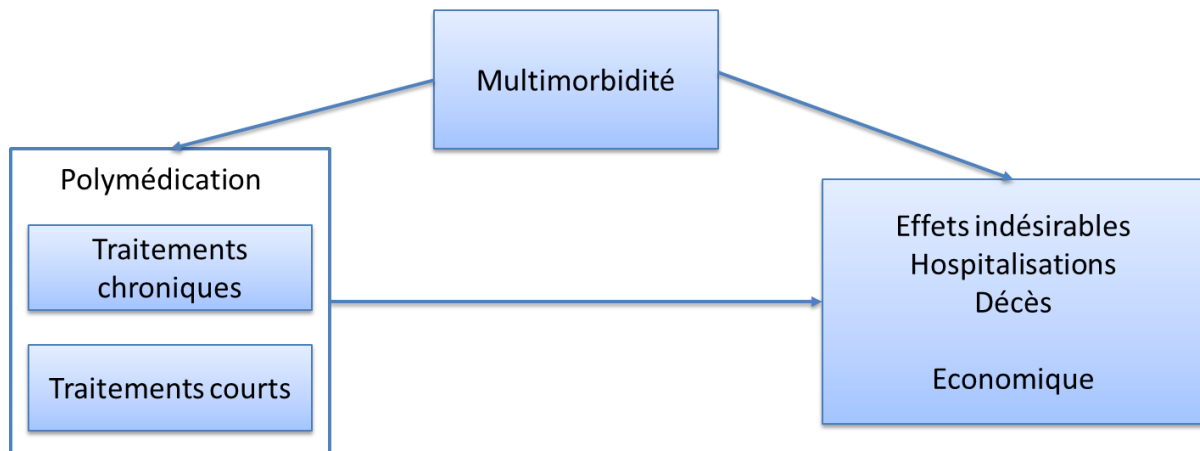


Figure 4 La multimorbidité est un facteur de confusion lors de l'étude la polymédication

Classiquement, les analyses peuvent être ajusté sur des pathologie spécifique, sur des scores de multimorbidité ou des index de fragilités. Chaque méthode présente des limites : (i) Ajuster sur des pathologies spécifiques oblige à sélectionner les pathologies et reste donc incomplet ; (ii) Utiliser un score de multimorbidité capture plus de pathologie mais va parfois pondérer une maladie spécifique de façon plus importante qu'un ensemble de pathologies. Nous avons fait le choix d'utiliser pour cette étude un score de fragilité développé par l'équipe de Yale au sein de laquelle les études ont été réalisées : Le VACS (*Veteran Aging Cohort Study*) index. C'est un score de fragilité, qui se base sur des paramètres biologiques et cliniques, notamment le taux de CD4, la fibrose hépatique, le VIH, l'IMC. Il a été initialement développé pour estimer la fragilité des vétérans vieillissant avec le VIH [84,85]. D'après d'autres études sur les vétérans américains, il a été montré qu'il prédit la mortalité chez les vétérans non infectés avec la même efficacité. Il a également été montré qu'il prédit aussi bien la mortalité à 30 jours après une hospitalisation qu'à long terme. Par ailleurs, il permettrait une meilleure prédiction de la mortalité que le score Charlson [86]. Cela peut s'expliquer par le fait que les paramètres utilisés témoignent directement de la santé des patients, et sont donc le reflet de la gravité de leur multimorbidité.

Les médicaments utilisés de façon chronique et les MPI, chroniques ou non, ont été comptés mensuellement. Un médicament a été considéré comme utilisé de façon chronique si la durée du traitement était continue sur 90 jours ou plus. La période de 90 jours était justifiée par le fait que la durée des traitements chez les vétérans était renseignée dans les données et non pas estimée par une moyenne de prescription ou la présence de conditionnement trimestriel.

Les MPI ont été identifiés selon les critères de Beers 2015. L'analyse a été ajustée en fonction de l'âge, de l'année de référence, du sexe, du groupe ethnique, du statut tabagique, de la consommation d'alcool et du score VACS (*Veteran Aging Cohort Study*). Le risque de décès toutes causes trois mois après l'exposition a été estimé à partir de modèle de Cox dépendant du temps.

## D Résumé des travaux et principaux résultats

912 391 sujets ont été inclus dans l'étude. Leur âge moyen à l'inclusion était de 57,4 ans et ils étaient majoritairement des hommes (93,2 %). Par rapport aux sujets ayant 3 à 4 utilisations chroniques de médicaments, ceux qui en avaient 5 à 6, 7 à 9,  $\geq 10$  avaient un risque augmenté de décès toutes causes trois mois après l'exposition (Respectivement, les risques relatifs et leurs intervalles de confiance à 95 % étaient de 1,184 [1,151 - 1,218], 1,461 [1,407 - 1,517], 1,871 [1,770 - 1,978]). L'utilisation d'un MPI ou de plusieurs MPI était également associée à un risque plus élevé de décès toutes causes par rapport à l'absence de MPI (1,216 [1,182 - 1,250] et 1,354 [1,271 - 1,442], respectivement).



E Article en préparation : Risk of mortality associated with chronic polypharmacy and potentially inappropriate medications in United States veterans aged 49-70 year.

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# Risk of mortality associated with chronic polypharmacy and potentially inappropriate medications in United States veterans aged 49-70 years

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## Key points

- **Question:** To estimate the risk of death associated with chronic drug use and PIMs in US veterans in the context of polypharmacy.
- **Findings:** Chronic polypharmacy gradually increased the risk of all-cause death. Furthermore it also appeared to be a more important risk factor than PIMs.
- **Meaning:** As deprescription seems to occur lately, interventions to improve treatment quality should target in priority patients with polypharmacy. In this situation, PIMs list could help for deprescribing and must be completed by monitoring every benefit-risk balance of medications.

## Abstract

**Importance:** As treatment duration is linked to occurrence of adverse drug reactions, the risk of chronic polypharmacy, which focus on chronic drug use, needs to be evaluated according to the appropriateness.

**Objective:** To estimate the risk of all-cause death associated with chronic drug use and potentially inappropriate medications (PIMs) in US veterans born between 1945 and 1965.

**Design:** Time updated cohort study including individuals with occurrence of a chronic drug use initiation between October 1<sup>st</sup>, 2008 and September 30, 2017. Individuals were excluded if they had  $\geq$  5 chronic drug uses or PIMs in the first 12 month following their inclusion defining the baseline period. After this period individuals were followed until date of death or September 30, 2019.

**Setting:** Population-based study

**Participants:** United States veterans born from 1945-1965.

**Exposure(s) (for observational studies):** Chronic drug uses count and PIM, assessed monthly. Chronic drug use were defined by a continuous use of 90 days or more. PIMs were identified according to the

Beers criteria version 2015. Analysis were adjusted for age, year at baseline, sex, race, smoking status, alcohol consumption and Veterans Aging Cohort Study (VACS) index.

**Main Outcome(s) and Measure(s):** Monthly time updated Cox models estimating risk of all-cause death three months after exposure.

**Results:** 912,391 veterans were included in the study. Their mean age at baseline was 57.4 years and they were predominantly male (93.2%). Compared to individuals with 3-4 chronic drug uses, those with 5-6; 7-9;  $\geq 10$  chronic drug uses had a higher risk of all-cause death three months after exposure (hazard ratios and their 95% confidence intervals were 1.184 [1.151 - 1.218], 1.461 [1.407 - 1.517], 1.871 [1.770 - 1.978], respectively). One PIMs uses or more than one PIMS uses were also associated with a higher risk of all-cause death compared to no PIMs uses (1.216 [1.182 - 1.250] and 1.354 [1.271 -1.442], respectively).

**Conclusions and Relevance:** Chronic polypharmacy gradually increased the risk of all-cause death. Identified inappropriateness using PIMs list appeared not to be the only harmful mechanism of polypharmacy.

## Introduction

The prevalence of polypharmacy, commonly defined as the concomitant use of multiple medications, is increasing in developed countries [1–3]. The most common thresholds are 5 medications defining polypharmacy and 10 medications defining excessive polypharmacy, also called hyperpolypharmacy [4]. Overall, polypharmacy is associated with adverse drug reaction [5], drug-drug interactions [6], non-adherence [7], cognitive impairment [8], falls [9], hospitalization [10] and mortality [11]. Because treatment duration is linked to occurrence of adverse drug reactions, distinguishing chronic drug use in the context of polypharmacy would help to better identify these associated risks [12]. However, few studies distinguish chronic polypharmacy and risks associated to chronic drug use in this context remain unclear.

In addition, polypharmacy is associated with an increasing risk of having potentially inappropriate medications (PIMs), defined as a drug for which risks outweigh potential benefits [13]. Two approaches can be used to identify PIMs: implicit or explicit criteria [14]. Implicit criteria are clinician judgment based and apply specifically to a patient. Consequently, they are not generalizable in research. On the other hand, explicit criteria are consensus of experts published in PIMs lists. The Beers list, firstly published in 1991 and regularly updated, is often used by clinician in patients aged 65 and over [15–17] or in research for drug utilization or risk studies [14,18]. Prior studies showed these PIM are associated with mortality [19–21], hospitalization[22,23], falls [24] and adverse drug reactions [25]. Whereas Beers list regards elderly people, PIMs are frequent in middle-aged people [26]. Although PIMs are associated with risks in most studies, other studies conversely showed that polypharmacy is a better predictor of risk [27].

Polypharmacy and PIMs have been well established in United States (US) Veterans due to their multiple comorbidities and lifestyle [28–30]. As in overall populations, prior risks studies in veterans often focused either on polypharmacy or PIMs [23,24]. Yet, the connection between these situations appeals for studies investigating risk of polypharmacy according to appropriateness of patient's

treatments. The aim of this study was to estimate the risk of mortality associated with the use of chronic drugs in polypharmacy and PIMs in a cohort of middle-aged patients receiving care in the largest integrated healthcare system in the United States.

## Methods

### *Data source and cohort selection*

The VA provides healthcare benefits to more than 9 million veterans yearly through the Veteran Health Administration over 1,200 points of care (i.e., sites) nationwide including hospitals, medical centers, and community outpatient clinics. All care is recorded in an electronic health record with daily uploads into the VA Corporate Data Warehouse. The Corporate Data Warehouse record is nationwide since 1998 and includes pharmacy dispensing records outpatient and inpatient encounters, diagnoses, smoking and alcohol health behaviors, demographics and vital status. From this data was created the Birth Cohort that includes more than 4.5 million veterans born from 1945-1965 who had at least one counter with the VA since October 1, 1999.

Individuals from the birth cohort were included in the study cohort at the date of initiation of a chronic drug between October 1<sup>st</sup>, 2008 and September 30, 2017. At this date started the baseline period which lasted 12 months. In the baseline period, they were excluded if they had polypharmacy/hyperpolypharmacy or PIMs.

### *Outcome and follow-up*

All-cause mortality was obtained from the VA Vital Status File, which includes data from inpatient records, the VA Beneficiary Identification Records Locator Subsystem, Social Security Administration, and Centers for Medicare and Medicaid Services. Excellent reliability and validity of the Vital Status File has been established by comparison with the National Death Registry [31]. Follow-up started at the end of the baseline period. Individuals were followed until date of death or September 30, 2019. A Sensitivity analysis with a follow-up limited to 5 years was performed.

## *Variables and measures*

Pharmacy dispensing records included generic names, date of fill/refill and durations of prescription for which were estimates treatment courses. Chronic drug use was defined by a continuous use of 90 days or more. Between two refills a gap equal 50% of the last refill did not interrupt the chronic drug use. Chronic polypharmacy was defined as 5 -9 chronic drugs and chronic hyperpolypharmacy was defined as 10 chronic drugs. PIMs were identified according to the Beers criteria version 2015. Beers criteria are explicit criteria developed to identify PIMs in adults aged 65 years and older. It is composed of different list including PIMs in most older adults, PIMs with several conditions, interactions, drugs to use with caution, etc. [32]. We used the list regarded PIMs in most older adults and applied it regardless of age. All drugs considered are listed in supplementary material (Table S1). If individuals were inpatients a whole month (number of inpatient days recorded at the VA equal to the number of day alive in the month), the number of chronic drug uses and PIMs were equal to the number of the previous month.

Potential confounders included sociodemographic (age, sex, and race), year of inclusion, smoking status, alcohol use and health status. Smoking status was assessed as non-smoker, current smoker and former smoker based on patient self-report [33]. Alcohol consumption was assessed using the AUDIT-C, a three-question self-report alcohol screening questionnaire that detects heavy drinking and/or active alcohol use disorder [34]. AUDIT-C scores range from 0–12 with the likelihood of physiologic injury and mortality increasing as AUDIT-C scores increase [35]. An AUDIT-C score of zero is defined as no current alcohol use, 1–3 suggests lower-risk drinking, 4–7 suggests at-risk drinking, and  $\geq 8$  suggest hazardous or heavy episodic alcohol consumption. Since 2007, the VA has required annual AUDIT-C screening on all patients in primary care [36].

To adjust for residual underlying health status, we calculated the Veterans Aging Cohort Study Index (VACS Index). Briefly, the VACS Index assesses physiological frailty using a validated algorithm in

electronic health records. It consists of a score incorporating age, CD4 count, HIV-1 RNA, hemoglobin, a marker of liver fibrosis (FIB-4), estimated glomerular filtration rate (eGFR), and HCV status [37].

Individuals who had any missing data (time updated or fixed) at baseline were excluded from the study.

### *Statistical analysis*

Continuous variables were described at first month of follow-up by means and standard deviation (std).

Categorical variables were described at baseline by number of individuals (n) and percentages (%).

Among individuals who died, mean number of chronic drug uses and PIMs were described in the year before death according to polypharmacy status.

Each month during follow-up, chronic drugs used count was split into categorical indicators defined by 0 chronic drugs uses, 1 – 2 chronic drugs uses, 3-4 chronic drugs uses, 5-6 chronic drugs uses, 7-9 chronic drugs uses and 10 chronic drugs uses (hyperpolypharmacy) or more. Similarly, PIMs count were split into categorical indicators defined by 0 PIMs, 1 PIMs, 2 PIMs or more. These variables were described in terms of numbers and patient-years.

Mortality hazard ratios associated with chronic drug uses and PIMs were estimated using time-updated Cox models. Unadjusted models were performed separately for chronic drug uses and PIMs. Multivariate models were adjusted for age at baseline, sex, baseline year, race, smoking status, Audit-C and VACS index. Time-updated variables were assessed monthly and included chronic drug uses count, PIMs count, AUDIT-C, VACS index. AUDIT-C and VACS index were time updated every month. When several Audit-C were performed in the same month, the highest value was taken into account. When several VACS are assessed in a month, the average value was taken into account. If Audit-C or VACS index is missing at any month, the last value assessed was taken into account. If Audit-C or VACS index are missing in the baseline period but was assessed in the first year of follow-up, this value was considered as the value at baseline. Fixed variables were assessed at baseline and



included age, sex, race/ethnicity (White, Black, Hispanic, other), year at baseline, smoking status. Categorical variables 3-4 chronic drug uses and 0 PIMs were reference group, respectively. Hazard ratio estimated the risk of all-cause death three months after exposure. Two sensitivity analyses were performed considering risk of all-cause death: the month of exposure and 6 months after exposure.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

3,487,806 individuals born between 1945 and 1965 received one chronic medications and were included in the cohort. Among them 2 345 457 were excluded because they had at least 5 chronic drugs uses or at least one PIM in the baseline period. 229,958 were also excluded from the study because they had missing VACS, Audit-C or smoking status at baseline and were similar to patients with no missing data (Figure 1, Table S2).

Of the 912,391 individuals included, mean age at baseline was 57.4 years (std 6.5) and they were predominantly male (93.2%). Current smoker was the most frequent smoking status (39.2%). Mean Audit-C at baseline was 2.0 (std 2.5) which indicated a low alcohol use. Mean VACS index was 31.9 (8.2) (Table 1).

Death occurred in 87,402 individuals (9.6%). Mean numbers of chronic drugs uses and PIMs were stable until 3 months before death and decreased. Decreases of chronic drugs uses and PIMs were more substantial in individuals with chronic polypharmacy/hyperpolypharmacy at a year prior to death (Figure 2). 5,474 were inpatient during their last month of life (6.3%, table S3).

According to the adjusted model: compared to individuals with 3-4 chronic drug uses, those with 5-6; 7-9;  $\geq 10$  chronic drug uses had a higher risk of all-cause death three months after exposure (hazard ratios and their 95% confidence intervals were 1.184 [1.151 - 1.218], 1.461 [1.407 - 1.517], 1.871 [1.770 - 1.978], respectively). One PIMs uses or more than one PIMS uses were also associated with a

higher risk of all-cause death compared to no PIMs uses (1.216 [1.182 - 1.250] and 1.354 [1.271 - 1.442], respectively) (Table 2).

In sensitivity analysis, risk of death in 6 months were similar to risk in 3 months, for both chronic drug uses and PIMs. Risk of death in the month was lower than risk of death in 3 month for chronic drug uses and was higher for PIMs (Table 3). Sensitivity analysis with a follow-up to 5 years showed similar results to the main analysis (Table S4 to S6).

## Discussion

In this large cohort study, we showed that mortality increased gradually with the number of medications, up to 46.4% in individuals with chronic hyperpolypharmacy. Independently of number of medications, PIMs uses were also associated with an increased risk of all-cause death. Medications uses trajectories in the 3 months before death showed probable deprescription of medications, appropriate or not.

Some studies also reported that risks of death increased with the number of medications or polypharmacy. A systematic review and meta-analysis including 47 studies performed from 1992 to 2016 showed a higher risk of mortality associated with polypharmacy [38]. Conversely to most of included studies we focused only on chronic polypharmacy and found lower risk than the reported pooled results. A recent Danish study showed that hyperpolypharmacy increased the risk of death by 35% in individuals aged 65 or more [39]. Moreover, this study showed that any extra medication increased the risk of mortality by 2.7%. In our study, individuals with none chronic drugs had a higher risk of death than the reference group (3-4 chronic drug uses). A part of these individuals probably did not purchase their medication at the VA so we could not estimate their treatment properly. Using the reference group of individuals with 3-4 chronic drug uses we compared to certain VA users without polypharmacy and we showed also that the risk gradually increased with additional chronic drug uses in the context of chronic polypharmacy.

According to our results and a meta-analysis regarding population older than 60 years of age, PIMs also increased the risk of death [40]. In our study, 7 chronic drug uses or more increased more the risk of mortality than PIMs. Similarly, another cohort study of hospitalized elderly patients showed that polypharmacy was a better predictor of mortality than PIMs, drug-drug interactions and anticholinergic burden [27]. We could have assumed that the risk associated with polypharmacy was due to PIMs only. However our results showed that the number of chronic drug uses gradually increased the risk of death regardless of inappropriateness. These results suggest that PIMs are just one of many deadly characteristics of chronic polypharmacy.

Polypharmacy was indeed showed to be at a higher risk of long term mortality than short term mortality considering our main and sensitivity analysis results. Similarly, among Danish people, hyperpolypharmacy increased the risk of 30 days mortality by 17% and the risk of 1 year mortality by 23%. The decrease of the mean number of chronic drug uses we observed in the last 3 months could explain the lower risk at short term. In our study, the risk of immeasurable time bias in inpatients was controlled by assuming that patients kept their chronic drugs uses at admission during the whole hospitalization [41]. Moreover, the number of individuals who died as inpatient the last months was relatively low. Deprescription in patients whose health state is worsening may explain the decrease. Futhermore, we observed that deprescription before death was more substantial in individuals with chronic polypharmacy and hyperpolypharmacy than in individuals without polypharmacy.

Consequently, estimating a risk from the number of chronic drug uses before death lead to an underestimation similar to the healthy user/sick stopper bias observed in some studies [40]. Healthy individuals would be more tolerant and adherent to chronic polypharmacy, whereas those who had a worsened health status discontinued polypharmacy and started deprescription in order to improve the treatment or start palliative treatments. It is then important to consider exposure before deprescription when studying polypharmacy. For this reason we estimated all-cause death 3 months after exposure. Conversely, PIMs had a higher risk of short term mortality (sensitivity analysis considering the exposure at the month of death) than long-term mortality (main analysis and

sensitivity analysis considering the exposure 6 months before death). A previous study in nursing home showed that the mortality of the residents who took PIM continuously was unaffected, whereas mortality increased if PIM were taken intermittently in the 3 months before death [20]. This study showed that the healthy user/sick stopper bias also existed for PIMs. The risk we observed at the month before death was then probably underestimated. Since it was still higher than the long term risk we can assume that PIMs may have more immediate harmful effects than chronic polypharmacy. Our sensitivity analyses with a shorter total follow-up confirmed the long term risk of chronic drug uses and the immediate risk of PIMs, suggesting that these were not decreasing in people with long exposure to chronic drug uses.

Our study has limits, the VA eliminates insurance-associated barriers to care and medication acquisition. Therefore, our results may not be generalizable to a system where cost and insurance are paramount determinants of healthcare utilization. Furthermore, the VA population is predominantly male and our analysis only focused on veterans born in the 1945-1965 period. However, this range covers both middle aged and elderly providing people with prevalent chronic diseases. Our data does not include over-the-counter (OTC) drugs if they are not purchased at the VA which is a limitation for the complete identification of drug treatments. This might have had a negligible impact in our study that focused on chronically used drugs. Lastly, since we only use one list of the Beers criteria, the risk of mortality associated with PIMs may be underestimated. Furthermore, Beers list was created to help clinician to identify PIMs in older adults but it cannot identify all inappropriate drugs [42]. However, VA data also have several strengths. The VA health system is America's largest integrated health care system providing comprehensive services to over 9 million Veterans each year via approximately 1,200 sites of care [43] and represents a large proportion of racial and ethnic minority patients. Accuracy and exhaustiveness of pharmacy utilization at the VA provided good estimates of chronic drug uses and PIMs.

## Conclusion

Chronic polypharmacy gradually increased the risk of all-cause death. Identified inappropriateness using PIMs list appeared not to be the only harmful mechanism of polypharmacy.

As deprescription seems to occur lately, interventions to improve treatment quality should be performed regularly among patients in polypharmacy. A high number of chronic drug use should alert physician on the urgency of monitoring the patient's treatment. PIMs lists could help for deprescribing and must be completed by monitoring every benefit-risk balance of medications.

## Additional sections

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**Data availability statement:** Due to US Department of Veterans Affairs (VA) regulations and our ethics agreements, the analytic data sets used for this study are not permitted to leave the VA firewall without a Data Use Agreement. This limitation is consistent with other studies based on VA data. However, VA data are made freely available to researchers with an approved VA study protocol.

**Ethic Statement:** This study was approved by the institutional review boards of VA Connecticut Healthcare System and Yale University. It has been granted a waiver of informed consent and is Health Insurance Portability and Accountability Act compliant.

**Conflict of interest statement:** None declared

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## Tables

Table 1 Description of veterans included in the study at baseline (12 months after inclusion)

	Veterans	
	912,391	
<b>Age</b> -Mean (std)	57.4	(6.5)
<b>Sex</b>		
Male – n(%)	850,099	(93.2)
Female – n(%)	62,292	(6.8)
<b>Race</b>		
White n-(%)	610,865	(67.0)
Black n-(%)	182,241	(20.0)
Hispanic n-(%)	49,438	(5.4)
Other n-(%)	69,847	(7.7)
<b>Smoking</b>		
Never n-(%)	294,046	(32.2)
Current n-(%)	357,742	(39.2)
Past n-(%)	260,603	(28.6)
<b>Baseline year</b> - Mean (std)	2011.3	(3.1)
<b>Audit-C</b> - Mean (std)	2.0	(2.5)
<b>VACS index</b> - Mean (std)	31.9	(8.2)

Table 2 Risks of death in 3 months associated with exposure to chronic drug uses and potentially inappropriate medications (PIMs)

	Patient-years	Events	Unadjusted Hazard ratio	95CI	Adjusted <sup>1</sup> Hazard ratio	95CI
0 chronic drugs uses	2,095,924	28,817	1.183	[ 1.160 - 1.207 ]	1.340	[ 1.309 - 1.372 ]
1 – 2 chronic drugs uses	1,875,935	17,780	0.823	[ 0.805 - 0.841 ]	0.942	[ 0.920 - 0.965 ]
3 – 4 chronic drugs uses (ref)	1,287,605	15,161	1		1	
5 – 6 chronic drugs uses	593,754	9,811	1.357	[ 1.323 - 1.392 ]	1.184	[ 1.151 - 1.218 ]
7 – 9 chronic drugs uses	334,540	8,182	1.964	[ 1.911 - 2.019 ]	1.461	[ 1.407 - 1.517 ]
≥ 10 chronic drugs uses	151,832	5,671	2.946	[ 2.856 - 3.040 ]	1.871	[ 1.770 - 1.978 ]
0 PIMs (ref)	5,198,602	63,739	1		1	
1 PIMs	863,475	15,322	1.365	[ 1.340 - 1.390 ]	1.216	[ 1.182 - 1.250 ]
≥ 2 PIM	277,260	6,361	1.715	[ 1.671 - 1.761 ]	1.354	[ 1.271 - 1.442 ]

95CI: 95% Confidence interval; PIMs: Potentially inappropriate medications; Ref: Reference group

<sup>1</sup>Adjusted for age at baseline, sex, race, baseline year, smoking status, Audit-C, Veteran Aging Cohort Study (VACS) Index

Table 3-1 Sensitivity analysis: Risks of death in the month associated with exposure to chronic drug uses and potentially inappropriate medications (PIMs)

	Patient-years	Events	Unadjusted Hazard ratio	95CI	Adjusted <sup>1</sup>	
0 chronic drugs uses	2,103,730	33,985	1.476	[ 1.447 - 1.506 ]	1.721	[ 1.673 - 1.770 ]
1 – 2 chronic drugs uses	1,880,443	19,473	0.951	[ 0.930 - 0.972 ]	1.112	[ 1.084 - 1.141 ]
3 – 4 chronic drugs uses (ref)	1,291,373	14,393	1		1	
5 – 6 chronic drugs uses	596,105	8,835	1.274	[ 1.240 - 1.309 ]	1.100	[ 1.064 - 1.137 ]
7 – 9 chronic drugs uses	336,389	6,526	1.629	[ 1.581 - 1.679 ]	1.143	[ 1.064 - 1.228 ]
≥ 10 chronic drugs uses	153,066	4,190	2.278	[ 2.197 - 2.363 ]	1.320	[ 1.190 - 1.463 ]
0 PIMs (ref)	5215112	67,997	1		1	
1 PIMs	867065	14,300	1.190	[ 1.168 - 1.213 ]	1.306	[ 1.264 - 1.348 ]
≥ 2 PIM	278696	5,105	1.296	[ 1.258 - 1.336 ]	1.468	[ 1.365 - 1.578 ]

95CI: 95% Confidence interval; PIMs: Potentially inappropriate medications; Ref: Reference group

<sup>1</sup>Adjusted for age at baseline, sex, race, baseline year, smoking status, Audit-C, Veteran Aging Cohort Study (VACS) Index

Table 3-2 Risks of death in 6 months associated with exposure to chronic drug uses and potentially inappropriate medications (PIMs)

	Patient-years	Events	Unadjusted Hazard ratio	95CI	Adjusted <sup>1</sup> Hazard ratio	95CI
0 chronic drugs uses	2,088,922	27,659	1.135	[ 1.113 - 1.182 ]	1.281	[ 1.252 - 1.311 ]
1 – 2 chronic drugs uses	1,871,563	17,765	0.820	[ 0.802 - 0.875 ]	0.930	[ 0.909 - 0.952 ]
3 – 4 chronic drugs uses (ref)	1,283,935	15,074	1		1	
5 – 6 chronic drugs uses	591,305	9,685	1.366	[ 1.331 - 1.402 ]	1.213	[ 1.179 - 1.248 ]
7 – 9 chronic drugs uses	332,522	7,791	1.932	[ 1.879 - 1.987 ]	1.495	[ 1.442 - 1.549 ]
≥ 10 chronic drugs uses	150,434	5,307	2.890	[ 2.799 - 2.983 ]	1.951	[ 1.850 - 2.057 ]
0 PIMs (ref)	5,183,130	62,636	1		1	
1 PIMs	859,959	14,577	1.343	[ 1.318 - 1.368 ]	1.168	[ 1.136 - 1.202 ]
≥ 2 PIM	275,685	6,068	1.706	[ 1.660 - 1.752 ]	1.292	[ 1.212 - 1.378 ]

95CI: 95% Confidence interval; PIMs: Potentially inappropriate medications; Ref: Reference group

<sup>1</sup>Adjusted for age at baseline, sex, race, baseline year, smoking status, Audit-C, Veteran Aging Cohort Study (VACS) Index

# Figures

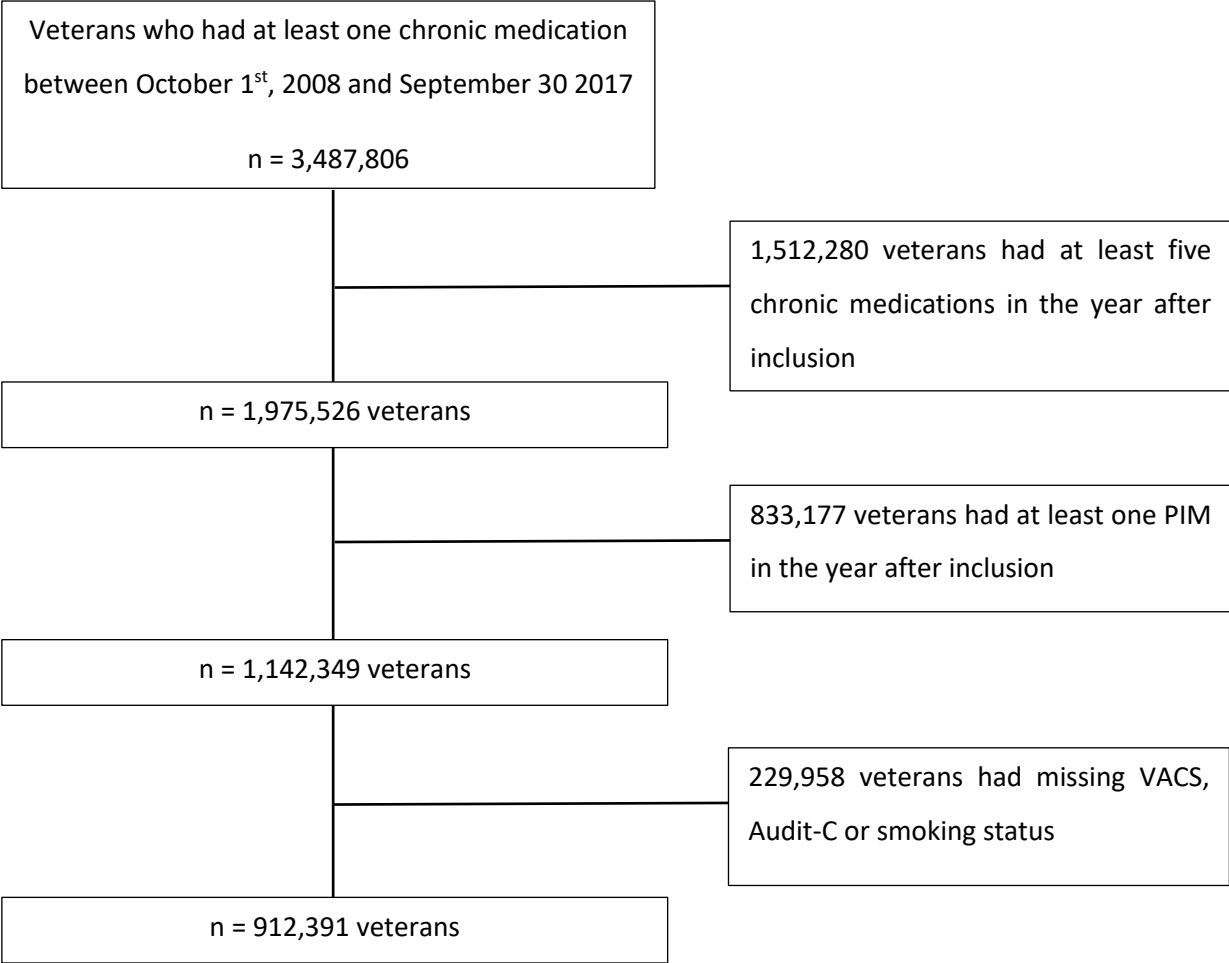


Figure 1 Flow chart

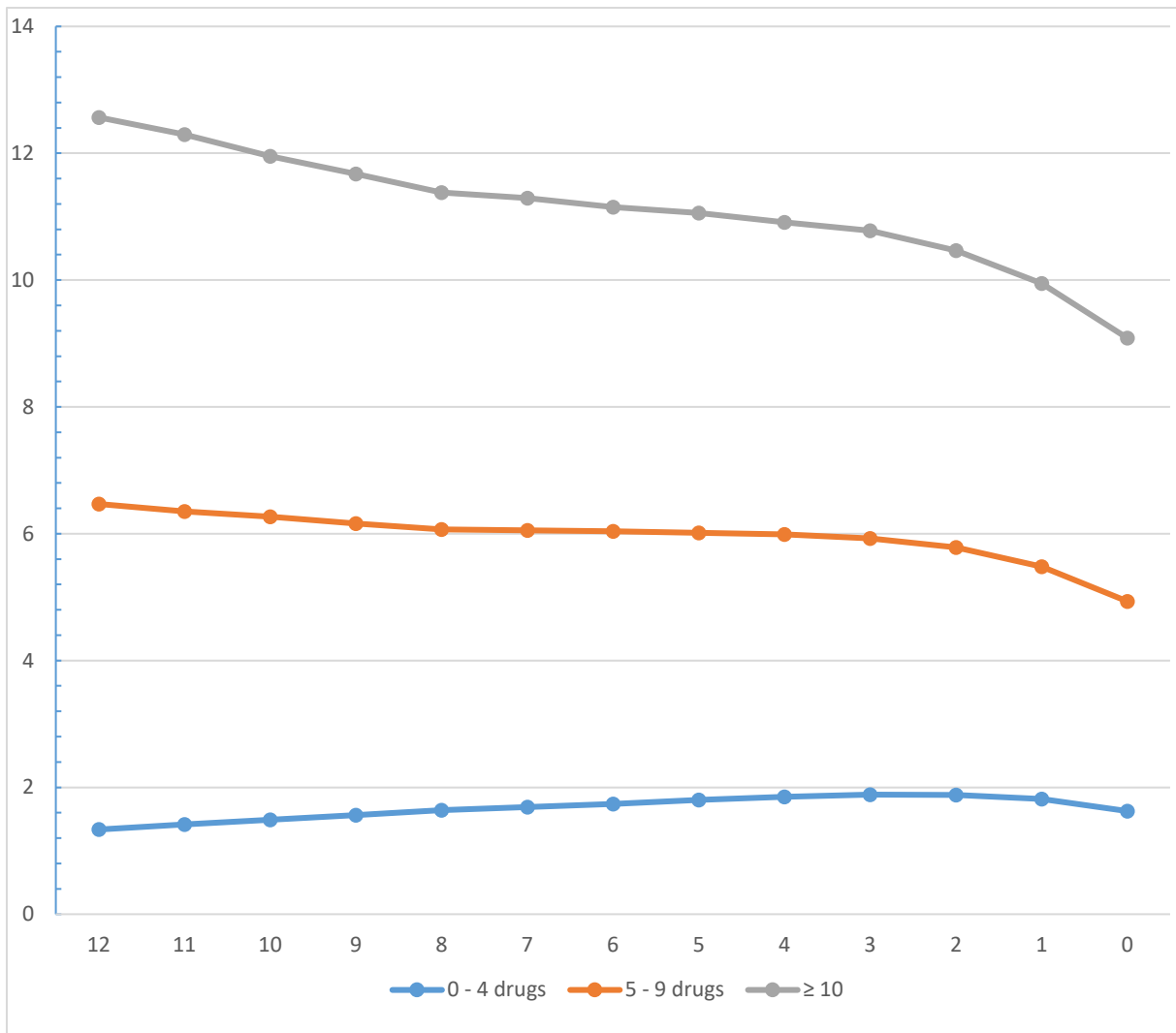


Figure 2a Means number of chronic medications per month in the year before death according to the polypharmacy status 12 months before death



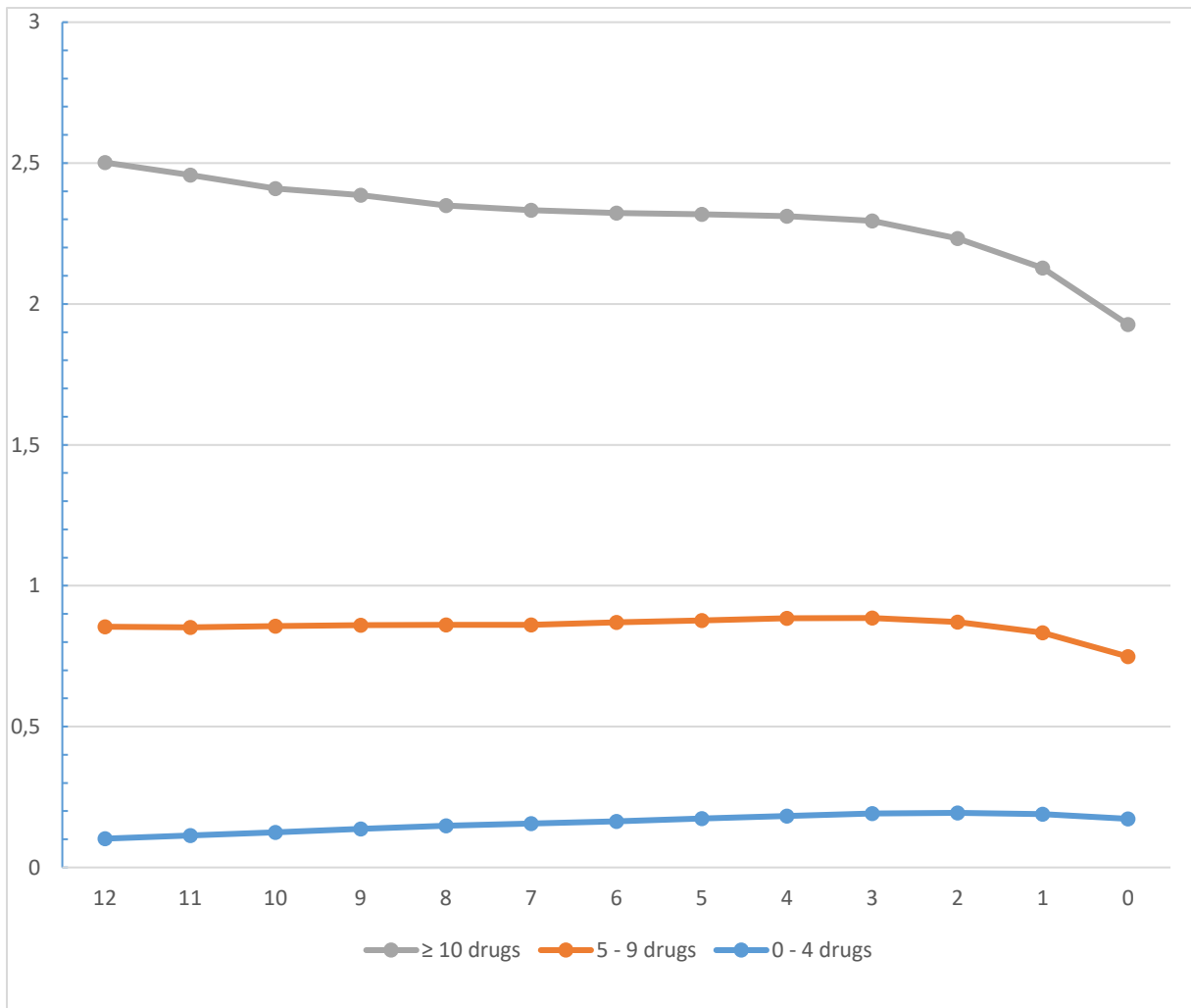


Figure 2b Means number of PIMs per month in the year before death according to the polypharmacy status 12 months before death

## F Discussion des principaux résultats

La polymédication chronique augmentait le risque de décès toute cause de façon graduelle. Les MPI étaient également à risque de décès. Il est important de noter que le risque décès toute cause associé à un nombre de médicaments chronique de 7 ou plus est plus important que celui d'un MPI ou plus. Au sein de la polymédication globale, la polymédication chronique est donc à risque de décès et la présence de MPI n'explique que partiellement le risque.

Par ailleurs, la déprescription des médicaments semblait être effectuée tardivement. Les interventions visant à améliorer la qualité des traitements devraient donc être effectuées régulièrement chez les patients. Un nombre élevé d'utilisations chroniques de médicaments devrait alerter le médecin sur l'urgence de surveiller le traitement du patient. Bien que les liste MPI puissent aider à la prescription, celle-ci doit être complétée par l'évaluation de la balance bénéfices-risques de chaque médicament.

## V Conclusion générale et perspectives

Les études concernant la polymédication dans la littérature proposent des définitions multiples et des descriptions qui ne sont le plus souvent pas spécifiques de la polymédication chronique. L'indicateur de polymédication chronique que nous avons développé permet de centrer la recherche sur cette polymédication spécifique des traitements pris sur le long terme. Au cours de nos analyses, nous avons observé des prévalences plus faibles que ce qui avait été reporté dans la littérature scientifique. Cependant de par leur définition, ces études se concentraient sur la polymédication globale, comptabilisant tous les types de traitements. D'autres études ont utilisé une définition plus spécifique de la polymédication chronique et proche de celle que nous avons développée. Cependant ces définitions n'identifiaient que partiellement la polymédication chronique, d'où des résultats différents de ceux que nous avons observés. Les bases de données françaises nous ont permis d'étudier la polymédication à tout âge et tout contexte socioéconomique. Nous avons montré dans cette situation que la polymédication chronique reste fréquente, concernant plus de 5 % de l'ensemble de la population française.

La polymédication est le plus souvent étudiée dans la population des personnes âgées. L'augmentation de la prévalence des multimorbidités avec l'âge justifie souvent ce choix, les chercheurs estimant que la probabilité d'être en polymédication est plus importante chez les sujets âgés que chez les sujets plus jeunes, en bonne santé ou avec peu de pathologies. Nous avons en effet montré que la polymédication chronique concerne plus d'un quart des personnes âgées et que la prévalence atteint son pic entre 80 et 90 ans. Cependant, elle est également non négligeable chez les adultes d'âge moyen, concernant plus de 5 % des personnes de 40 à 70 ans en France. Elle pourrait être d'autant plus préoccupante au sein de populations vulnérables. En effet, nous avons montré que près d'un tiers des vétérans américains d'âge moyen étaient concernés par la polymédication chronique, soit cinq fois plus que la prévalence observée dans la population française à cet âge. Bien que les mécanismes d'entrée en polymédication restent à explorer, notamment chez les sujets jeunes, la polymédication est un phénomène global qui doit être surveillé dans l'ensemble de la population, quel que soit l'âge ou la situation socio-économique.

La prévalence élevée de la polymédication ne présume pas, à elle seule, d'une mauvaise utilisation des médicaments. Afin d'approfondir la description de la polymédication chronique, nous avons choisi de distinguer la part appropriée de la part inappropriée. Plusieurs outils pouvaient être utilisés pour la détection de MPI, par exemple des listes d'interactions, des listes pharmacologiques (anticholinergiques) ou des listes de MPI identifiés par un panel d'experts (critères explicites). Nous avons choisi d'utiliser les critères de Beers, de Laroche et de PROMPT car ils ont l'avantage d'identifier

un large panel de médicaments, sans être spécifique d'un organe ou d'une classe pharmacologique. Cependant ils n'identifient qu'une part des MPI et leur applicabilité peut être limitée en fonction de la base de données.

Malgré cette possible sous-estimation de la prévalence des MPI, nous avons montré que la polymédication chronique est fréquemment inappropriée. Elle concernerait environ deux tiers des sujets en polymédication chronique, que ce soit parmi les personnes âgées en France ou parmi les vétérans américains âgés de 49 à 70 ans. L'augmentation de la prévalence des MPI en hyperpolymédication chronique dans ces deux populations suggère que la part inappropriée de la polymédication est d'autant plus importante dès que le nombre de médicaments augmente. Lors du passage en hyperpolymédication chronique, l'augmentation du nombre de médicaments pourrait être en partie le résultat de l'ajout de MPI. Par ailleurs, la prévalence des MPI n'est pas négligeable chez les sujets plus jeunes et suggèrent que les interventions de déprescription devraient s'appliquer à tout âge. Près de la moitié des adultes d'âge moyen en polymédication étaient concernés par un MPI et trois quart par l'hyperpolymédication.

Par ailleurs, les travaux de cette thèse permettent de distinguer deux types de polymédications chroniques inappropriées :

- les médicaments qui devraient être ciblés en priorité par des interventions de déprescription. Ces médicaments sont souvent pris de façon chronique sans indication de traitement d'une condition chronique. Ce sont par exemple les IPP, les benzodiazépines, et les AINS, qui sont connus pour être fréquemment initiés sans indication médicale valable ou reconduits sans réévaluation.
- les médicaments qui devraient être ciblés lors d'interventions d'optimisation des prescriptions. Ce sont souvent des médicaments indiqués dans le traitement de pathologie chronique mais ne suivant pas les recommandations de prise en charge ou ayant des alternatives avec une meilleure balance bénéfice-risque. Par exemple dans le traitement du diabète, l'utilisation de sulfamides hypoglycémifiants, à risque d'effets indésirables, ou de l'insuline rapide sans traitement de fond par insuline lente serait potentiellement inappropriée et fréquente.

Dans la littérature scientifique, il a été montré que la polymédication et les MPI sont associés à la survenue d'effets indésirables, d'hospitalisations et de décès. Afin de mieux comprendre les risques spécifiques de la polymédication chronique, nous avons conduit une étude de risque à partir de la population des vétérans et nous avons suivi leur exposition aux médicaments chroniques et aux MPI.

Cette étude a montré que la polymédication chronique était associée à une augmentation du risque de décès. Nous avons observé que ce risque augmentait graduellement avec le nombre de médicaments, en particulier à partir de sept médicaments chroniques concomitants. L'identification et la caractérisation de la polymédication sembleraient ainsi plus pertinentes par l'utilisation de seuils multiples. Le seuil de cinq médicaments ou plus, bien que très utile pour la comparaison des résultats dans la littérature scientifique, pourrait ne pas être le plus adapté l'étude du risque associé à la polymédication. Les analyses de sensibilité réalisées nous ont également appris que dans les mois qui précèdent le décès les patients se voient déprescrire leurs médicaments, et ce d'autant plus que leur nombre est important initialement. Cela montre que les interventions de déprescription semblent être réalisées probablement trop tardivement et plutôt en lien avec une altération de l'état général. La surveillance et l'optimisation des traitements devraient se faire régulièrement et en priorité à l'entrée en polymédication. Les MPI sont également associés à une augmentation de la mortalité et cela, indépendamment du nombre de médicaments chroniques utilisés. Cependant, l'utilisation de ces médicaments inappropriés ne semble pas expliquer à elle seule la surmortalité associée à la polymédication chronique. Ceci nous amène aux perspectives de ce travail de thèse. Chercher quels autres leviers pourrait permettre d'améliorer la santé des patients en polymédication et de mieux comprendre ses mécanismes qui impactent la santé publique (Figure 5).

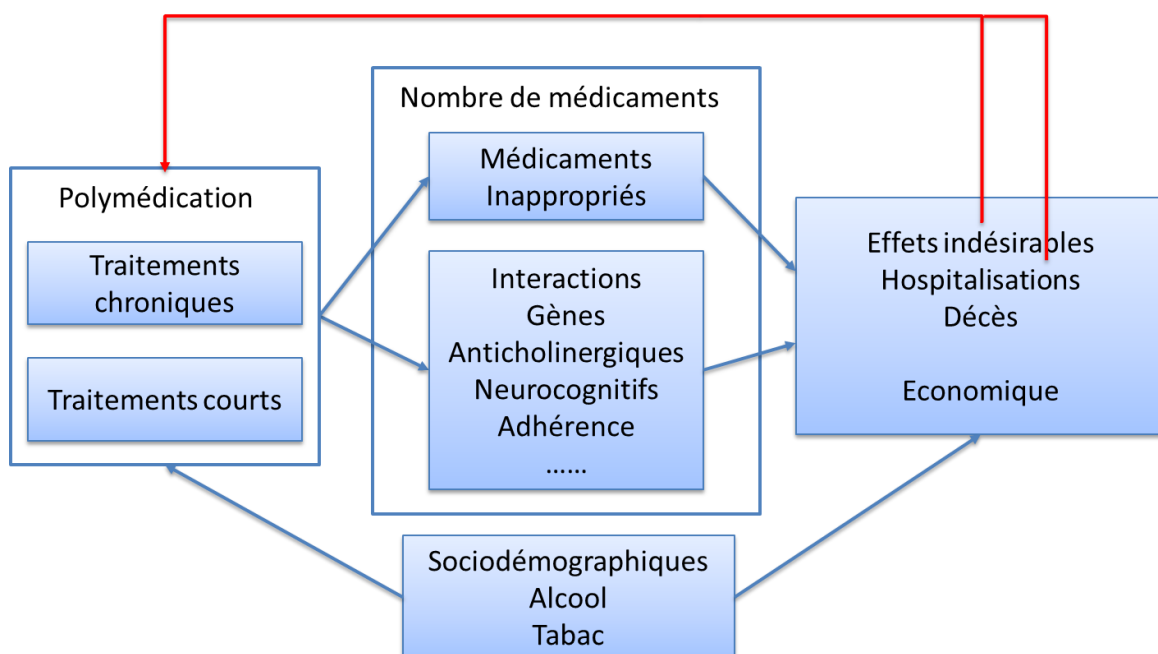


Figure 5 Perspectives: pistes de recherches des mécanismes de la polymédication qui pourraient impacter la santé publique

Plusieurs pistes sont à explorer. En plus des MPI, on pourrait analyser les interactions médicamenteuses, les interaction médicaments-gènes ou certaines classes pharmacologiques

spécifique, par exemple les anticholinergiques ou les médicaments neurocognitifs. D'autres pistes concernant l'usage des médicaments comme par exemple l'adhérence pourraient être explorées. Il existe également des mécanismes qui vont créer un cercle vicieux de la polymédication. C'est par exemple le cas lorsque l'on traite un effet indésirable dû à la polymédication par un autre médicament ou lorsque des hospitalisations amènent à la prescription de nouveaux médicaments. Enfin il y a les facteurs qui gravitent autour de la polymédication et qui impactent à la fois la santé publique, la multimorbidité et le nombre de médicaments. C'est le cas des facteurs sociodémographiques et du mode de vie, par exemple la consommation d'alcool ou de tabac.

Des interventions doivent être mises en place pour améliorer les qualités des traitements et diminuer les risques liés à la polymédication chronique. Puisque les médicaments ont pour but d'améliorer la santé et de traiter des pathologies, ils sont nécessaires pour les patients. La diminution de l'impact sur la santé publique de la polymédication ne peut donc pas passer uniquement par une réduction aveugle du nombre de médicaments. Elle doit reposer sur ces leviers identifiés par les chercheurs, par exemple sur l'identification des MPI par l'utilisation des listes explicites, complétées par la surveillance régulière de la balance bénéfice-risque de chaque médicament par un professionnel de santé. Cette évaluation doit être systématique pour tout patient entrant en polymédication quel que soit l'âge et l'état de santé.

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## VII Annexes

### A Annexe I – Publications et communications issues du travail de thèse

#### **Publications**

1. Guillot J, Maumus-Robert S, Bezin J. Polypharmacy: A general review of definitions, descriptions and determinants. *Therapie*. 2020 Sep-Oct;75(5):407-416.
2. Guillot J, Maumus-Robert S, Pariente A, Bezin J. Chronic polypharmacy: a population-based study regardless of age. *Fundam Clin Pharmacol*. (1<sup>ère</sup> soumission).
3. Guillot, J.; Maumus-Robert, S.; Marceron, A.; Noize, P.; Pariente, A.; Bezin, J. The Burden of Potentially Inappropriate Medications in Chronic Polypharmacy. *J. Clin. Med*. 2020, 9, 3728.
4. Guillot J, Rentsch CT, Gordon KS, Justice AC, Bezin J. The burden of potentially inappropriate medications in United States veterans aged 49-70 years increases with chronic polypharmacy. *Int J Epidemiol*. (1<sup>ère</sup> soumission).
5. Guillot J, Rentsch CT, Gordon KS, Skanderson M, Pariente A, Bezin J, Justice AC. Risk of mortality associated with chronic polypharmacy and potentially inappropriate medications in United States veterans aged 49-70 year (en preparation)

#### **Communications affichées**

1. 34<sup>ème</sup> International Conference on Pharmacoepidemiology, 22-26 Aout, 2018
2. Guillot J, Maumus-Robert S, Pariente A, Bezin J. A population based description of chronic polypharmacy by sex and age. 34<sup>ème</sup> congrès international de pharmacoépidémiologie (34<sup>th</sup> ICPE) 22-26 Aout, 2018, Prague Congress Centre, Prague, République Tchèque.
3. Guillot J, Maumus-Robert S, Pariente A, Bezin J. A population based description of chronic polypharmacy by sex and age. 23<sup>ème</sup> congrès annuel de la Société Française de Pharmacologie Thérapeutique (SFPT), 12-14 Juin 2019, Lyon. Poster modéré (Prix du meilleur poster modéré dans la session pharmaco-épidémiologie).

#### **Communications orales**

1. Guillot, J.; Maumus-Robert, S.; Marceron, A.; Noize, P.; Pariente, A.; Bezin, Description of Potential Inappropriateness of Chronic Polypharmacy. VACS Polypharmacy Summit –14 février 2020. VA CT Healthcare System, West Haven, CT, USA.

2. Guillot, J.; Maumus-Robert, S.; Marceron, A.; Noize, P.; Pariente, A.; Bezin, J. Description of appropriateness of chronic polypharmacy: a nationwide cohort study ISPE 2020 Mid-Year (annulée à cause de la Covid-19).
3. Guillot J, Rentsch CT, Gordon KS, Justice AC, Bezin J. The Burden of Potentially Inappropriate Medications in Veterans according to Chronic Polypharmacy. The ETI Seminar, Hosted by PRIME, VACS and CERC. 23 novembre 2020 VA CT Healthcare System, West Haven, CT, USA. (Téléconférence Webex).

### **Rapport d'étude**

1. Rapport scientifique de fin d'étude transmis à l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) : mode d'entrée des assurés sociaux en polymédication. Programme de recherche MONAUPOLY. Étude 1 : description de la polymédication chronique

B Annexe II - Supplementary material: Chronic polypharmacy: a population-based study regardless of age

## **Chronic polypharmacy: a population-based study regardless of age**

*Chronic polypharmacy according to age*

### **Supplementary material**

#### **Appendices 1: Instructions for the interactive sunburst diagrams**

Figure 2 represents the density of exposure of chronic drugs in chronic polypharmacy and is available as an interactive diagram. This interactive diagram was created with RStudio (Version 1.0.153 – © 2009-2017 RStudio, Inc.)

Move your mouse cursor over the different ATC class to display the density of exposure in percent and the hierarchy of the ATC classification. The percent displayed represents the exposure to the specific ATC class over the overall exposure of chronic drugs in polypharmacy.

The five circles of the sunburst represent the five levels of the ATC classification. The diagram allows following the hierarchy of the code from the level one (smaller circle on the center) to the level five (bigger circle on the edge).

**Pour cette thèse**, les diagrammes présentés sont disponibles en version interactive à l'adresse web suivante : <https://jguillot.shinyapps.io/polypharmacy/>



ou en scannant le flash code suivant :

Appendices 2: Supplementary figure and tables

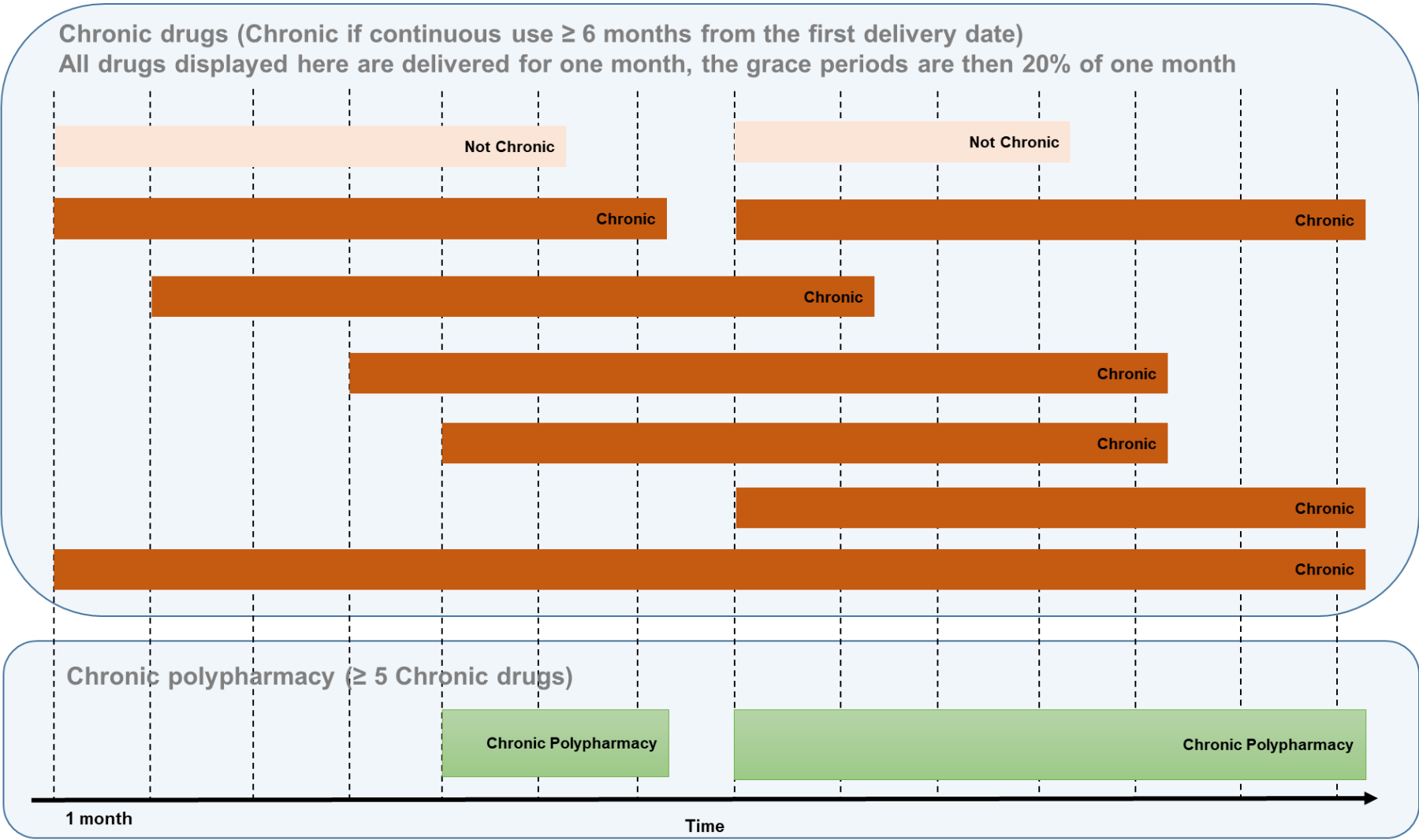


FIGURE S-6 Definition of exposure to a chronic medication and chronic polypharmacy



**TABLE S-I** Prevalence and incidence of chronic polypharmacy in 2015 in the population according to age classes

Age classes	[0-3[ n = 6,308	[3-10[ n = 53,199	[10-18[ n = 57,900	[18-40[ n = 152,610	[40-60[ n = 164,905	[60-70[ n = 69,587	[70-80[ n = 41,452	[80-90[ n = 29,991	≥ 90 n = 8,910
<b>Polypharmacy,</b>									
Prevalence n (%)	0 (0.0)	2 (0.0)	6 (0.0)	293 (0.2)	4,549 (2.8)	8,071 (11.6)	8,950 (21.6)	8,749 (29.2)	2,103 (23.6)
Incidence, n (%)	0 (0.0)	1 (0.0)	3 (0.0)	108 (0.1)	1,073 (0.7)	1,601 (2.3)	1,561 (3.8)	1,516 (5.1)	354 (4.0)
<b>Hyperpolypharmacy</b>									
Prevalence, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	18 (0.0)	365 (0.2)	746 (1.1)	894 (2.2)	832 (2.8)	165 (1.9)
Incidence, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.0)	113 (0.1)	215 (0.3)	252 (0.6)	267 (0.9)	51 (0.6)

n: sample size

**TABLE S-II** Exposure to the ten most frequent pharmacological classes (level 2 of ATC) in chronic polypharmacy according to age

Level 2 of ATC	Population		<75 y-o		≥ 75 y-o		Difference <sup>a</sup>
	Drug-years	%	Drug-years	%	Drug-years	%	
C10 - Lipid modifying agents	13,491	10.0	7,646	10.9	5,846	9.1	1.8
C09 - Agents acting on the renin-angiotensin system	13,186	9.8	6,923	9.8	6,264	9.7	0.1
B01 - Antithrombotic agents	11,581	8.6	5,643	8.0	5,938	9.2	-1.2
C03 - Diuretics	11,538	8.6	5,404	7.7	6,134	9.5	-1.8
A10 - Drugs used in diabetes	10,565	7.8	7,051	10.0	3,514	5.5	4.5
C07 - Beta blocking agents	8,854	6.6	4,651	6.6	4,203	6.5	0.1
A02 - Drugs for acid related disorders	8,692	6.5	4,295	6.1	4,398	6.8	-0.7
C08 - Calcium channel blockers	7,883	5.9	3,989	5.7	3,894	6.0	-0.3
N05 - Psycholeptics	6,789	5.0	4,149	5.9	2,640	4.1	1.8
N06 - Psychoanaleptics	4,503	3.3	2,280	3.2	2,223	3.5	-0.3
R03 - Drugs for obstructive airway diseases	3,456	2.6	1,966	2.8	1,490	2.3	0.5
G04 - Urologicals	3,199	2.4	1,281	1.8	1,918	3.0	-1.2
C01 - Cardiac therapy	3,088	2.3	1,112	1.6	1,976	3.1	-1.5
A12 - Mineral supplements	3,072	2.3	1,231	1.8	1,841	2.9	-1.1
N02 - Analgesics	2,845	2.1	1,392	2.0	1,453	2.3	-0.3

ATC: Anatomic, therapeutic, chemical; y-o: years old; <sup>a</sup> : difference, for a given ATC code between density of exposure in younger people (< 75 years old) and the one in elderly (≥ 75 years old) in percent points, difference >0 means that density of exposure is higher in younger people than in the elderly and vice versa, a null difference means no difference of density of exposure between younger people and elderly.

**TABLE S-III** Exposure to the fifteen most frequent drug classes (level 4 of ATC) in chronic polypharmacy according to age

Level 4 of ATC	EGB Population		< 75 years old		≥ 75 years old		Differences <sup>a</sup>
	Drug-years	%	Drug-years	%	Drug-years	%	
	C10AA - HMG CoA reductase inhibitors	25,795	19.1	14,118	20.1	11,677	
B01AC - Platelet aggregation inhibitors excluding heparin	9,654	7.2	4,913	7.0	4,740	7.4	-0.4
A02BC - Proton pump inhibitors	8,338	6.2	4,106	5.8	4,232	6.6	-0.7
C07AB - Beta blocking agents, selective	7,980	5.9	4,217	6.0	3,763	5.8	0.2
C08CA - Dihydropyridine derivatives	6,852	5.1	3,433	4.9	3,419	5.3	-0.4
C09CA - Angiotensin II receptor blockers	6,787	5.0	3,462	4.9	3,325	5.2	-0.3
C09AA - Angiotensin-converting-enzyme inhibitor	6,242	4.6	3,378	4.8	2,864	4.4	0.4
C03AA – Thiazides	4,777	3.5	2,574	3.7	2,203	3.4	0.3
A10BA - Biguanides	4,173	3.1	2,848	4.0	1,324	2.1	1.9
N05BA - Benzodiazepine derivatives	3,547	2.6	1,987	2.8	1,560	2.4	0.4
C03CA - Sulfamides	3,349	2.5	1,030	1.5	2,319	3.6	-2,1
H03AA - Thyroid hormones	2,531	1.9	1,210	1.7	1,320	2.1	-0.4
M04AA - Preparations inhibiting uric acid production	2,308	1.7	1,162	1.7	1,146	1.8	-0.1
A10BH - Dipeptidyl peptidase 4 (DPP-4) inhibitors	2,305	1.7	1,570	2.2	735	1.1	1,1
A10BB - Sulfonylureas	2,198	1.6	1,382	2.0	816	1.3	0,7

ATC: Anatomic, therapeutic, chemical; <sup>a</sup> : difference, for a given ATC code between density of exposure in younger people (< 75 years old) and the one in elderly ( $\geq 75$  years old) in percent point, difference  $>0$  means that density of exposure is higher in younger people than in elderly and vice versa, a null difference means no difference of density of exposure between younger people and elderly.

**TABLE S-IV** Exposure to the fifteen most frequent drugs (level 5 of ATC) in chronic polypharmacy according to age

Level 5 of ATC	EGB Population		< 75 years old		≥ 75 years old		Differences <sup>a</sup>	
	Drug-years	%	Drug-years	%	Drug-years	%		
B01AC06 - Acetylsalicylic acid	25,795	19.1	14,118	20.1	11,677	18.1	-0.4	
C03AA03 - Hydrochlorothiazide	4,777	3.5	2,574	3.7	2,203	3.4	0.3	
A10BA02 - Metformin	4,173	3.1	2,848	4.0	1,324	2.1	1.9	
C07AB07 - Bisoprolol	3,919	2.9	1,974	2.8	1,945	3.0	-0.2	
C10AA05 - Atorvastatin	3,576	2.7	1,998	2.8	1,579	2.5	0.3	
C08CA01 - Amlodipine	3,553	2.6	1,869	2.7	1,684	2.6	0.1	
A02BC05 - Esomeprazole	3,242	2.4	1,681	2.4	1,562	2.4	0.0	
C03CA01 - Furosemide	3,240	2.4	993	1.4	3,522	3.5	-2.1	
C09AA04 - Perindopril	2,697	2.0	1,472	2.1	1,225	1.9	0.2	
C10AA07 - Rosuvastatin	2,656	2.0	1,608	2.3	1,048	1.6	0.7	
H03AA01 – Levothyroxine sodium	2,524	1.9	1,206	1.7	1,318	2.0	-0.3	
C10AA01 – Simvastatin	2,435	1.8	1,385	2.0	1,050	1.6	0.4	
B01AC04 – Clopidogrel	2,360	1.8	1,183	1.7	1,177	1.8	-0.1	
C09AA05 – Ramipril	2,114	1.6	1,174	1.7	940	1.5	0.2	
C08CA13 - Lercanidipine	2,060	1.5	994	1.4	1,066	1.7	-0.3	

ATC: Anatomic, therapeutic, chemical; <sup>a</sup> : difference, for a given ATC code between density of exposure in younger people (< 75 years old) and the one in elderly (≥ 75 years old) in percent point, difference >0 means that density of exposure is higher in younger people than in elderly and vice versa, a null difference means no difference of density of exposure between younger people and elderly.

**TABLE S-V** Description of the population according to age in the sensitivity analyses

	EGB Population n = 584,862	< 75 years old n = 526,494	≥ 75 years old n = 58,368
No hospitalization sensitivity analysis			
Age, mean (sd)	42.2 (23.6)	37.6 (20.2)	83.1 (6.1)
Sex, n (%)			
Men	288,839 (49.4)	266,151 (50.6)	22,688 (38.9)
Women	296,023 (50.6)	260,343 (49.4)	35,680 (61.1)
Died in 2015, n (%)	4,604 (0.8)	1,551 (0.3)	3,053 (5.2)
No nursing home sensitivity analysis	Population n = 569,605	< 75 years old n = 517,518	≥ 75 years old n = 52,087
Age, mean (sd)	41.3 (23.2)	37.1 (20.0)	82.7 (5.6)
Sex, n (%)			
Men	280,671 (49.3)	260,911 (50.4)	19,760 (37.9)
Women	288,934 (50.7)	256,607 (49.6)	32,327 (62.1)
Died in 2015, n (%)	3,893 (0.7)	1,401 (0.3)	2,492 (4.8)

n: sample size; sd: standard deviation

**TABLE S-VI** Prevalence and incidence of chronic polypharmacy in 2015 according to age for the main and sensitivity analyses

	Polypharmacy		Hyperpolypharmacy	
	Prevalent	Incident	Prevalent	Incident
<b>Population</b>				
Main analysis n (%) / n = 584,862	32,723 (5.6)	6,217 (1.1)	3,020 (0.5)	903 (0.2)
No hospitalization sensitivity analysis n (%) / n = 584,862	32,502 (5.6)	6,198 (1.1)	2,975 (0.5)	889 (0.2)
No nursing home sensitivity analysis n (%) / n = 569,605	32,689 (5.7)	6,217 (1.1)	3,014 (0.5)	903 (0.2)
<b>&lt; 75 years old</b>				
Main analysis n (%) / n = 526,494	17,146 (3.3)	3,527 (0.7)	1,572 (0.3)	443 (0.1)
No hospitalization sensitivity analysis n (%) / n = 526,494	17,048 (3.2)	3,512 (0.7)	1,545 (0.3)	435 (0.1)
No nursing home sensitivity analysis n (%) / n = 517 518	17,137 (3.3)	3,527 (0.7)	1,570 (0.3)	443 (0.1)
<b>≥ 75 years old</b>				
Main analysis n (%) / n = 58,368	15,577 (26.7)	2,690 (4.6)	1,448 (2.5)	460 (0.8)
No hospitalization sensitivity analysis n (%) / n = 58,368	15,454 (26.5)	2,686 (4.6)	1,430 (2.4)	454 (0.8)
No nursing home sensitivity analysis n (%) / n = 52 087	15,552 (29.9)	2,690 (5.2)	1,444 (2.8)	460 (0.9)

n : sample

**TABLE S-VII** Exposure to drug classes (level 1 of ATC) in chronic polypharmacy according to age (main analysis and sensitivity analyses)

Level 1 of ATC	EGB population			< 75 years old			≥ 75 years old		
	Main analysis (%)	No hospit (%)	No nursing home (%)	Main analysis (%)	No hospit (%)	No nursing home (%)	Main analysis (%)	No hospit (%)	No nursing home (%)
A - Alimentary tract and metabolism, (%)	19.1	19.1	19.1	20.1	20.1	20.1	18.1	18.1	18.1
B - Blood and blood forming organs, (%)	9.2	9.2	9.2	8.5	8.5	8.5	10.0	10.0	10.0
C - Cardiovascular system, (%)	44.6	44.6	44.6	43.5	43.6	43.5	45.7	45.7	45.7
D – Dermatologicals, (%)	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3
G - Genito urinary system and sex hormones, (%)	2.7	2.7	2.7	2.2	2.2	2.2	3.1	3.1	3.1
H - Systemic hormonal preparations, excluding sex hormones and insulins, (%)	2.3	2.3	2.3	2.1	2.1	2.1	2.5	2.5	2.5
J - Antiinfectives for systemic use, (%)	0.3	0.3	0.3	0.5	0.5	0.5	< 0.1	0.1	0.1
L - Antineoplastic and immunomodulating agents, (%)	0.5	0.5	0.5	0.7	0.7	0.7	0.4	0.4	0.4
M - Musculo-skeletal system, (%)	2.8	2.8	2.8	2.6	2.6	2.6	3.0	3.0	3.0
N - Nervous system, (%)	12.6	12.6	12.6	13.7	13.6	13.7	11.5	11.5	11.5
P - Antiparasitic products, insecticides and repellents, (%)	< 0.1	< 0.1	< 0.1	< 0.1	0.1	0.1	< 0.1	< 0.1	< 0.1
R - Respiratory system, (%)	4.0	4.0	4.0	4.5	4.5	4.5	3.4	3.4	3.4
S - Sensory organs, (%)	1.5	1.5	1.5	1.1	1.1	1.1	1.9	2.0	1.9
V – Various, (%)	< 0.1	0.1	0.1	< 0.1	0.1	0.1	< 0.1	0.1	0.1

ATC: Anatomic, therapeutic, chemical; hospit.: hospitalization.



**TABLE S-VIII** Exposure to the fifteen most frequent drug classes (level 2 of ATC) in chronic polypharmacy according to age (main analysis and sensitivity analyses)

Level 2 of ATC	Population			<75 years old			≥ 75 years old		
	Main analysis (%)	No hospit (%)	No nursing home (%)	Main analysis (%)	No hospit (%)	No nursing home (%)	Main analysis (%)	No hospit (%)	No nursing home (%)
C10 - Lipid modifying agents	10.0	10.0	10.0	10.9	10.9	10.9	9.1	9.1	9.1
C09 - Agents acting on the renin-angiotensin system	9.8	9.8	9.8	9.8	9.9	9.8	9.7	9.7	9.7
B01 - Antithrombotic agents	8.6	8.6	8.6	8.0	8.0	8.0	9.2	9.2	9.2
C03 – Diuretics	8.6	8.6	8.6	7.7	7.7	7.7	9.5	9.5	9.5
A10 - Drugs used in diabetes	7.8	7.9	7.8	10.0	10.0	10.0	5.5	5.5	5.5
C07 - Beta blocking agents	6.6	6.6	6.6	6.6	6.6	6.6	6.5	6.5	6.5
A02 - Drugs for acid related disorders	6.5	6.4	6.5	6.1	6.1	6.1	6.8	6.8	6.8
C08 - Calcium channel blockers	5.9	5.9	5.9	5.7	5.7	5.7	6.0	6.1	6.0
N05 – Psycholeptics	5.0	5.0	5.0	5.9	5.9	5.9	4.1	4.1	4.1
N06 - Psychoanaleptics	3.3	3.3	3.3	3.2	3.2	3.2	3.5	3.4	3.5
R03 - Drugs for obstructive airway diseases	2.6	2.6	2.6	2.8	2.8	2.8	2.3	2.3	2.3
G04 - Urologicals	2.4	2.4	2.4	1.8	1.8	1.8	3.0	3.0	3.0
C01 - Cardiac therapy	2.3	2.3	2.3	1.6	1.6	1.6	3.1	3.1	3.1
A12 - Mineral supplements	2.3	2.3	2.3	1.8	1.7	1.8	2.9	2.9	2.9
N02 – Analgesics	2.1	2.1	2.1	2.0	2.0	2.0	2.3	2.2	2.3

ATC: Anatomic, therapeutic, chemical; hospit.: hospitalization.

**TABLE S-IX** Exposure to the fifteen most frequent drug classes (level 4 of ATC) in chronic polypharmacy according to age (main analysis and sensitivity analyses)

Level 4 of ATC	Population			< 75 years old			≥ 75 years old		
	Main analysis (%)	No hospit (%)	No nursing home (%)	Main analysis (%)	No hospit (%)	No nursing home (%)	Main analysis (%)	No hospit (%)	No nursing home (%)
C10AA - HMG CoA reductase inhibitors	8.0	8.0	8.0	8.5	8.5	8.5	7.4	7.4	7.4
B01AC - Platelet aggregation inhibitors excluding heparin	7.2	7.2	7.2	7.0	7.0	7.0	7.4	7.4	7.4
A02BC - Proton pump inhibitors	6.2	6.2	6.2	5.8	5.8	5.8	6.6	6.6	6.6
C07AB - Beta blocking agents, selective	5.9	5.9	5.9	6.0	6.0	6.0	5.8	5.8	5.8
C08CA - Dihydropyridine derivatives	5.1	5.1	5.1	4.9	4.9	4.9	5.3	5.3	5.3
C09CA - Angiotensin II receptor blockers	5.0	5.1	5.0	4.9	4.9	4.9	5.2	5.2	5.2
C09AA - Angiotensin-converting-enzyme inhibitor	4.6	4.6	4.6	4.8	4.8	4.8	4.4	4.5	4.4
C03AA - Thiazidiques Non Associes	3.5	3.6	3.5	3.7	3.7	3.7	3.4	3.4	3.4
A10BA - Biguanides	3.1	3.1	3.1	4.0	4.1	4.1	2.1	2.1	2.1
N05BA - Benzodiazepine derivatives	2.6	2.6	2.6	2.8	2.8	2.8	2.4	2.4	2.4
C03CA - Sulfamides	2.5	2.5	2.5	1.5	1.4	1.5	3.6	3.6	3.6
H03AA - Thyroid hormones	1.9	1.9	1.9	1.7	1.7	1.7	2.1	2.0	2.1
M04AA - Preparations inhibiting uric acid production	1.7	1.7	1.7	1.7	1.7	1.7	1.8	1.8	1.8
A10BH - Dipeptidyl peptidase 4 (DPP-4) inhibitors	1.7	1.7	1.7	2.2	2.2	2.2	1.1	1.2	1.1
A10BB - Sulfonylureas	1.6	1.6	1.6	2.0	2.0	2.0	1.3	1.3	1.3

ATC: Anatomic, therapeutic, chemical; hospit.: hospitalization.

C Annexe III Supplementary material: The Burden of Potentially Inappropriate Medications in Chronic Polypharmacy

Supplementary material : The Burden of Potentially Inappropriate Medications in Chronic Polypharmacy

Table S1. Description of Beers/Laroche criteria.

Criteria	Beers/Laroche number	ATC Used	Requirement/Exclusion
1 Antiemetics	Laroche n°30	"A03FA05" "A04AD05"	
2 First-generation antihistamines	Beers n°1 Laroche n°6;7;30	"R06AD01" "R06AE01" "R06AE51" "R06AB01" "R06AB51" "R06AA08" "R06AB04" "R06AB54" "R06AA04" "R06AA54" "R06AB06" "R06AB56" "R06AB02" "R06AB52" "R06AA09" "R06AA59" "N05BB01" "N05BB51" "R06AE05" "R06AE55" "R06AD07" "R06AD08" "R06AB05" "R06AX23" "R06AD02" "R06AD52" "R06AC01" "R03DA12" "R06AX07"	
3 Antiparkinsonian agents	Beers n°2 Laroche n°24	"N04AC01" "N04AA02" "N04AA12" "N04AA01"	
4 Anticholinergic antispasmodics	Beers n°3 Laroche n°29;8	"A03BA01" "A03CB03" "A03BA04" "A03CA02" "A03AA07" "A03AA08" "A03CB03" "A03BA03" "A03CB31" "A03BB03" "A03CB01" "G04BD04" "A03AB05" "A03CA34" "A04AD01" "N05CM05" "A04AD51" "A03BB01" "A03DB04" "G04BD08" "G04CA53" "A03AB17" "A03DA07" "G04BD07" "A03CB" "A03DB"	
5 Antipsychotic drugs	Laroche n°5	"N05AA01" "N05AB02" "N05AC01" "N05AA02" "N05AC04" "N05AA06" "N05AB03"	
6 Antithrombotics	Beers n°4;5 Laroche n°16;31	"B01AC07" "B01AC05"	Exclusion of combination Dipyridamole + aspirine extended release
7 Disopyramide	Beers n°9 Laroche n°15	C01BA03	
8 Short-acting calcium-channel blockers: nifedipine & nicardipine	Beers n°12 Laroche n°12	"C08CA05" "C08CA04"	Exclusion of extended release forms
9 Antidepressants (Tricyclic antidepressants (TCAs)/Paroxetine)	Beers n°14 Laroche n°4	N06AA09" "N06CA01" "N06AA17" "N06AA04" "N06AA01" "N06AA16" "N06AA12" "N06AA02" "N06AA21" "N06AA10" "N06AB05" "N06AA11" "N06AA06"	
10 Barbiturates	Beers n°16	"N05CA02" "N05CA01" "N03AA02" "N05CA06"	
11 Benzodiazepines Short and intermediate acting	Beers n°17 Laroche n°27	"N05BA12" "N05BA21" "N05CD04" "N05CD11" "N05BA06" "N05BA56" "N05CD06" "N05BA04" "N05CD07" "N05CD05"	

12 Benzodiazepines Long acting	Beers n°18 Laroche n°10	"N05BA08" "N05BA09" "N05BA05" "N05BA02" "N03AE01" "N05BA01" "N05CD03" "N05CD01" "N05BA18" "N05CD02" "N05BA16" "N05BA11" "N05CD10"	
13 Meprobamate	Beers n°19 Laroche n°28	"N05BC01" "N05BC51" "N05CX01"	
14 Hypnotics (z-drugs)	Beers n°20 Laroche n°27	"N05CF04" "N05CF02" "N05CF03" "N05CF01"	
15 Ergoloid mesylates	Beers n°21 Laroche n°26	"C04AE01" "C04AE51" "C04AA01" "C04AE04" "C04AE54" "N04BC03" "C04AX10" "G04BE06" "C04AX21" "C04AE02" "C04AD03" "N06BX03" "N04BC08" "C04AE54" "C05CA54" "C04AX17" "C04AX07" "C05CA51"	
16 Desiccated thyroid	Beers n°23	"H03AA05"	
17 Megestrol	Beers n°27	"L02AB01" "G03AC05" "G03DB02" "G03FA08" "G03FB04" "G03AA04" "G03AB01"	
18 Sulfonylureas - long acting	Beers n°28 Laroche n°19	"A10BB06" "A10BB02" "A10BB12" "A10BD06" "A10BD04" "A10BB01" "A10BB07"	
19 Mineral oil, given orally	Beers n°30	"A06AA01" "A06AA51" "A06AD61"	
20 Cimetidine	Laroche n°17	"A02BA01" "A02BA51"	
21 Stimulant laxatives	Laroche n°18	"A06AB02" "A06AB52" "A06AA02" "A06AG10" "A06AB05" "A06AB08" "A06AB58" "A06AB07" "A06AB57" "A06AB06" "A06AB56" "A06AB06" "A06AB56"	
22 Phenylbutazone	Laroche n°2	"M01AA01" "M02AA01" "M01BA01"	
23 Meperidine	Beers n°32	"N02AB02" "N02AG03" "N02AB52" "N02AB72"	
24 Indomethacin Ketorolac	Beers n°34 Laroche n°1	"M01AB01" "C01EB03" "M02AA23" "S01BC01" "S01CC02" "M01AB51" "M01AB15" "S01BC05" "S01FB51"	
25 Pentozocine (ex-Beers 2015)	ex Beers n°35 (Present in the 2015 version, removed in the 2019 update)	"N02AD01"	
26 Skeletal muscle relaxants	Beers n°36 Laroche n°20	"M03BA02" "M03BA52" "M03BA72" "M03BB03" "M03BB53" "M03BB73" "M03BX08" "M03BA03" "M03BA53" "M03BA73" "N04AB02" "M03BC01" "M03BC51" "M03BX07"	
27 Central alpha-agonists	Beers n°8 Laroche n°11	"C02AB" "C02LB" "C02AC01" "N02CX02" "S01EA04" "C02LC01" "C02LC51" "C02AC02" "C02AC05" "C02LC05" "C02AC06"	
28 Estrogens with or without progestins	Beers n°24	"G03CA01" "G03AA15" "G03AB07" "G03AA09" "G03AB05" "G03AA16" "G03AA12" "L02AA03" "G03AA01" "G03AA10"	Exclusion of vaginal administration

		"G03AB06" "G03AA07" "G03AB03" "G03AA03" "G03AB02" "G03AA08" "G03AA04" "G03AB01" "G03AA13" "G03AA05" "G03AB04" "G03AA11" "G03AB09" "G03AA06" "G03AA02" "G03CA03" "G03AB08" "G03CA53" "G03AA17" "G03AA14" "G03CA04" "G03CC06" "G03CA06" "G03CA07" "G03CC04" "G03CA09" "G03CA57" "G03CC07" "G03CB01" "G03CC02" "G03CB02" "G03CC05" "L02AA01" "G03CB03" "G03CC03" "G03CB04" "G03CX01" "G03FA01" "G03FB05" "G03FA02" "G03FA03" "G03FA04" "G03FA05" "G03FA06" "G03FA07" "G03FB02" "G03FA08" "G03FB04" "G03FA09" "G03FA10" "G03FB01" "G03FA11" "G03FB09" "G03FA12" "G03FB06" "G03FA13" "G03FA14" "G03FB08" "G03FA15" "G03FA16" "G03FB11" "G03FA17" "G03FB03" "G03FB07" "G03FB10" "G03FB12" "G03EA01" "G03EA02" "G03EA03" "G03HB01" "L02AA02" "L02AA04"		
29 Reserpine	Laroche n°13 Beers n°8	"C02AA02" "C02LA01" "C02LA51" "C02LA71" "C02AA52"		
30 Antipsychotics, first (conventional) and second (atypical) generation <sup>1</sup>	Beers n°15	"N05A"	Exclusion of Lithium (N05AN) Exclusion of patients with schizophrenia or bipolar disorder (ICD-10 : F20-29; F31; Z51.1)	
31 Insulin, sliding scale <sup>1</sup>	Beers n°26	"A10AB"	Exclusion of fast/ intermediate acting insulin when used at the same time than long acting insulin	
32 NonsSteroidal Anti-Inflammatory Drugs (NSAIDs), oral without Pump proton inhibitor (PPI) <sup>1</sup>	Beers n°33	"N02BA01" "M01" "H02AA01" "H02AA02" "H02AA03" "H02AB01" "A07EA04" "H02AB02" "A01AC02" "H02AB03" "H02AB04" "H02BX01" "H02AB05" "H02AB06" "A07EA01" "A01AC54" "H02AB07" "A07EA03" "H02AB08" "A01AC01" "H02AB09" "A01AC03" "A07EA02" "H02AB10" "H02AB11" "H02AB12" "H02AB13" "H02AB14" "H02AB15" "H02AB17" "A07EA05" "A07EA06" "A07EA07" "M01BA01" "M01BA02" "M01BA03"	Exclusion of low dose aspirin. Exclusion of NSAID used at the same time than PPI	
33 Pump proton inhibitor (PPI) without chronic use of NSAID or corticosteroids <sup>1</sup>	Beers n°32	"A02BC"	Exclusion of PPI used at the same time than Aspirin (high dose), NSAID, corticoids	
34 Psychotics in Parkinsons disease	Beers list inappropriate with	"N05A"	Parkinson patients identified by hospitalizations and long term cover with ICD 10 code : G20	

	disease : Parkinson disease		Or patients with at least 3 fill/refill of a Parkinson drugs (Identified by "N04BA02" "N04BA03" "N04BC01" "N04BC02" "N04BC04" "N04BC07" "N04BD01" "N04BD02" "N04BX01" "N04BX02") Exclusion of lithium (N05AN)
35 (ex Beers 2015) Drugs inappropriate in chronic seizure	Beers list inappropriate with disease : Chronic seizure Present in 2015, removed in the 2019 update	"N06AX12" "A08AA62" "N05AA01" "N05AH02" "N06AA21" "N05AH03" "N05AC02" "N05AF04" "N02AX02" "N02AJ14" "N02AJ15" "N02AJ13"	Chronic seizure/ epilepsy patients identified by hospitalizations and long term cover with ICD 10 code : G40 - 41
36 Antipsychotics and history of fall or fractures <sup>1</sup>	Beers list inappropriate with disease : History of fall and fractures	"N05A"	History of fall and fractures identified by hospitalizations with ICD 10 code : W0 – 1; M84 Exclusion of lithium (N05AN)
37 Antidepressants (TCA, Selective serotonin reuptake inhibitors (SSRIs), or Serotonin–norepinephrine reuptake inhibitors (SNRIs)) with history of fall or fractures <sup>1</sup>	Beers list inappropriate with disease : History of fall and fractures	"N06AA" "N06AB" "G04BX14" "N06AX21" "N06AX16" "N06AX17" "N06AX23" "N06AX06"	History of fall and fractures identified by hospitalizations with ICD 10 code : W0 – 1; M
38 Opioids and history of fall or fractures <sup>1</sup>	Beers list inappropriate with disease : History of fall and fractures	"N02A"	History of fall and fractures identified by hospitalizations with ICD 10 code : W0 – 1; M

<sup>1</sup>Partially applicable criterion. PPIs: proton pump inhibitors; NSAIDs: nonsteroidal anti-inflammatory drugs, TCAs: Tricyclic antidepressants, SSRIs: Selective serotonin reuptake inhibitors, SNRIs: Serotonin–norepinephrine reuptake inhibitors.

**Table S2.** Description of PROMPT inappropriate criteria.

Criteria	PROMPT number	ATC Used	Requirement/Exclusion
PR0 stimulant laxatives (except if concurrent use of opioids)	PROMPT n°1	"A06AB02" "A06AB52" "A06AA02" "A06AG10" "A06AB05" "A06AB08" "A06AB58" "A06AB07" "A06AB57" "A06AB06" "A06AB56" "A06AB06" "A06AB56"	Exclusion of patients who have not received a non stimulant laxative the year before (means first line treatment; ATC: "A06AB02" "A06AB52" "A06AA02" "A06AG10" "A06AB05" "A06AB08" "A06AB58" "A06AB07" "A06AB57" "A06AB06" "A06AB56" "A06AB06" "A06AB56") Exclusion of patient who used an opioid at the same time (ATC: N02A)
PR1 Association of esomeprazole/omeprazole and clopidogrel	PROMPT n°3	"B01AC04" "A02BC01" "A02BC05"	Both inappropriate only if used at the same time (day)
PR2 Cardio-selective calcium-channel blockers and beta blockers	PROMPT n°6	"C08DB01" "C05AE03" "C08DA01" "C07A"	Both inappropriate only if used at the same time (day)
PR3 Dipyridamol – short acting	PROMPT n°7	B01AC07	Exclusion of combination Dipyridamole + aspirine extended release
PR4 First generation antihistamines	PROMPT n°8	"R06AD01" "R06AE01" "R06AE51" "R06AB01" "R06AB51" "R06AA08" "R06AB04" "R06AB54" "R06AA04" "R06AA54" "R06AB06" "R06AB56" "R06AB02" "R06AB52" "R06AA09" "R06AA59" "N05BB01" "N05BB51" "R06AE05" "R06AE55" "R06AD07" "R06AD08" "R06AB05" "R06AX23" "R06AD02" "R06AD52" "R06AC01" "R03DA12" "R06AX07"	
PR5 Theophylline in monotherapy	PROMPT n°9	"R03DA04" "R03DB04" "R03DA54" "R03DA74"	Exclusion of patients using a inhaled corticoid at the same time (ATC: "R03BA")
PR6 Oral corticoid (without use of bisphosphonate)	PROMPT n°10	"H02AA01" "H02AA02" "H02AA03" "H02AB01" "A07EA04" "H02AB02" "A01AC02" "H02AB03" "H02AB04" "H02BX01" "H02AB05" "H02AB06" "A07EA01" "A01AC54" "H02AB07" "A07EA03" "H02AB08" "A01AC01" "H02AB09" "A01AC03" "A07EA02" "H02AB10" "H02AB11" "H02AB12" "H02AB13" "H02AB14" "H02AB15" "H02AB17" "A07EA05" "A07EA06" "A07EA07" "M01BA01" "M01BA02" "M01BA03"	Exclusion of patient using a bisphosphonate at the same time (ATC: "M05BA")



PR7 Association of Selective serotonin reuptake inhibitors (SSRIs) and Venlafaxine <sup>1</sup>	PROMPT n°12	"N06AB" "N06AX16"	Both inappropriate only if used at the same time (day)
PR8 Tricyclic antidepressants (TCA) in first line treatment	PROMPT n°13	"N06AA"	Exclusion of patients who have received another antidepressant before (in the same year or the year before, it means first line treatment; ATC: "N06A" except N06AA)
PR91 Benzodiazepines – Short and intermediate acting	PROMPT n°14	"N05BA12" "N05BA21" "N05CD04" "N05CD11" "N05BA06" "N05BA56" "N05CD06" "N05BA04" "N05CD07" "N05CD05"	
PR92 Benzodiazepines – long acting	PROMPT n°14	"N05BA08" "N05BA09" "N05BA05" "N05BA02" "N03AE01" "N05BA01" "N05CD03" "N05CD01" "N05BA18" "N05CD02" "N05BA16" "N05BA11" "N05CD10"	
PR10 Hypnotics	PROMPT n°15	"N05CF04" "N05CF02" "N05CF03" "N05CF01"	
PR11 Carbamazepine used with Erythromycin/Clarithromycin	PROMPT n°16	"N03AF01"	Exclusion of day when patients received/used Erythromycin/Clarithromycin even if this latter was not chronic (cumulative use of at least 6 months)
PR12 Opioid (use without laxative)	PROMPT n°17	"N02A"	Exclusion of patient using a laxative at the same time (ATC: "A06")
PR13 Nitrofurantoin chronic	PROMPT n°18	"J01XE01" "J01XE51"	
PR14 Sulfonylureas - long acting	PROMPT n°19	"A10BB"	
PR15 Chronic Non-steroidal anti-inflammatory drugs (NSAIDs)	PROMPT n°20	"M01A"	
PR16 Association of two drugs among NSAIDs, Low dose aspirin or SSRI, without use of a Proton pump inhibitors (PPIs)	PROMPT n°22	"B01AC06" "N06AB" "G04BX14"	Exclusion of patient using a laxative at the same time (ATC: "A02BC")

PPIs: proton pump inhibitors; NSAIDs: nonsteroidal anti-inflammatory drugs, TCAs: Tricyclic antidepressants, SSRIs: Selective serotonin reuptake inhibitors.

**Table S3.** Overlaps in combined Beers/Laroche list and PROMPT list.

	Beers/ Laroche criteria from table S1	PROMPT criteria from table S2
First-generation antihistamines	2	PR4
Short-acting calcium-channel blockers: nifedipine & nicardipine	8	PR2
Tricyclic antidepressants (TCAs)	9	PR8
Benzodiazepines	11	PR91
Short and intermediate acting Benzodiazepines	12	PR92
Long acting Hypnotics (z-drugs)	14	PR10
Sulfonylureas - long acting	18	PR14
Stimulant laxatives	21	PR0
Non-cyclooxygenase-selective NSAIDs, oral	32 without Pump proton inhibitor (PPI)	PR15
Pump proton inhibitor (PPI) without chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids	33 all PPIs without chronic use of NSAID or corticosteroids	PR1 (interaction Omeprazole clopidogrel)
Antidepressants (TCA, Selective serotonin reuptake inhibitors (SSRIs), or Serotonin-norepinephrine reuptake inhibitors (SNRIs))	37 with history of fall or fractures	PR7 Association of SSRI and Venlafaxine1
Opioids	38 with history of fall or fractures	PR12 use without laxative

PPIs: proton pump inhibitors; NSAIDs: nonsteroidal anti-inflammatory drugs, TCAs: Tricyclic antidepressants, SSRIs: Selective serotonin reuptake inhibitors, SNRIs: Serotonin-norepinephrine reuptake inhibitors.

**Table S4.** Prevalences of long term diseases according to chronic polypharmacy in 2016 in older adults.

Long-term diseases <sup>1</sup> per age class	Cohort	Chronic Polypharmacy	Chronic Hyperpolypharmacy
<b>Older adults (n)</b>	<b>117,545</b>	<b>27,834</b>	<b>2868</b>
1 - Stroke, n (%)	3639 (3.10)	1534 (5.51)	164 (5.72)
2 - Bone marrow failure and chronic cytopenia, n (%)	196 (0.17)	63 (0.23)	12 (0.42)
pl3 - Ischemic artery disease, n (%)	4727 (4.02)	2323 (8.35)	305 (10.63)
4 - Schistosomiasis, n (%)	0 (0.00)	0 (0.00)	0 (0.00)
5 - Heart failure, arrhythmia or valvular heart disease, n (%)	10,529 (8.96)	4610 (16.56)	502 (17.50)
6 - Chronic liver disease and cirrhosis, n (%)	738 (0.63)	211 (0.76)	33 (1.15)
7 - Primary immunodeficiency or HIV positive, n (%)	151 (0.13)	65 (0.23)	13 (0.45)
8 - Diabetes (type 1 or type 2), n (%)	17,020 (14.48)	8553 (30.73)	1408 (49.09)
9 - Major neuromuscular disease (including myopathy) and severe epilepsy, n (%)	959 (0.82)	333 (1.20)	47 (1.64)
10 - Haemoglobinopathy - Haemolysis - chronic hereditary or acquired and major, n (%)	24 (0.02)	6 (0.02)	1 (0.03)
11 - Haemophilia, n (%)	123 (0.10)	34 (0.12)	10 (0.35)
12 - Major high blood pressure, n (%)	6,677 (5.68)	3554 (12.77)	556 (19.39)
13 - Coronary artery disease, n (%)	9,682 (8.24)	5241 (18.83)	682 (23.78)

Long-term diseases <sup>1</sup> per age class	Cohort	Chronic Polypharmacy	Chronic Hyperpolypharmacy
14 – Major chronic respiratory failure, n (%)	2658 (2.26)	1183 (4.25)	267 (9.31)
15 - Alzheimer or other dementia, n (%)	4,230 (3.60)	1242 (4.46)	112 (3.91)
16 – Parkinson diseases, n (%)	1305 (1.11)	497 (1.79)	69 (2.41)
17 - Inborn errors of metabolism, n (%)	261 (0.22)	69 (0.25)	2 (0.07)
18 - Cystic fibrosis, n (%)	1 (0.00)	0 (0.00)	0 (0.00)
19 – Major chronic nephropathy and primary nephrotic syndrome, n (%)	1262 (1.07)	612 (2.20)	95 (3.31)
20 - Paraplegia, n (%)	105 (0.09)	29 (0.10)	3 (0.10)
21 - Vasculitis - Systemic lupus erythematosus - Systemic scleroderma, n (%)	539 (0.46)	205 (0.74)	22 (0.77)
22 - Rheumatoid arthritis, n (%)	1333 (1.13)	476 (1.71)	66 (2.30)
23 - Long term psychiatric disease, n (%)	3807 (3.24)	1513 (5.44)	283 (9.87)
24 – Crohn disease and ulcerative colitis, n (%)	293 (0.25)	79 (0.28)	13 (0.45)
25 - Multiple sclerosis, n (%)	165 (0.14)	54 (0.19)	6 (0.21)
26 – Scoliosis, idiopathic and evolving, n (%)	58 (0.05)	16 (0.06)	0 (0.00)
27 – Major Spondyloarthropathy, n (%)	266 (0.23)	81 (0.29)	11 (0.38)
28 – Organ transplantation follow-up, n (%)	56 (0.05)	27 (0.10)	4 (0.14)
29 – Active tuberculosis or Leprosy, n (%)	56 (0.05)	12 (0.04)	1 (0.03)
30 - Cancer or leukemia, n (%)	15,077 (12.83)	4079 (14.65)	431 (15.03)

<sup>1</sup>list of 30 specifically individualized chronic diseases defined by the French Health Care Insurance System.

**Table 5.** Prevalences of long term diseases according to polypharmacy in 2016 in middle-aged adults.

Long-term diseases <sup>1</sup> per age class	Cohort	Chronic Polypharmacy	Chronic Hyperpolypharmacy
<b>Middle-aged adults (n)</b>	<b>159,243</b>	<b>8666</b>	<b>760</b>
1 - Stroke, n (%)	1315 (0.83)	374 (2.71)	43 (5.66)
2 - Bone marrow failure and chronic cytopenia, n (%)	39 (0.02)	3 (0.03)	0 (0.00)
3 - Ischemic artery disease, n (%)	1599 (1.00)	478 (5.52)	57 (7.50)
4 - Schistosomiasis, n (%)	0 (0.00)	0 (0.00)	0 (0.00)
5 – Heart failure, arrhythmia or valvular heart disease, n (%)	1908 (1.20)	568 (6.55)	74 (9.74)
6 – Chronic liver disease and cirrhosis, n (%)	1109 (0.70)	159 (1.83)	16 (2.11)
7 - Primary immunodeficiency or HIV positive, n (%)	662 (0.42)	157 (1.81)	15 (1.97)
8 - Diabetes (type 1 or type 2), n (%)	9602 (6.03)	2980 (34.39)	417 (54.87)
9 – Major neuromuscular disease (including myopathy) and severe epilepsy, n (%)	1000 (0.63)	197 (2.27)	17 (2.24)
10 - Haemoglobinopathy – Haemolysis – chronic hereditary or acquired and major, n (%)	31 (0.02)	4 (0.05)	0 (0.00)
11 - Haemophilia, n (%)	110 (0.07)	19 (0.22)	1 (0.13)

Long-term diseases <sup>1</sup> per age class	Cohort	Chronic Polypharmacy	Chronic Hyperpolypharmacy
12 - Major high blood pressure, n (%)	1446 (0.91)	595 (6.87)	82 (10.79)
13 - Coronary artery disease, n (%)	3566 (2.24)	1545 (17.83)	167 (21.97)
14 - Major chronic respiratory failure, n (%)	1,221 (0.77)	350 (4.04)	75 (9.87)
15 - Alzheimer or other dementia, n (%)	90 (0.06)	15 (0.17)	2 (0.26)
16 - Parkinson diseases, n (%)	156 (0.10)	39 (0.45)	5 (0.66)
17 - Inborn errors of metabolism, n (%)	260 (0.16)	28 (0.32)	4 (0.53)
18 - Cystic fibrosis, n (%)	1 (0.00)	0 (0.00)	0 (0.00)
19 - Major chronic nephropathy and primary nephrotic syndrome, n (%)	477 (0.30)	169 (1.95)	22 (2.89)
20 - Paraplegia, n (%)	138 (0.09)	20 (0.23)	2 (0.26)
21 - Vasculitis - Systemic lupus erythematosus - Systemic scleroderma, n (%)	364 (0.23)	66 (0.76)	12 (1.58)
22 - Rheumatoid arthritis, n (%)	997 (0.63)	145 (1.67)	20 (2.63)
23 - Long term psychiatric disease, n (%)	6301 (3.96)	1385 (15.98)	186 (24.47)
24 - Crohn disease and ulcerative colitis, n (%)	656 (0.41)	42 (0.48)	3 (0.39)
25 - Multiple sclerosis, n (%)	438 (0.28)	60 (0.69)	9 (1.18)
26 - Scoliosis, idiopathic and evolving, n (%)	54 (0.03)	9 (0.10)	0 (0.00)
27 - Major Spondyloarthropathy, n (%)	604 (0.38)	62 (0.72)	8 (1.05)
28 - Organ transplantation follow-up, n (%)	67 (0.04)	31 (0.36)	4 (0.53)
29 - Active tuberculosis or Leprosy, n (%)	53 (0.03)	3 (0.03)	0 (0.00)
30 - Cancer or leukemia, n (%)	6914 (4.34)	688 (7.94)	61 (8.03)

<sup>1</sup>list of 30 specifically individualized chronic diseases defined by the French Health Care Insurance System.

**Table 6.** Prevalence and exposure to potentially inappropriate medications in older adults with chronic polypharmacy according to Beers criteria, Laroche list.

	Older adults with chronic polypharmacy	Older adults with chronic hyperpolypharmacy	Exposure to chronic polypharmacy in older adults (%)
	n = 27,834	n = 2868	100
Potentially inappropriate medication - broad <sup>1</sup>	18,036 (64.8)	2544 (88.7)	13.5
Potentially inappropriate medication-narrow <sup>2</sup>	10,220 (36.7)	1730 (60.3)	6.7
Beers/Laroche criteria			
1 Antiemetics	0 (0.0)	0 (0.0)	0.0
2 First-generation antihistamines	659 (2.4)	159 (5.5)	0.3
3 Antiparkinsonian agents	133 (0.5)	21 (0.7)	0.1
4 Anticholinergic antispasmodics	626 (2.3)	119 (4.2)	0.3
5 Antipsychotic drugs	223 (0.8)	47 (1.6)	0.1
6 Antithrombotics	23 (0.1)	4 (0.1)	<0.1

	Older adults with chronic polypharmacy	Older adults with chronic hyperpolypharmacy	Exposure to chronic polypharmacy in older adults (%)
	n = 27,834	n = 2868	100
7 Disopyramide	23 (0.1)	0 (0.0)	< 0.1
8 Short-acting calcium-channel blockers: nifedipine & nifedipine	19 (0.1)	5 (0.2)	0.0
9 Antidepressants (Tricyclic antidepressants (TCAs)/Paroxetine)	1324 (4.8)	228 (8.0)	0.7
10 Barbiturates	87 (0.3)	10 (0.4)	0.1
11 Benzodiazepines Short and intermediate acting	3807 (13.7)	660 (23.0)	2.0
12 Benzodiazepines Long acting	1271 (4.6)	286 (10.0)	0.6
13 Meprobamate	0 (0.0)	0 (0.0)	0.0
14 Hypnotics (z-drugs)	1688 (6.1)	382 (13.3)	0.8
15 Ergoloid mesylates	380 (1.4)	71 (2.5)	0.2
16 Desiccated thyroid	0 (0.0)	0 (0.0)	0.0
17 Megestrol	0 (0.0)	0 (0.0)	0.0
18 Sulfonylureas - long acting	1071 (3.9)	201 (7.0)	0.6
19 Mineral oil, given orally	205 (0.7)	39 (1.4)	0.1
20 Cimetidine	3 (0.0)	0 (0.0)	0.0
21 Stimulant laxatives	1 (0.0)	0 (0.0)	0.0
22 Phenylbutazone	0 (0.0)	0 (0.0)	0.0
23 Meperidine	0 (0.0)	0 (0.0)	0.0
24 Indomethacin Ketorolac	24 (0.1)	6 (0.2)	< 0.1
25 Pentozocine (ex-Beers 2015)	0 (0.0)	0 (0.0)	0.0
26 Skeletal muscle relaxants	0 (0.0)	0 (0.0)	0.0
27 Central alpha-agonists	1404 (5.0)	308 (10.7)	0.8
28 Estrogens with or without progestins	181 (0.7)	35 (1.2)	0.1
29 Reserpine	0 (0.0)	0 (0.0)	0.0
30 Antipsychotics, first (conventional) and second (atypical) generation <sup>3</sup>	227 (0.8)	43 (1.5)	0.1
31 Insulin, sliding scale <sup>1</sup>	108 (0.4)	40 (1.4)	< 0.1
32 NonsSteroidal Anti-Inflammatory Drugs (NSAIDs), oral without Pump proton inhibitor (PPI) <sup>3</sup>	418 (1.5)	65 (2.3)	0.2
33 Pump proton inhibitor (PPI) without chronic use of NSAID or corticosteroids <sup>3</sup>	12,073 (43.4)	1924 (67.1)	6.3
34 Psychotics in Parkinsons disease	66 (0.2)	10 (0.4)	< 0.1
35 (ex Beers 2015) Drugs innappropriate in chronic seizure	34 (0.1)	7 (0.2)	< 0.1
36 Antipsychotics and history of fall or fractures <sup>3</sup>	86 (0.3)	14 (0.5)	< 0.1
37 Antidepressants (TCA, Selective serotonin reuptake inhibitors (SSRIs), or Serotonin–norepinephrine reuptake inhibitors (SNRIs)) with history of fall or fractures <sup>3</sup>	420 (1.5)	73 (2.6)	0.2
38 Opioids and history of fall or fractures <sup>3</sup>	134 (0.5)	35 (1.2)	0.1

<sup>1</sup>considering both fully and partially applicable criteria <sup>2</sup>considering only fully applicable criteria <sup>3</sup>partially applicable criteria, <sup>1,2,3</sup>more details are provided in table S1. PPIs: proton pump inhibitors; NSAIDs: nonsteroidal anti-inflammatory drugs, TCAs: Tricyclic antidepressants, SSRIs: Selective serotonin reuptake inhibitors, SNRIs: Serotonin–norepinephrine reuptake inhibitors.

**Table 7.** Prevalence and exposure to potentially inappropriate medications and interactions in middle-aged adults with chronic polypharmacy according to PROMPT criteria.

	Middle-aged adults with chronic polypharmacy	Middle-aged adults with chronic hyperpolypharmacy	Exposure to chronic polypharmacy in middle-aged adults (%)
	n = 8,666	n = 760	100
Potentially inappropriate medication	4009 (46.2)	570 (75.0)	10.4
PR0 stimulant laxatives (except if concurrent use of opioids)	0 (0.0)	0 (0.0)	0.0
PR1 Association of esomeprazole/omeprazole and clopidogrel	251 (2.9)	59 (7.8)	0.8
PR2 Cardio-selective calcium-channel blockers and beta blockers	28 (0.3)	4 (0.5)	0.1
PR3 Dipyridamol – short acting	2 (0.0)	0 (0.0)	0.0
PR4 First generation antihistamines	450 (5.2)	90 (11.8)	0.7
PR5 Theophylline in monotherapy	15 (0.2)	4 (0.5)	< 0.1
PR6 Oral corticoid (without use of bisphosphonate)	176 (2.0)	38 (5.0)	0.3
PR7 Association of Selective serotonin reuptake inhibitors (SSRIs)and Venlafaxine <sup>1</sup>	15 (0.2)	1 (0.1)	< 0.1
PR8 Tricyclic antidepressants (TCA) in first line treatment	107 (1.2)	16 (2.1)	0.2
PR91 Benzodiazepines – Short and intermediate acting	1395 (16.1)	232 (30.5)	2.7
PR92 Benzodiazepines – long acting	879 (10.1)	138 (18.2)	1.5
PR10 Hypnotics	637 (7.4)	115 (15.1)	1.0
PR11 Carbamazepine used with Erythromycin/Clarithromycin	2 (0.0)	1 (0.0)	0.0
PR12 Opioid (use without laxative)	639 (7.4)	143 (18.8)	1.1
PR13 Nitrofurantoin chronic	0 (0.0)	0 (0.0)	0.0
PR14 Sulfonylureas - long acting	1069 (12.3)	178 (23.4)	1.9
PR15 Chronic Non-steroidal anti-inflammatory drugs (NSAIDs)	80 (0.9)	14 (1.8)	0.1
PR16 Association of two drugs among NSAIDs, Low dose aspirin or SSRI, without use of a Proton pump inhibitors (PPIs) <sup>1</sup>	9 (0.1)	0 (0.0)	< 0.1

<sup>1</sup>This criteria considered both drugs in the association as potentially inappropriate, PPIs: proton pump inhibitors; NSAIDs: nonsteroidal anti-inflammatory drugs, TCAs: Tricyclic antidepressants, SSRIs: Selective serotonin reuptake inhibitors.

**Table 8.** The RECORD statement for pharmacoepidemiology (RECORD-PE) checklist of items, extended from the STROBE and RECORD statements, which should be reported in non-interventional pharmacoepidemiological studies using routinely collected health data.

Item No	STROBE items	RECORD items	RECORD-PE items	Page No
<b>Title and abstract</b>				
1	(a) Indicate the study’s design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. 1.2: If applicable, the geographical region and timeframe within which the study took place should be reported in the title or abstract. 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	—	1
<b>Introduction</b>				
Background rationale				
2	Explain the scientific background and rationale for the investigation being reported.	—	—	1
Objectives				
3	State specific objectives, including any prespecified hypotheses.	—	—	2
<b>Methods</b>				
Study design				
4	Present key elements of study design early in the paper.	—	4.a: Include details of the specific study design (and its features) and report the use of multiple designs if used. 4.b: The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant.	2
Setting				
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	—	—	2
Participants				
6	(a) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.	6.1: The methods of study population selection (such as codes or algorithms used to identify participants) should be listed in detail. If this is not possible, an explanation should be provided. 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1.a: Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and whether patients were allowed to enter the study population once or if multiple entries were permitted. See explanatory document for guidance related to matched designs.	Not applicable
Variables				
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1.a: Describe how the drug exposure definition was developed. 7.1.b: Specify the data sources from which drug exposure information for individuals was obtained.	Pages 2 - 3

				7.1.c: Describe the time window(s) during which an individual is considered exposed to the drug(s). The rationale for selecting a particular time window should be provided. The extent of potential left truncation or left censoring should be specified. 7.1.d: Justify how events are attributed to current, prior, ever, or cumulative drug exposure. 7.1.e: When examining drug dose and risk attribution, describe how current, historical or time on therapy are considered. 7.1.f: Use of any comparator groups should be outlined and justified. 7.1.g: Outline the approach used to handle individuals with more than one relevant drug exposure during the study period.	
<b>Data sources/measurement</b>					
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	—		8.a: Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the drug(s) of interest was prescribed.	Pages 2-3
<b>Bias</b>					
9	Describe any efforts to address potential sources of bias.	—	—		Not applicable
<b>Study size</b>					
10	Explain how the study size was arrived at.	—	—		Page 3
<b>Quantitative variables</b>					
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	—	—		Page 3
<b>Statistical methods</b>					
12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross sectional study—if applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.	—		12.1.a: Describe the methods used to evaluate whether the assumptions have been met. 12.1.b: Describe and justify the use of multiple designs, design features, or analytical approaches.	Not applicable
<b>Data access and cleaning methods</b>					
12		—		12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. 12.2: Authors should provide information on the data cleaning methods used in the study.	Table S1 and S2
<b>Linkage</b>					
12		—		12.3: State whether the study included person level, institutional level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page 2
<b>Results</b>					
<b>Participants</b>					



13	(a) Report the numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	13.1: Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the text or by means of the study flow diagram.	—	Page 3
Descriptive data				
14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—summarise follow-up time (eg, average and total amount).	—	—	Pages 3 - 4
Outcome data				
15	Cohort study—report numbers of outcome events or summary measures over time. Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross sectional study—report numbers of outcome events or summary measures.	—	—	Pages 4 - 6
Main results				
16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables are categorised. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	—	—	Not applicable
Other analyses				
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	Not applicable
<b>Discussion</b>				
Key results				
18	Summarise key results with reference to study objectives.	—	—	Page 6
Limitations				
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	19.1.a: Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest.	Page 7
Interpretation				
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	—	20.a: Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when relevant. [A: Original text indicated this item was RECORD (ie, not RECORD-PE)?]	Pages 6 - 8
Generalisability				
21	Discuss the generalisability (external validity) of the study results.	—	—	Page 6 - 8

Other information				
Funding				
22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	—	—	Page 8
Accessibility of protocol, raw data, and programming code				
22	—	22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	—	Not applicable

RECORD=reporting of studies conducted using observational routinely collected data; RECORD-PE=RECORD for pharmacoepidemiological research; STROBE=strengthening the reporting of observational studies in epidemiology.

**\*REFERENCE: Langan SM, Schmidt S, Wing K, Ehrenstein V, Nicholls S, Filion K, Klungel O, Petersen I, Sorensen H, Guttman A, Harron K, Hemkens L, Moher D, Schneeweiss S, Smeeth L, Sturkenboom M, von Elm E, Wang S, Benchimol EI. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement for Pharmacoepidemiology (RECORD-PE). *BMJ* 2018; 363: k3532.**

D Annexe IV - Supplementary material: The burden of potentially inappropriate medications in United States veterans aged 49-70 years increases with chronic polypharmacy

The burden of potentially inappropriate medications in United States veterans aged 49-70 years increases with chronic polypharmacy

Supplementary material

Table S4 Drugs identified as potentially inappropriate medications defined by Beers and Laroche criteria according to the VA generic name and specific requirement of the definition.

Inappropriateness	Generic name	requirements
Beers1 – Anticholinergics - First-generation antihistamines	Brompheniramine ; Chlorpheniramine ; Clematine ; Cyproheptadine ; Dexbrompheniramine ; Dexchlorpheniramine ; Dimenhydrinate ; Diphenhydramine ; Doxylamine ; Hydroxyzine ; Meclizine ; Promethazine ; Pyrilamine ; Triprolidine	None
Beers2 - Anticholinergics - Antiparkinsonian agent	Benztropine ; Trihexyphenidyl	None
LarocheB2 - Anticholinergics - Antiparkinsonian agent	Biperiden	None
Beers3 – Anticholinergics - Antispasmodics	Atropine ; Belladonna alkaloid ; Clidinium ; Dicyclomine ; Homatropine ; Hyosciamine ; Methylscopolamine ; Propantheline ; Scopolamine ; chlordiazepoxide	None
LarocheB3 – Anticholinergics - Antispasmodics	Diphenoxylate; Oxybutinin; Solifenacin; Tolterodine	None
Beers4 – Antithrombotics - Dipyridamole	Dipyridamole	None
Beers4_(V 2015) – Antithrombotics - Ticlopidine	Ticlopidine	None
Beers6 - Anti-infective - Nitrofurantoin	Nitrofurantoin	None
Beers8 – Cardiovascular - Central alpha agonist	Clonidine ; Guanfacine ; Methyldopa ; Reserpine	None
Beers9 – Cardiovascular - Disopyramidine	Disopyramide	None
Beers12 – Cardiovascular – Nifedipine\ Nicardipine Immediate release	Nicardipine ; Nifedipine	Were inappropriate only immediate release drugs
Beers14 - Central Nervous System - antidepressants	Amitriptyline ; Amoxapine ; Clomipramine ; Desipramine ; Imipramine ; Nortriptyline ; Paroxetine ; Protriptyline ; Trimipramine	None

Inappropriateness	Generic name	requirements
LarocheB14 - Central Nervous System - antidepressants	Doxepine ; Maprotiline	None
Beers15 - Central Nervous System - Antipsychotics	Aripiprazole ; Asenapine; Chlorpromazine; Clozapine; Droperidol; Fluphenazine; Haloperidol; Iloperidone; Loxapine; Lurasidone; Mesoridazine; Molindone; Olanzapine; Paliperidone; Perphenazine; Pimozide; Prochlorperazine; Quetiapine; Risperidone; Thioridazine; Tiotixene(Thiothixene); Trifluoperazine ; Ziprasidone	Not applied to veterans with schizophrenia or bipolar disorders
Beers16 - Central Nervous System - Barbituriques	Butabarbital ; Mephobarbital ; Phenobarbital ; Secobarbital	None
Beers17 - Central Nervous System - Benzodiazepines Short/intermediate acting	Alprazolam ; Estazolam ; Lorazepam ; Oxazepam ; Temazepam ; Triazolam	Not applied to veterans with anxiety
Laroche17 – Gastrointestinal - Stimulant Laxatives	Bisacodyl ; Cimetidine ; Docusate ; Sennosides	None
Beers18 - Central Nervous System - Benzodiazepines Long acting	Chlordiazepoxide ; Clonazepam ; Clorazepate ; Diazepam ; Flurazepam	None
Beers19 - Central Nervous System - Meprobamate	Meprobamate	None
Beers20 - Central Nervous System - Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (Z-drugs)	Eszopiclone ; Zaleplon ; Zolpidem	None
Beers21 - Central Nervous System - Ergoloid mesylates or Isoxsuprine	Ergoloid mesylates	None
LarocheB21 - Central Nervous System - Other Cerebral vasodilators	Pentoxifylline	None
Beers23 – Endocrine - Thyroid	desiccated thyroid	None

Inappropriateness	Generic name	requirements
Beers26 – Endocrine – Insulin sliding scale	Insulin	Were considered inappropriate only when rapid and intermediate insulin (regular, human, Aspart, Glulisine, Apidra, Lispro, Humulin, Humalog, Novolog, Novolin) were not used at the same time than slow insulin (Degluteq, Detemir, Glargine, Lantus, Levemir)
Beers27 – Endocrine – Megestrol	Megestrol	None
Beers28 – Endocrine - Sulfonylureas, long acting	Chlorpropamide ; Glimepiride ; Glyburide (glibenclamide)	None
LarocheB28 – Endocrine - Sulfonylureas, long acting	Glipizide	None
Beers29 – Gastrointestinal - Metoclopramide	Metoclopramide	None
Beers31 – Gastrointestinal - Pump Proton Inhibitors	Dexlansoprazole ; Esomeprazole ; Lansoprazole ; Omeprazole ; Pantoprazole ; Rabeprazole	Not applied to veterans with oesophagitis, helicobacter, current chronic use of nonsteroidal anti-inflammatory drugs, all-dose aspirin or corticoid
Beers32 - Pain Medications - Meperidine	Meperidine (or pethidine)	None
Beers33 - Pain Medications - Nonsteroidal anti-inflammatory drugs	Celecoxib; Diclofenac; Etodolac; Ibuprofen; Ketoprofen; Meloxicam; Nabumetone; Naproxen ; Oxaprozin ; Piroxicam ; Sulindac	Not applied to veterans with current chronic use of Pump Proton Inhibitors Aspirin was excluded
Beers34 - Pain Medications - Indomethacin et ketorolac	Indomethacin ; Ketorolac	None
Beers35 - Pain Medications - Skeletal muscle relaxants	Carisoprodol ; Cyclobenzaprine ; Methocarbamol	
Chronic_seizures_or_epilepsy	Bupropion ; Chlorpromazine; Clozapine; Olanzapine; Thioridazine; Tiotixene(Thiothix); Tramadol	Applied only to veterans with Chronic seizure or epilepsy

Inappropriateness	Generic name	requirements
Delirium	Aripiprazole ; Asenapine; Beclomethasone; Budesonide; Chlorpromazine; Clozapine; Dexamethasone; Droperidol; Famotidine; Fludrocortisone; Fluphenazine; Haloperidol; Hydrocortisone; Iloperidone; Loxapine; Lurasidone; Mesoridazine; Methylprednisolone; Molindone; Olanzapine; Paliperidone; Perphenazine; Pimozide; Prednisolone; Prednisone; Prochlorperazine; Quetiapine; Ranitidine; Risperidone; Thioridazine; Tiotixene(Thiothixene); Triamcinolone ; Trifluoperazine ; Ziprasidone	Applied only to veterans with history of delirium
Dementia_or_cognitive_impairment	Aripiprazole ; Asenapine; Chlorpromazine; Cimetidine ; Clozapine; Droperidol; Famotidine ; Fluphenazine; Haloperidol; Iloperidone; Loxapine; Lurasidone; Mesoridazine; Molindone; Olanzapine; Paliperidone; Perphenazine; Pimozide; Prochlorperazine; Quetiapine; Ranitidine;Risperidone; Thioridazine; Tiotixene(Thiothixene) ; Trifluoperazine; Ziprasidone	Applied only to veterans with dementia or cognitive impairment
Heart_failure	Celecoxib; Cilostazol; Diclofenac; Etodolac; Ibuprofen; Indomethacin; Ketorolac; Meloxicam; Nabumetone; Naproxen; Oxaprozin; Pioglitazone; Piroxicam ; Sulindac	Applied only to veterans with heart failure Aspirin was excluded
History_of_falls_or_fracture	Amitriptyline ; Buprenorphine ; Citalopram ; Clomipramine ; Codeine ; Desipramine ; Desvenlafaxine ; Doxepine ; Duloxetine ; Escitalopram ; Fentanyl ; Fluoxetine ; Fluvoxamine ; Hydrocodone ; Hydromorphone ; Imipramine ; Methadone; Milnacipran; Morphine; Nefazodone; Nortriptyline; Opium; Oxycodone; Paroxetine ; Sertraline ; Tramadol ; Venlafaxine	Applied only to veterans with history of falls or fractures

Inappropriateness	Generic name	requirements
Parkinson	Aripiprazole ; Asenapine ; Chlorpromazine ; Droperidol ; Fluphenazine ; Haloperidol ; Iloperidone ; Loxapine ; Lurasidone ; Mesoridazine ; Metoclopramide ; Molindone ; Olanzapine ; Paliperidone ; Perphenazine ; Pimozide ; Prochlorperazine ; Risperidone ; Thioridazine ; Thiothixene ; Trifluoperazine ; Ziprasidone	Applied only to veterans with diagnosed Parkinson disease



Table S5 Codes from the International classification of disease 9th edition (ICD 9<sup>th</sup>) used to identify clinical requirements

Clinical Requirements	ICD – 9 codes
Anxiety	300; 300,01; 300,02; 300,09; 799,2
Bipolar disorder	296,0; 296,00; 296,01; 296,02; 296,03; 296,04; 296,05; 296,06; 296,1; 296,10; 296,11; 296,12; 296,13; 296,14; 296,15; 296,16; 296,4; 296,40; 296,41; 296,42; 296,43; 296,44; 296,45; 296,46; 296,5; 296,50; 296,51; 296,52; 296,53; 296,54; 296,55; 296,56; 296,6; 296,60; 296,61; 296,62; 296,63; 296,64; 296,65; 296,66; 296,7; 296,70; 296,71; 296,72; 296,73; 296,74; 296,75; 296,76; 296,8; 296,80; 296,81; 296,82; 296,89; 296,9; 296,90; 296,99; V11.1
Chronic seizures or epilepsy	345.00; 345.01; 345.10; 345.11; 345.2; 345.3; 345.40; 345.41; 345.50; 345.51; 345.60; 345.61; 345.70; 345.71; 345.80; 345.81; 345.90; 345.91; 779.0; 780.02; 780.31; 780.32; 780.33; 780.39
Delirium	290.3; 291.0; 291.1; 292.0; 293.0; 293.1; 292.81; 780.09
Dementia or cognitive impairment	
Helicobacter pylori Infection	041.86 (if occurred in the previous year)
Heart failure	402,01; 402,01; 402,11; 402,91; 404,01; 404,03; 404,11; 404,13; 404,91; 404,93; 428,0; 428,1; 428.2; 428.3; 428.4; 428.9
History of gastric or duodenal ulcers	531; 532; 533; 534
History of falls or fractures	880; 881; 884; 885.9; 886.9; 888
Oesophagitis (Barnett)	530.85
Oesophagitis (Erosive)	530.19
Pathological hypersecretory condition	251.5; 536.8; 537.0; 585.9
Parkinson disease	332.0
Schizophrenia	295,0; 295,00; 295,01; 295,02; 295,03; 295,04; 295,05; 295,1; 295,10; 295,11; 295,12; 295,13; 295,14; 295,15; 295,2; 295,20; 295,21; 295,22; 295,23; 295,24; 295,25; 295,3; 295,30; 295,31; 295,32; 295,33; 295,34; 295,35; 295,4; 295,40; 295,41; 295,42; 295,43; 295,44; 295,45; 295,5; 295,50; 295,51; 295,52; 295,53; 295,54; 295,55; 295,6; 295,60; 295,61; 295,62; 295,63; 295,64; 295,65; 295,8; 295,80; 295,81; 295,82; 295,83; 295,84; 295,85; 295,9; 295,90; 295,91; 295,92; 295,93; 295,94; 295,95; V11.0

Table S6 Prevalence of Potentially inappropriate medications defined by Beers and Laroche criteria according to polypharmacy in 2016

	Birth cohort		Chronic polypharmacy		Chronic Hyperpolypharmacy	
	2 748 705		834 436		201 375	
Potentially inappropriate medications (PIMs) – Overall – n(%)	837 031	(30.45)	559 341	(67.03)	169 842	(84.34)
Beers1 – Anticholinergics - First-generation antihistamines – n(%)	44 156	(1.61)	35 368	(4.24)	17 231	(8.56)
Beers2 - Anticholinergics - Antiparkinsonian agent – n(%)	8540	(0.31)	6578	(0.79)	2723	(1.35)
LarocheB2 - Anticholinergics - Antiparkinsonian agent – n(%)	0	(0.00)	0	(0.00)	0	(0.00)
Beers3 – Anticholinergics – Antispasmodics – n(%)	4063	(0.15)	3433	(0.41)	1833	(0.91)
LarocheB3 – Anticholinergics – Antispasmodics – n(%)	26 910	(0.98)	21 794	(2.61)	10 069	(5.00)
Beers4 – Antithrombotics – Dipyridamole – n(%)	2673	(0.10)	2356	(0.28)	1026	(0.51)
Beers4_ex – Antithrombotics – Ticlopidine – n(%)	2	(0.00)	0	(0.00)	0	(0.00)
Beers6 - Anti-infective – Nitrofurantoin – n(%)	769	(0.03)	609	(0.07)	293	(0.15)
Beers8 – Cardiovascular - Central alpha agonist – n(%)	21 073	(0.77)	17 564	(2.10)	7653	(3.80)
Beers9 – Cardiovascular – Disopyramidine – n(%)	64	(0.00)	40	(0.00)	19	(0.01)
Beers12 – Cardiovascular – Nifedipine\ Nicardipine Immediate release – n(%)	837	(0.03)	589	(0.07)	191	(0.09)

Beers14 - Central Nervous System – antidepressants – n(%)	57 385	(2.09)	42 232	(5.06)	16 878	(8.38)
LarocheB14 - Central Nervous System – antidepressants – n(%)	5514	(0.20)	4233	(0.51)	1878	(0.93)
Beers15 - Central Nervous System – Antipsychotics – n(%)	29 638	(1.08)	22 579	(2.71)	9791	(4.86)
Beers16 - Central Nervous System – Barbituriques – n(%)	687	(0.02)	437	(0.05)	154	(0.08)
Beers17 or Beers18 - Central Nervous System – any Benzodiazepines	47 313	(1.72)	35 619	(4.27)	15 560	(7.73)
Beers17 - Central Nervous System - Benzodiazepines Short/intermediate acting – n(%)	15 027	(0.55)	11 355	(1.36)	4835	(2.40)
Beers18 - Central Nervous System - Benzodiazepines Long acting – n(%)	32 689	(1.19)	24 616	(2.95)	10 902	(5.41)
Beers19 - Central Nervous System – Meprobamate – n(%)	0	(0.00)	0	(0.00)	0	(0.00)
Beers20 - Central Nervous System - Nonbenzodiazepine. benzodiazepine receptor agonist hypnotics (Z-drugs) – n(%)	33 186	(1.21)	24 643	(2.95)	10 236	(5.08)
Beers21 - Central Nervous System - Ergoloid mesylates or Isoxsuprine– n(%)	2	(0.00)	1	(0.00)	1	(0.00)

LarocheB21 - Central Nervous System - Other Cerebral vasodilators – n(%)	775	(0.03)	660	(0.08)	337	(0.17)
Beers23 – Endocrine - Thyroid – n(%)	389	(0.01)	138	(0.02)	38	(0.02)
Beers26 – Endocrine – Insulin sliding scale – n(%)	74 824	(2.72)	58 455	(7.01)	23 431	(11.64)
Beers27 – Endocrine – Megestrol – n(%)	686	(0.02)	546	(0.07)	242	(0.12)
Beers28 or LarocheB28 – Endocrine – Any sulfonylureas	169 007	(6.15)	135 500	(16.24)	45385	(22.54)
Beers28 – Endocrine - Sulfonylureas. long acting – n(%)	14 856	(0.54)	12 263	(1.47)	4279	(2.12)
LarocheB28 – Endocrine - Sulfonylureas. Glipizide – n(%)	155 316	(5.65)	124 307	(14.90)	41 545	(20.63)
Beers29 – Gastrointestinal – Metoclopramide – n(%)	1688	(0.06)	1544	(0.19)	905	(0.45)
Beers31 – Gastrointestinal - Pump Proton Inhibitors – n(%)	353 572	(12.86)	232 363	(27.85)	68 155	(33.84)
Laroche17 – Gastrointestinal - Stimulant Laxatives – n(%)	81 579	(2.97)	72 164	(8.65)	39 982	(19.85)
Beers32 - Pain Medications – Meperidine – n(%)	18	(0.00)	15	(0.00)	9	(0.00)
Beers33 - Pain Medications – Nonsteroidal anti-inflammatory drugs – n(%)	131 150	(4.77)	83 944	(10.06)	25 277	(12.55)
Beers34 - Pain Medications - Indomethacin et ketorolac – n(%)	1838	(0.07)	1323	(0.16)	544	(0.27)

Beers35 - Pain Medications - Skeletal muscle relaxants – n(%)	43 731	(1.59)	36 006	(4.32)	17 513	(8.70)
PIMs with Chronic seizures or epilepsy – n(%)	3600	(0.13)	2925	(0.35)	1452	(0.72)
PIMs with Delirium – n(%)	0	(0.00)	0	(0.00)	0	(0.00)
PIMs with Dementia or cognitive impairment – n(%)	1785	(0.06)	1482	(0.18)	718	(0.36)
PIMs with Heart failure – n(%)	6249	(0.23)	5682	(0.68)	3402	(1.69)
PIMs with History of falls or fracture – n(%)	16 978	(0.62)	13 629	(1.63)	6515	(3.24)
PIMs with Parkinson disease – n(%)	0	(0.00)	0	(0.00)	0	(0.00)

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PIMs: Potentially inappropriate medications

E Annexe V: Supplementary material: Risk of mortality associated to chronic polypharmacy and potentially inappropriate medications in United States veterans aged 49-70 years

Risk of mortality associated to chronic polypharmacy and potentially inappropriate medications in United States veterans aged 49-70 years

Supplementary material

Table S7 Potentially Inappropriate Medications (PIMs) defined by Beers criteria, version 2015, PIMs in most older adults

Classes	Generic names
Anticholinergics	Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Dimenhydrinate Diphenhydramine (oral) Doxylamine Hydroxyzine Meclizine Promethazine Triprolidine
Antiparkinsonian agents	Benztropine (oral) Trihexyphenidyl
Antispasmodics	Atropine (excludes ophthalmic) Belladonna alkaloids Clidinium-Chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine
Antithrombotics	Dipyridamole, oral short-acting Ticlopidine
Anti-infective	Nitrofurantoin
Cardiovascular	Doxazosin Prazosin Terazosin Clonidine Guanabenz Guanfacine Methyldopa Reserpine (>0.1 mg/d) Disopyramide Dronedarone Digoxin Nifedipine, immediate release
Antidepressants	Amitriptyline Amoxapine Clomipramine Desipramine Doxepin >6 mg/d Imipramine Nortriptyline Paroxetine

Classes	Generic names
	Protriptyline
	Trimipramine
Antipsychotics	chlorpromazine
	fluphenazine
	trifluoperazine
	periciazine
	haloperidol
	droperidol
	ziprasidone
	flupentixol
	zuclopenthixol
	risperidone
	aripiprazole
	paliperidone
	asenapine
	clozapine
	olanzapine
	quetiapine
	amisulpride
Barbiturates	Amobarbital
	Butabarbital
	Butalbital
	Mephobarbital
	Pentobarbital
	Phenobarbital
	Secobarbital
Benzodiazepines	Alprazolam
	Estazolam
	Lorazepam
	Oxazepam
	Temazepam
	Triazolam
	Clorazepate
	Chlordiazepoxide
	Clonazepam
	Diazepam
	Flurazepam
	Quazepam
	Meprobamate
	Eszopiclone
	Zolpidem
	Zaleplon
Ergoloid	Isoxsuprine
Androgens	Methyltestosterone
	Testosterone
Insulin	Insulin
	Megestrol
Sulfonylureas	Chlorpropamide
	Glyburide



Classes	Generic names
Gastrointestinal	Metoclopramide Mineral oil, given orally
Proton-pump inhibitors	omeprazole pantoprazole lansoprazole rabeprazole esomeprazole dexlansoprazole
Analgesics	Meperidine Aspirin >325 mg/d Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin Indomethacin Ketorolac, includes parenteral Pentazocine
Skeletal muscle relaxants	Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine
Genitourinary	Desmopressin

Table S8 description at baseline of veterans with no missing data at baseline vs. veterans with any missing data (excluded from the study)

Variable	Veterans with no missing data		Veterans with missing data	
	912,391		229,958	
<b>Outcome</b>				
Death n(%)	87,402	9.6	23,777	10.3
<b>Exposure</b>				
Total Med count				
Mean (std)	1.3	(1.3)	1.1	(1.3)
Total PIM count				
Mean (std)	0.0	(0.1)	0.0	(0.1)
<b>Covariates</b>				
<b>Sex</b>				
1 - Male – n(%)	850,099	(93.2)	213,563	(92.9)
2 - Female – n(%)	62,292	(6.8)	16,395	(7.1)
<b>Race</b>				
1 - White n-(%)	610,865	(67.0)	151,655	(66.0)
2 - Black n-(%)	182,241	(20.0)	42,818	(18.6)
3 - Hispanic n-(%)	49,438	(5.4)	10,877	(4.7)
4 - Other n-(%)	69,847	(7.7)	24,608	(10.7)
<b>Smoking ( missing n=16,470)</b>				
0 - Never n-(%)	294,046	(32.2)	69,911	(32.8)
1 - Current n-(%)	357,742	(39.2)	79,707	(37.3)
2 - Past n-(%)	260,603	(28.6)	63,870	(29.9)
<b>Age at Baseline</b>				
Mean (std)	57.4	(6.5)	57.7	(6.9)
<b>Baseline year</b>				
Mean (std)	2011.3	(3.1)	2011.7	(3.8)
<b>Audit-C (missing n=65713)</b>				
Mean (std)	2.0	(2.5)	2.0	(2.4)
<b>VACS score (missing n=170009)</b>				
Mean (std)	31.9	(8.2)	31.0	(8.9)

Tableau S3 Veterans who were inpatients according to the month preceding death. Veterans were defined inpatient if the number of inpatients days was equal the number of days in the month

	Whole cohort	No polypharmacy	Polypharmacy (5-9 chronic meds)	Hyperpolypharmacy ( $\geq 10$ chronic meds)
Veterans who died	87402	66691	16221	4490
Inpatient at month of death	5474 (6.3)	3910 (5.9)	1215 (7.5)	349 (7.8)
Inpatient one month before death	2058 (2.4)	1482 (2.2)	447 (2.8)	129 (2.9)
Inpatient 3 month before	1137 (1.3)	816 (1.2)	246 (1.5)	75 (1.7)
Inpatient 6 month before death	787 (0.9)	569 (0.9)	155 (1.0)	63 (1.4)

Table S4 Sensitivity analysis with a follow-up maximum 5 years, Risks of death in 3 months associated with exposure to chronic drug uses and potentially inappropriate medications (PIMs)

	Patient-years	Events	Unadjusted Hazard ratio	95CI	Adjusted <sup>1</sup> Hazard ratio	95CI
0 chronic drugs uses	1,389,899	16,861	1.112	[ 1.084 - 1.142 ]	1.232	[ 1.195 - 1.270 ]
1 – 2 chronic drugs uses	1,283,827	11,147	0.800	[ 0.777 - 0.823 ]	0.914	[ 0.887 - 0.943 ]
3 – 4 chronic drugs uses (ref)	783,583	8,572	1		1	
5 – 6 chronic drugs uses	286,208	4,657	1.465	[ 1.414 - 1.519 ]	1.208	[ 1.160 - 1.258 ]
7 – 9 chronic drugs uses	126,996	3,254	2.287	[ 2.196 - 2.383 ]	1.519	[ 1.434 - 1.608 ]
≥ 10 chronic drugs uses	43,635	1,770	3.599	[ 3.417 - 3.790 ]	1.905	[ 1.730 - 2.097 ]
0 PIMs (ref)	3,376,699	36,732	1		1	
1 PIMs	425,539	7,022	1.474	[ 1.437 - 1.513 ]	1.252	[ 1.204 - 1.302 ]
≥ 2 PIM	111,943	2,507	1.973	[ 1.894 - 2.056 ]	1.386	[ 1.265 - 1.518 ]

95CI: 95% Confidence interval; PIMs: Potentially inappropriate medications.

<sup>1</sup>Adjusted for age at baseline, sex, race, baseline year, smoking status, Audit-C, Veteran Aging Cohort Study (VACS) Index, significant interaction between chronic drug uses and PIMs

Table S5 Sensitivity analysis with a follow-up maximum 5 years, Risks of death in the month associated with exposure to chronic drug uses and potentially inappropriate medications (PIMs)

	Patient-years	Events	Unadjusted Hazard ratio	95CI	Adjusted <sup>1</sup> Hazard ratio	95CI
0 chronic drugs uses	1,394,382	7,572	1.452	[ 1.414 - 1.491 ]	1.637	[ 1.584 - 1.693 ]
1 – 2 chronic drugs uses	1,286,428	19,393	0.952	[ 0.925 - 0.980 ]	1.107	[ 1.070 - 1.144 ]
3 – 4 chronic drugs uses (ref)	785,581	11,628	1		1	
5 – 6 chronic drugs uses	287,276	3,841	1.347	[ 1.295 - 1.401 ]	1.056	[ 1.009 - 1.105 ]
7 – 9 chronic drugs uses	127,697	2,396	1.859	[ 1.775 - 1.947 ]	1.129	[ 1.056 - 1.207 ]
≥ 10 chronic drugs uses	44,004	1,193	2.656	[ 2.498 - 2.824 ]	1.225	[ 1.090 - 1.376 ]
0 PIMs (ref)	3,218,228	37,845	1		1	
1 PIMs	535,063	6,282	1.263	[ 1.230 - 1.298 ]	1.318	[ 1.264 - 1.374 ]
≥ 2 PIM	278,696	1,896	1.422	[ 1.358 - 1.490 ]	1.432	[ 1.300 - 1.577 ]

95CI: 95% Confidence interval; PIMs: Potentially inappropriate medications.

<sup>1</sup>Adjusted for age at baseline, sex, race, baseline year, smoking status, Audit-C, Veteran Aging Cohort Study (VACS) Index, significant interaction between chronic drug uses and PIMs

Table S5 Sensitivity analysis with a follow-up maximum 5 years, Risks of death in 6 months associated with exposure to chronic drug uses and potentially inappropriate medications (PIMs)

	Patient-years	Events	Unadjusted Hazard ratio	95CI	Adjusted <sup>1</sup> Hazard ratio	95CI
0 chronic drugs uses	1,385,786	16,706	1.074	[ 1.046 - 1.102 ]	1.182	[ 1.148 - 1.217 ]
1 – 2 chronic drugs uses	1,280,808	11,367	0.793	[ 0.771 - 0.816 ]	0.896	[ 0.870 - 0.924 ]
3 – 4 chronic drugs uses (ref)	781,410	8,795	1		1	
5 – 6 chronic drugs uses	285,025	4,714	1.452	[ 1.401 - 1.505 ]	1.238	[ 1.190 - 1.289 ]
7 – 9 chronic drugs uses	126,196	3,100	2.140	[ 2.053 - 2.230 ]	1.520	[ 1.438 - 1.608 ]
≥ 10 chronic drugs uses	43,196	1,648	3.303	[ 3.132 - 3.484 ]	1.950	[ 1.780 - 2.135 ]
0 PIMs (ref)	3,367,487	37,189	1		1	
1 PIMs	423,808	6,767	1.410	[ 1.374 - 1.448 ]	1.187	[ 1.142 - 1.234 ]
≥ 2 PIM	111,323	2,374	1.859	[ 1.783 - 1.939 ]	1.288	[ 1.175 - 1.411 ]

95CI: 95% Confidence interval; PIMs: Potentially inappropriate medications.

<sup>1</sup>Adjusted for age at baseline, sex, race, baseline year, smoking status, Audit-C, Veteran Aging Cohort Study (VACS) Index, significant interaction between chronic drug uses and PIMs

## Polymédication chronique : description et risque

La polymédication est définie comme l'administration de nombreux médicaments de façon simultanée ou comme l'administration d'un nombre excessif de médicaments. L'objectif général de la thèse était de décrire la polymédication chronique et le risque associé à partir des bases de données médico-administratives.

Un indicateur de description de la polymédication chronique, défini par l'usage concomitant et chronique de 5 médicaments ou plus, a été développé pour décrire la prévalence et les médicaments impliqués. À partir des données de l'Assurance Maladie Française, nous avons estimé que la polymédication chronique concernait plus de 5 % des français de tout âge, et impliquait majoritairement les médicaments cardiovasculaires. Afin d'approfondir la caractérisation de la polymédication chronique, une description de la part potentiellement inappropriée a été conduite en utilisant les données de l'Assurance Maladie Française et de la Veterans Health Administration aux États-Unis. À partir de ces données nous avons estimé que la part inappropriée de la polymédication chronique était majeure puisque concernant, en France, 65 % des sujets âgés ( $\geq 65$  ans) et 46 % des sujets d'âge moyen (45-64 ans), et aux États-Unis, 67 % des vétérans. Les inhibiteurs de la pompe à proton, les médicaments psychiatriques et les médicaments du diabète étaient les médicaments potentiellement inappropriés les plus fréquents. La polymédication, qu'elle soit appropriée ou non est un facteur de risque de mortalité. Chez les vétérans américains nous avons montré que la polymédication chronique et les médicaments potentiellement inappropriés augmentaient le risque de décès.

**Mots clés :** Polymédication ; Pharmaco-épidémiologie ; Base de données ; Etude d'utilisation ; Risque

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## Chronic polypharmacy: description and risk

Polypharmacy is defined as the administration of many drugs at the same time or as the administration of an excessive number of drugs. The main objective of this thesis was to describe chronic polypharmacy and the associated risk, from medico-administrative databases.

A specific indicator of chronic polypharmacy, defined by five or more concomitant and chronic drug uses, was developed to describe the prevalence and the involved drugs. Based on data from the National French Health Insurance, we estimated that chronic polypharmacy concerned more than 5% of all aged French individuals, and involved mainly cardiovascular drugs. To further describe chronic polypharmacy, a description of inappropriateness was carried out using data from the National French Health Insurance and the United States Veterans Health Administration. We estimated that the inappropriateness of chronic polypharmacy was major. It concerned 65% of French older adults ( $\geq 65$  years old), 46% of French middle-aged adults (45-64 years old) in France, and 67% of American veterans. Proton pump inhibitors, psychiatric drugs and diabetes drugs were the most common potentially inappropriate medications. Furthermore, we have shown that chronic polypharmacy, whether appropriate or not, is associated with increased mortality. In American veterans, chronic polypharmacy and potentially inappropriate medications both increased the risk of all-cause death.

**Keywords:** Polypharmacy; Pharmacoepidemiology; Database; Drug utilization study; risk

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