Public University of Navarra

Department of Health Science

Pharmacological treatment optimization in older patients

Optimización del tratamiento farmacológico en el paciente anciano

Doctoral Thesis

Marta Gutiérrez Valencia

2019

Supervisor

Dr. Nicolás Martínez Velilla

Tutor

Dr. Mikel Izquierdo Redin

Table of contents

Table Index

Figure Index

List of abbreviations

ACOVE	Assessing Care Of Vulnerable Elders
AGU	Acute Geriatric Unit
AOU	Assessment Of Underutilization of medication tool
ARS	Anticholinergic Risk Scale
ATC	Anatomical Therapeutic and Chemical
BADL	Basic activities of daily living
BMI	Body mass index
CBRG	Cochrane Back Review Group
CCB	Calcium channel blockers
CGA	Comprehensive Geriatric Assessment
CGCOF	Consejo General de Colegios Oficiales de Farmacéuticos
CHS	Cardiovascular Health Study
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CSHA	Canadian Study of Health and Aging
DRP	Drug related problem
ENSE	National Health Survey of Spain
FI	Frailty Index
HR	Hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile range
IRR	Incidence rate ratio
LIMM	Lund Integrated Medicines Management
MAI	Medication Appropriateness Index
MeSH	Medical Subject Headings
MMSE	Mini-Mental State Examination
NOM	Negative Outcomes associated with Medications
NOS	Newcastle-Ottawa Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs

OR	Odds Ratio
PIP	Potentially inappropriate prescribing
PPO	Potential prescribing omissions
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRM	Problema relacionado con medicamentos (Spanish)
SD	Standard Deviation
SEFH	Spanish Society of Hospital Pharmacy
START	Screening Tool to Alert doctors to the Right Treatment
STOPP	Screening Tool of Older Persons' potentially inappropriate Prescriptions
UGA	Unidad de geriatría de agudos (Spanish)
USD	United States Dollars
VGI	Valoración geriátrica integral (Spanish)

Declaration and list of publications

This doctoral thesis is a compendium of 6 articles that has been published or accepted for publication in international peer-reviewed journals.

Marta Gutiérrez Valencia, as PhD student is the main author of all the articles, and has been the major contributor to the conception and designs of the studies, acquisition, analysis and interpretation of data, drafting the articles and final approval to be published.

List of publications

- Prevalence of polypharmacy and associated factors in older adults in Spain: Data from the National Health Survey 2017. Gutiérrez-Valenciahttp://www.elsevier.es/es-revista-medicina-clinica-2-avance-resumen-prevalencia-polifarmacia-factores-asociados-adultos-S0025775319300259 - aff0005 M, Aldaz Herce P, Lacalle-Fabo E, Contreras Escámez B, Cedeno-Veloz B, Martínez-Velilla N. 2019 Feb 23. doi: 10.1016/j.medcli.2018.12.013 [Epub ahead of print] (Original article in Spanish. Translated in Chapter 1)
- The relationship between Frailty and Polypharmacy in older people: a Systematic Review. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. Br J Clin Pharmacol. 2018 Jul;84(7):1432-1444. doi: 10.1111/bcp.13590
- Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes. Gutiérrez-Valencia M, Izquierdo M, Lacalle-Fabo E, Marín-Epelde I, Ramón-Espinoza MF, Domene-Domene T, Casas-Herrero Á, Galbete A, Martínez-Velilla N. Eur J Clin Pharmacol. 2018 Jul;74(7):961-970. doi: 10.1007/s00228-018-2452-2

- Impact of hospitalization in an acute geriatric unit on polypharmacy and potentially inappropriate prescriptions: A retrospective study. Gutiérrez-Valencia M, Izquierdo M, Malafarina V, Alonso-Renedo J, González-Glaría B, Larrayoz-Sola B, Monforte-Gasque MP, Latasa-Zamalloa P, Martínez-Velilla N. Geriatr Gerontol Int. 2017 Dec;17(12):2354-2360. doi: 10.1111/ggi.13073
- Interventions to optimize pharmacologic treatment in hospitalized older adults: a systematic review. Gutiérrez Valencia M, Martínez Velilla N, Lacalle Fabo E et al. Rev Clin Esp. 2016 May;216(4):205-21. doi: 10.1016/j.rce.2016.01.005. (Article published in English and Spanish. Translation by the journal)
- A medicine optimization strategy in an acute geriatric unit: the pharmacist in the geriatric team. Gutiérrez-Valencia M, Izquierdo M, Beobide-Telleria I, Ferro-Uriguen A, Alonso-Renedo J, Casas-Herrero Á, Martínez-Velilla N. Geriatr Geront Int (accepted for publication)

Related Conference papers

- Adherence to treatment in older adults admitted to an acute geriatric unit and associated factors. Accepted poster for the 24th Congress of the European Association of Hospital Pharmacy, Barcelona, 27-29 March 2019. Marta Gutiérrez-Valencia, Marta Castresana-Elizondo, María Pilar Monforte-Gasque, Esther Lacalle-Fabo, Javier Alonso-Renedo, Nicolás Martínez-Velilla.
- Sensitivity and specificity of STOPP/START criteria to detect drug-related problems in older adults. Gutiérrez-Valencia M, Acín-Gericó MT, Contreras-Escámez B, Ramón-Espinoza MF, Marín-Epelde I, Casas-Herrero Á, Martínez-Velilla N. 14th International Congress of the EuGMS. Berlin, 10-12 October 2018.
- Implementation of a patient-centered medicine-optimization strategy in an acute geriatric unit: the pharmacist in the geriatric team. Gutiérrez Valencia M, Castresana-Elizondo M, Monforte Gasque MP, Agulló Fenoll Á, Aldave Cobo P, de la Riva Bohigas R, Sarobe Carricas M, Martínez-Velilla N. 63º Congreso Sociedad Española de Farmacia Hospitalaria. Palma, 8-10 November 2018

- Deprescripción de estatinas en pacientes mayores en una unidad de geriatría de agudos. Gutiérrez Valencia M, Monforte Gasque MP, Castresana Elizondo M, de la Riva Bohigas R, Aldave Cobo P, Agulló Fenoll Á, Sarobe Carricas M, Martínez-Velilla N. 63º Congreso Sociedad Española de Farmacia Hospitalaria. Palma, 8-10 Novermber 2018

- Prevalencia de uso de hipolipemiantes en prevención primaria y secundaria en adultos mayores en España y su relación con la presencia de diabetes. Gutiérrez Valencia M., Arribas Cerezo Á., Adanero Calvo I., Ramón Espinoza M.F., Marín Epelde I., Domene Domene T., Corres García I., Martínez Velilla N. 40º Congreso Nacional SEMERGEN. Palma, 17-20 October 2018

- Prevalencia de uso de psicofármacos en adultos mayores no institucionalizados en España por sexo y grupos de edad. Gutiérrez Valencia M., Corres García I., Ramón Espinoza M.F., Domene Domene T., Marín Epelde I., Arribas Cerezo Á., Adanero Calvo I., Martínez Velilla N. 40º Congreso Nacional SEMERGEN. Palma, 17-20 October 2018

- Aplicación del "modelo de selección y Atención Farmacéutica de pacientes crónicos" de la SEFH a pacientes de una unidad de agudos de geriatría. M. Gutiérrez-Valencia, M.F. Ramón-Espinoza, T. Domene-Domene, I. Marín-Epelde, N. Martínez-Velilla. 60º Congreso de la Sociedad Española de Geriatría y Gerontología & 31º Congreso de la Sociedad Canaria de Geriatría y Gerontología. Las Palmas de Gran Canaria, 13-15 June 2018

- Identificación de medicamentos de alto riesgo en pacientes que ingresan en una unidad de agudos de Geriatría. M. Gutiérrez-Valencia, T. Domene-Domene, I. Marín-Epelde, M.F. Ramón-Espinoza, N. Martínez-Velilla. 60º Congreso de la Sociedad Española de Geriatría y Gerontología & 31º Congreso de la Sociedad Canaria de Geriatría y Gerontología. Las Palmas de Gran Canaria, 13-15 Jun 2018

- Polifarmacia en ancianos frágiles y robustos institucionalizados. M. Gutiérrez-Valencia, I. Marín-Epelde, M.F. Ramón-Espinoza, T. Domene-Domene, Á. Casas-Herrero, A. Galbete, N. Martínez-Velilla. 8ª Reunión Nacional de la Sociedad Española de Medicina Geriátrica (SEMEG), Barcelona, 12-14 April 2018

- Prevalence of underprescription of recommended medications in frail and robust older adults in nursing homes, M. Gutiérrez-Valencia, N. Martínez-Velilla, M. López-Sáez de Asteasu, F. Zambom-Ferraresi, I. Marín-Epelde, M.F. Ramón-Espinoza, A. García-Baztán, the 23rd EAHP Congress in Gothenburg, Sweden, 21-23 March 2018
- Uso simultáneo de inhibidores de acetilcolinesterasa y medicamentos con actividad anticolinérgica en pacientes geriátricos hospitalizados. Marta Gutiérrez Valencia, Javier Preciado Goldaracena, Marta Coma Punset, Julia Polo García, Marta Castresana Elizondo, Beatriz Larrayoz Sola, Maite Sarobe Carricas, Nicolás Nicolás Martínez Velilla. 62º Congreso Sociedad Española de Farmacia Hospitalaria. Madrid, 18-21 October 2017
- Análisis de interacciones farmacológicas potencialmente graves en pacientes mayores en una unidad de agudos de geriatría. Marta Gutiérrez Valencia, Julia Polo García, Marta Coma Punset, Javier Preciado Goldaracena, María Pilar Monforte Gasque, Beatriz Larrayoz Sola, Maite Sarobe Carricas, Nicolás Martínez Velilla. 62º Congreso Sociedad Española de Farmacia Hospitalaria. Madrid, 18-21 October 2017
- Pharmacological Impact of Hospitalization in an Acute Geriatric Unit. Nicolas Martinez-Velilla, Marta Gutiérrez Valencia, Beatriz Larrayoz Sola, Javier Alonso Renedo, M Pilar Monforte Gasque, Mikel López-Sáez de Asteasu, Fabricio Zambom Ferraresi, Alvaro Casas Herrero. 21st IAGG World Congress of Gerontology and Geriatrics, San Francisco, 23-27 July 2017
- Prescripción al alta de una unidad de agudos de geriatría y su asociación con resultados en salud. Marta Gutiérrez-Valencia, María Elviro-Llorens, María Pilar Monforte-Gasque, Marta Castresana-Elizondo, Fabrício Zambom-Ferraresi, Mikel López-Sáez De Asteasu, Nicolás Martínez-Velilla. Comunicación oral 59º Congreso de la Sociedad Española de Geriatría y Gerontología & 29º Congreso de la Sociedad Galega de Xerontoloxía e Xeriatría. A Coruña, 7-9 June 2017

Summary

The use of medications in the elderly is a complex issue influenced by many health and non-health related factors. Drug therapy is one of the most important tools available for preserving and improving health. However, polypharmacy and the inappropriate use of medications can imply adverse effects and situations of vulnerability that condition negative health outcomes. The following work intends to study this phenomenon in different areas —at population or community level, in institutionalized and hospitalized patients—, analyzing its relationship with different factors that may be of interest in the elderly patient, and especially with frailty. Finally, it focuses on the hospitalized elderly, one of the most vulnerable sectors to pharmacological iatrogenesis, investigating the impact of hospitalization on pharmacological therapy, reviewing the different strategies that have been proposed for pharmacological optimization in these patients and exploring the usefulness of an intervention specifically adapted to these patients in our environment.

The most relevant methodology and results are summarized below:

Chapter 1: Prevalence of polypharmacy and associated factors in older adults in Spain: Data from the National Health Survey 2017

Background and objective: to estimate the prevalence of polypharmacy and hyperpolypharmacy in non-institutionalized older adults in Spain and assess the associated factors.

Material and methods: a cross-sectional study based on data from the National Health Survey of Spain 2017, with participants over 65 years old. The prevalence of polypharmacy (≥5 medications) and hyperpolypharmacy (≥10) was estimated, as well as the association with several factors through multivariate logistic regression. A sensitivity analysis was also carried out considering the possible consumption of more than one drug for the same indication (polytherapy).

Results: 7023 participants were included, with a mean age of 76.0 (SD 7.6) years, 59.4% women and an average consumption of 3.3 (SD 2.2) drugs per person. The prevalence of polypharmacy was 27.3% (95% CI 26.2-28.3), being 0.9% (95% CI 0.7-1.1) in the case of hyperpolypharmacy. The sensitivity analysis showed that the prevalence could be at least 37.5% and the average number of drugs 3.9 (SD 2.5) when considering polytherapy. The number of chronic diseases, the degree of dependence for the basic activities of daily living, the self-perceived health and contacts with the health system were the factors most associated with polypharmacy. Sensory deficits and incontinence were negatively associated.

Conclusions: the prevalence of polypharmacy in the elderly in primary care continues to increase, and could be widely underestimated. In addition to the multimorbidity, factors such as functional capacity or geriatric syndromes, which are essential in elderly people, modulate the habits of consumption and prescription of drugs in this population.

Chapter 2: The relationship between Frailty and Polypharmacy in older people: a Systematic Review

Aims: Frailty is a complex geriatric syndrome resulting in decreased physiological reserves. Frailty and polypharmacy are common in older adults and the focus of extensive studies, although little is known about the impact they may have on each other. This is the first systematic review analysing the available evidence on the relationship between frailty and polypharmacy in older adults.

Methods: Systematic review of quantitative studies. A comprehensive literature search for publications in English or Spanish was performed on MEDLINE, CINAHL, the Cohrane Database and PsycINFO in September 2017 without applying restrictions on the date of publication. Studies reporting any relationship between frailty and polypharmacy in older adults were considered.

Results: A total of 25 publications were included, all of them observational studies. Evaluation of Fried's frailty criteria was the most common approach, followed by the Edmonton Frail Scale and FRAIL scale. Sixteen of 18 cross-sectional analyses and five of

seven longitudinal analyses demonstrated a significant association between an increased number of medications and frailty. The causal relationship is unclear and appears to be bidirectional. Our analysis of published data suggests that polypharmacy could be a major contributor to the development of frailty.

Conclusions: A reduction of polypharmacy could be a cautious strategy to prevent and manage frailty. Further research is needed to confirm the possible benefits of reducing polypharmacy in the development, reversion or delay of frailty.

Chapter 3: The Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes

Purpose: Frailty, polypharmacy, and underprescription are considered a major matter of concern in nursing homes, but the possible relationships between them are not well known. The aim is to examine the possible association between medication underprescription, polypharmacy, and frailty in older people living in nursing homes.

Methods: A cross-sectional analysis from a concurrent cohort study, including 110 subjects ≥ 65 years living in two nursing homes. Four frailty scales were applied; polypharmacy was defined as ≥ 5 medications and underprescription was measured with Screening Tool to Alert to Right Treatment (START) criteria. Logistic regression models were performed to assess the associations.

Results: The mean age was 86.3 years (SD 7.3) and 71.8% were female. 73.6% of subjects took ≥ 5 chronic medications and 60.9% met one or more START criteria. The non-frail participants took more medications than the frail subjects according to the imputated frailty Fried criteria (8.1 vs 6.7, p = 0.042) and the FRAIL-NH scale (7.8 vs 6.8, p=0.026). Multivariate analyses did not find an association between frailty and polypharmacy. Frail participants according to the Fried criteria met a higher number of START criteria (1.9 vs 1.0, p = 0.017), and had a higher prevalence of underprescription (87.5 vs 50.0%), reaching the limit of statistical significance in multivariate analysis.

Conclusion: The positive association found in previous studies between frailty and polypharmacy cannot be extrapolated to institutionalized populations. There is a trend towards higher rates of underprescription in frail subjects. Underprescription in frail

older adults should be redefined and new strategies to measure it should be developed.

Chapter 4: Impact of hospitalization in an acute geriatric unit on polypharmacy and potentially inappropriate prescriptions: A retrospective study

Aim: Polypharmacy is a highly prevalent geriatric syndrome, and hospitalizations can worsen it. The aim of the present study was to analyze the influence of hospitalization on polypharmacy and indicators of quality of prescribing, and their possible association with health outcomes.

Methods: A retrospective study of 200 patients discharged from an acute geriatric unit was carried out. Indicators of quality of prescription were registered at admission and discharge: polypharmacy defined as ≥5 medications, hyperpolypharmacy (≥10), potentially inappropriate prescribing by Beers and Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria, potentially prescribing omissions by Screening Tool to Alert doctors to the Right Treatment (START) criteria, drug interactions and anticholinergic burden measured with the Anticholinergic Risk Scale. Mortality, emergency room visits and hospital admissions occurring during 6 months after discharge were also registered.

Results: The total number of drugs increased at discharge (9.1 vs 10.1, P < 0.001), without increasing chronic medications (8.5 vs 8.3, P = 0.699). No significant variations were observed in the prevalence of polypharmacy (86.5% vs 82.2%), potentially inappropriate prescribing (68.5%vs 71.5%), potential prescribing omissions (58%vs 58%) or drug interactions (82.5%vs 83.5%). Patients with anticholinergic drugs tended to increase, not reaching statistical significance (39.5% vs 44.5%; P = 0.064). Polypharmacy was associated with emergency room visits (OR 2.62, 95% CI 1.07–6.40; P = 0.034), and hyperpolypharmacy with hospitalizations (OR 2.49, 95% CI 1.25–4.93; P = 0.009).

Conclusions: After hospitalization in an acute geriatric unit, the prevalence of polypharmacy, potentially inappropriate prescribing, potential prescribing omissions, interactions or anticholinergic drugs is still very high. Polypharmacy is a risk factor for

hospitalization and emergency room visits. Measuring indicators of quality of prescription might be useful to design interventions to optimize pharmacotherapy and improve health outcomes in elderly acute patients.

Chapter 5: Interventions to optimize pharmacologic treatment in hospitalized older adults: a systematic review

Objective: To summarise the evidence on interventions aimed at optimising the drug treatment of hospitalised elderly patients.

Material and methods: We conducted a search in the main medical literature databases, selecting prospective studies of hospitalised patients older than 65 years who underwent interventions aimed at optimising drug treatment, decreasing polypharmacy and improving the medication appropriateness, health outcomes and exploitation of the healthcare system.

Results: We selected 18 studies whose interventions consisted of medication reviews, detection of predefined drugs as potentially inappropriate for the elderly, counselling from a specialised geriatric team, the use of a computer support system for prescriptions and specific training for the nursing team. Up to 14 studies assessed the medication appropriateness, 13 of which showed an improvement in one or more of the parameters. Seven studies measured the impact of the intervention on polypharmacy, but only one improved the outcomes compared with the control. Seven other studies analysed mortality, but none of them showed a reduction in that rate. Only 1 of 6 studies showed a reduction in the number of hospital readmissions, and 1 of 4 studies showed a reduction in the number of emergency department visits.

Conclusions: Despite the heterogeneity of the analysed interventions and variables, we obtained better results in the process variables (especially in medication appropriateness) than in those that measured health outcomes, which had greater variability.

Chapter 6: A medicine optimization strategy in an acute geriatric unit: the pharmacist in the geriatric team

Aim: Older patients admitted to acute geriatric units (AGU) use frequently many medications and are particularly vulnerable to adverse drug events, so specific interventions in this setting are needed. In this study, we describe a new medicine optimization strategy in an AGU and explore its potential in reducing polypharmacy and improving medication appropriateness.

Methods: Prospective study with patients aged ≥ 75 years who were admitted to an AGU in a tertiary hospital. An intervention based on a pharmacist clinical interview, medication history, and a structured medication review within a comprehensive geriatric assessment (CGA) was proposed. The differences regarding polypharmacy as the primary outcome (≥5 chronic drugs), hyperpolypharmacy (≥10), number of drugs, drug-related problems (DRP) and Screening Tool of Older Person's Prescription (STOPP)/ Screening Tool to Alert doctors to Right Treatment (START) criteria between admission and discharge were evaluated.

Results: From October 2016 to April 2017, 234 patients were enrolled, aged 87.6 years (SD = 4.6); 143 (61.1%) were female. The intervention resulted in a statistically significant improvement in polypharmacy (-10.2%, 95%CI,-15.3,-5.2), hyperpolypharmacy (-16.6%, 95%CI,-22.3,-11.0), number of medications (-1.4, 95%CI,-1.8,-1.0), STOPP criteria (-19.2%, 95%CI,-24.9,-13.6), START criteria (-6.8%, 95%CI,-10.1,-3.5) and DRP (-2.7, 95%CI,-2.9,-2.4) ($p<0.001$ for all).

Conclusions: A systematic pharmacist-led intervention at hospital admission to an AGU within a CGA was associated to a decrease in polypharmacy, drug related problems and potentially inappropriate prescribing.

Resumen

El uso de medicamentos en ancianos es un asunto complejo influido por muchos factores tanto relacionados como ajenos al ámbito de la salud. La terapia farmacológica es una de las herramientas más importantes de las que disponemos para conservar o mejorar la salud. Sin embargo, la polifarmacia y el uso inadecuado de medicamentos pueden implicar efectos adversos y situaciones de vulnerabilidad que condicionen resultados negativos en salud. En el siguiente trabajo se pretende estudiar este fenómeno en distintos ámbitos —a nivel poblacional o comunitario, en pacientes institucionalizados y hospitalizados—, analizando su relación con distintos factores que pueden ser de interés en el paciente mayor, y especialmente con la fragilidad. Finalmente se centra en los ancianos hospitalizados, uno de los sectores más vulnerables a la iatrogenia farmacológica, indagando en el impacto de la hospitalización sobre la terapia farmacológica, revisando las distintas estrategias que se han propuesto para la optimización farmacológica en estos pacientes y explorando la utilidad de una intervención específicamente adaptada a estos pacientes en nuestro medio. La metodología y resultados más relevantes se resumen a continuación:

Capitulo 1: Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017

Fundamento y objetivo: Estimar la prevalencia de polifarmacia e hiperpolifarmacia en adultos mayores no institucionalizados en España y analizar los factores asociados.

Material y métodos: Estudio transversal a partir de datos de la Encuesta Nacional de Salud de España 2017, con participantes de 65 años o más. Se estimó la prevalencia de polifarmacia (≥5 medicamentos) e hiperpolifarmacia (≥10), y la asociación con diversos factores mediante regresión logística multivariante. Se realizó un análisis de sensibilidad considerando el posible consumo de más de un fármaco para la misma indicación (politerapia).

Resultados: Se incluyeron 7.023 participantes, con edad media de 76,0 (desviación estándar [DE] 7,6) años, 59,4% mujeres y consumo medio de 3,3 (DE 2,2) medicamentos por persona. La prevalencia de polifarmacia fue de 27,3% (intervalo de confianza del 95%: 26,2-28,3) y la de hiperpolifarmacia de 0,9% (intervalo de confianza del 95%: 0,7-1,1). El análisis de sensibilidad estimó que la prevalencia podría ascender al menos a un 37,5% y la media a 3,9 (DE 2,5) al considerar la politerapia. Los factores que más se asocian a la polifarmacia fueron el número de enfermedades crónicas, el grado de dependencia para las actividades básicas de la vida diaria, el estado de salud percibido o los contactos con el sistema sanitario; y de forma inversa los déficits sensoriales y la incontinencia.

Conclusiones: La prevalencia de polifarmacia en adultos mayores en atención primaria continúa aumentando, y podría estar ampliamente infraestimada. Además de la pluripatología, factores como la capacidad funcional o los síndromes geriátricos, fundamentales en personas mayores, modulan los hábitos de consumo y prescripción de medicamentos en esta población.

Capítulo 2: Relación entre polifarmacia y fragilidad en el anciano: una revisión sistemática.

Objetivos: La fragilidad es un síndrome geriátrico complejo que produce una disminución de las reservas fisiológicas. La fragilidad y la polifarmacia son comunes en los adultos mayores y han sido objeto de numerosos estudios, aunque no es bien conocido el impacto que pueden tener entre sí. Esta es la primera revisión sistemática que analiza la evidencia disponible sobre la relación entre la fragilidad y la polifarmacia en adultos mayores.

Métodos: Revisión sistemática de estudios cuantitativos. En septiembre de 2017, se realizó una búsqueda bibliográfica exhaustiva de publicaciones en inglés o español en MEDLINE, CINAHL, la Cohrane Database y PsycINFO sin aplicar restricciones por fecha de publicación. Se consideraron los estudios que analizaron cualquier relación entre la fragilidad y la polifarmacia en adultos mayores.

Resultados: se incluyeron un total de 25 publicaciones, todas ellas estudios observacionales. La evaluación de los criterios de fragilidad de Fried fue el enfoque más común, seguido por la escala de fragilidad de Edmonton y la escala FRAIL. Dieciséis de los 18 análisis transversales y cinco de los siete análisis longitudinales demostraron una asociación significativa entre un mayor número de medicamentos y la fragilidad. La relación causal no está clara y parece ser bidireccional. Nuestro análisis de los datos publicados sugiere que la polifarmacia podría ser un importante contribuyente al desarrollo de la fragilidad.

Conclusiones: Una reducción de la polifarmacia podría ser una estrategia cautelosa para prevenir y manejar la fragilidad. Se necesita más investigación para confirmar los posibles beneficios de reducir la polifarmacia en el desarrollo, reversión o retraso de la fragilidad.

Capítulo 3: La relación entre la fragilidad, la polifarmacia y la infraprescripción en adultos mayores que viven en residencias

Fundamento y objetivo: La fragilidad, la polifarmacia y la infraprescripción se consideran un problema importante en las residencias, pero las posibles relaciones entre ellos no son bien conocidas. El objetivo es examinar la posible asociación entre la infraprescripción de medicamentos, la polifarmacia y la fragilidad en las personas mayores que viven en residencias.

Métodos: un análisis transversal de un estudio de cohorte en marcha, que incluye 110 sujetos ≥ 65 años que viven en dos residencias de ancianos. Se aplicaron cuatro escalas de fragilidad. La polifarmacia se definió como ≥ 5 medicamentos y la prescripción insuficiente se midió con los criterios START (*Screening Tool to Alert to Right Treatment*). Se realizaron modelos de regresión logística para evaluar las asociaciones.

Resultados: la edad media fue de 86.3 años (DE 7.3) y el 71.8% eran mujeres. El 73.6% de los sujetos consumían ≥ 5 medicamentos crónicos y el 60.9% presentaban uno o más criterios START. Los participantes no frágiles consumían más medicamentos que los sujetos frágiles según los criterios de fragilidad de Fried (8.1 vs 6.7, p = 0.042) y la escala FRAIL-NH (7.8 vs 6.8, p = 0.026). Los análisis multivariantes no encontraron

asociación entre fragilidad y polifarmacia. Los participantes frágiles según los criterios de Fried presentaban un mayor número de criterios START (1.9 frente a 1.0, p = 0.017) y una mayor prevalencia de infraprescripción según estos criterios (87.5 frente a 50.0%), alcanzando el límite de significación estadística en el análisis multivariado.

Conclusión: la asociación positiva encontrada en estudios previos entre fragilidad y polifarmacia no puede extrapolarse a poblaciones institucionalizadas. Hay una tendencia hacia tasas más altas de infraprescripción en sujetos frágiles. La infraprescripción en adultos mayores frágiles debe redefinirse y se deben desarrollar nuevas estrategias para medirla.

Capítulo 4: Impacto de la hospitalización en una Unidad de Agudos de Geriatría sobre la polifarmacia y las prescripciones potencialmente inadecuadas: un estudio retrospectivo

Objetivo: La polifarmacia es un síndrome geriátrico altamente prevalente, y los ingresos hospitalarios pueden empeorarlo. El objetivo del presente estudio fue analizar la influencia de la hospitalización en ancianos en la polifarmacia y distintos indicadores de la calidad de la prescripción, y su posible asociación con resultados de salud.

Métodos: se realizó un estudio retrospectivo de 200 pacientes dados de alta de una Unidad de Agudos de Geriatría. Se registraron al ingreso y al alta los siguientes indicadores de calidad de prescripción: polifarmacia definida como ≥5 medicamentos, hiperpolifarmacia (≥10), prescripciones potencialmente inadecuada según criterios de Beers y criterios STOPP, prescripciones potencialmente omitidas según criterios START, interacciones de medicamentos y carga anticolinérgica del tratamiento medida con la escala ARS. También se registraron la mortalidad, las visitas a urgencias y los ingresos hospitalarios durante los 6 meses posteriores al alta, y se analizó mediante regresión logística multivariante su posible relación con los indicadores de calidad de la prescripción.

Resultados: El número total de fármacos aumentó al alta (9,1 frente a 10,1; p <0,001), sin aumentar los medicamentos crónicos (8,5 frente a 8,3; p=0,699). No se observaron variaciones significativas en la prevalencia de la polifarmacia (86,5%

vs 82,2%), criterios STOPP (68,5% vs 71,5%), criterios START (58% vs 58%) o las interacciones de medicamentos (82,5% vs 83,5%). Los pacientes con fármacos anticolinérgicos tendieron a aumentar, no alcanzando significación estadística (39,5% vs 44,5%; p = 0,064). La polifarmacia se asoció con las visitas a urgencias (OR 2,62, IC 95% 1,07–6,40; p = 0,034) y la hiperpolifarmacia con las hospitalizaciones (OR 2,49, IC 95% 1,25–4,93; p = 0,009).

Conclusiones: después de la hospitalización en una Unidad de Agudos de Geriatría, la prevalencia de la polifarmacia, las prescripciones potencialmente inadecuadas, las prescripciones potencialmente omitidas, las interacciones o el uso de fármacos anticolinérgicos aún son muy altos. La polifarmacia es un factor de riesgo para la hospitalización y las visitas urgencias en ancianos. La medición de los indicadores de calidad de la prescripción podría ser útil para diseñar intervenciones para optimizar la farmacoterapia y mejorar los resultados de salud en pacientes ancianos en unidades de agudos.

Capítulo 5: Intervenciones para optimizar el tratamiento farmacológico en ancianos hospitalizados: una revisión sistemática

Objetivo: Resumir la evidencia sobre las intervenciones orientadas a optimizar el tratamiento farmacológico en ancianos hospitalizados.

Material y métodos: Se realizó una búsqueda en las principales bases de datos bibliográficas, seleccionando estudios prospectivos en pacientes mayores de 65 años hospitalizados que realizaran intervenciones dirigidas a optimizar el tratamiento farmacológico, disminuir la polifarmacia y mejorar la adecuación terapéutica, los resultados en salud o el aprovechamiento del sistema sanitario.

Resultados: Se seleccionaron 18 estudios. Las intervenciones consistieron en revisiones de medicación, detección de medicamentos predefinidos como potencialmente inadecuados en ancianos, asesoramiento de un equipo especializado en geriatría, uso de un sistema informático de apoyo a la prescripción o formación específica al equipo de enfermería. Hasta 14 estudios evaluaron la adecuación terapéutica, demostrando 13 de ellos una mejoría en alguno de los parámetros. Siete estudios midieron el

impacto de la intervención sobre la polifarmacia, pero solo uno mejoró los resultados respecto al control. Otros siete estudios analizaron la mortalidad, no demostrándose una disminución de la misma en ninguno. Solo uno de seis estudios mostró una reducción de reingresos hospitalarios y uno de cuatro estudios una disminución de las visitas a urgencias.

Conclusiones: Pese a la heterogeneidad de las intervenciones y de las variables analizadas, se obtuvieron mejores resultados en las variables de proceso, especialmente en la adecuación terapéutica, que en aquellas que midieron resultados en salud, donde hubo una mayor variabilidad.

Capítulo 6: Una estrategia de optimización de tratamientos en una unidad de agudos de geriatría: el farmacéutico en el equipo de geriatría

Objetivo: los pacientes mayores ingresados en unidades geriátricas de agudos (UGA) utilizan con frecuencia muchos medicamentos y son particularmente vulnerables a los eventos adversos de medicamentos, por lo que se necesitan intervenciones específicas en este contexto. En este estudio, describimos una nueva estrategia de optimización de medicamentos en una UGA y exploramos su potencial para reducir la polifarmacia y mejorar la adecuación de la medicación.

Métodos: estudio prospectivo con pacientes de ≥ 75 años que ingresaron en una UGA en un hospital terciario. Se propuso una intervención basada en una entrevista clínica con el farmacéutico, historial farmacoterapéutico y una revisión estructurada de la medicación dentro de una valoración geriátrica integral (VGI). Se analizaron las diferencias con respecto a la polifarmacia (resultado primario, ≥5 medicamentos crónicos), la hiperpolifarmacia (≥10), el número de medicamentos, los problemas relacionados con los medicamentos (PRM) y los criterios STOPP (Screening Tool of Older Person's Prescription)/ START (Screening Tool to Alert doctors to Right Treatment) entre el ingreso y el alta.

Resultados: entre octubre de 2016 y abril de 2017, se reclutaron 234 pacientes, con una edad media de 87,6 años (DE = 4,6); 143 (61.1%) eran mujeres. La intervención dio como resultado una mejoría estadísticamente significativa en la polifarmacia (-10.2%,

IC 95%, -15.3, -5.2), hiperpolifarmacia (-16.6%, IC 95%, -22.3, -11.0), número de medicamentos (-1.4, IC del 95%, -1.8, -1.0), criterios STOPP (-19.2%, IC del 95%, -24.9, -13.6), criterios START (-6.8%, IC del 95%, -10.1, -3.5) y PRM (- 2.7, IC del 95%, -2.9, -2.4) (p <0.001 para todos ellos).

Conclusiones: una intervención sistemática dirigida por un farmacéutico en el ingreso hospitalario en una UGA en el contexto de una VGI se asoció a una disminución de la polifarmacia, problemas relacionados con los medicamentos y prescripción potencialmente inadecuada.

Acknowledgments

Thanks to the Complejo Hospitalario de Navarra for the opportunity to take my first steps in research with IV Specialized Healthcare Posttraining Program and for being always open to this project.

My deepest gratitude to my supervisor Nicolás Martínez Velilla, for your confidence from the first moment, for teaching me everything with generosity and for demanding and taking care of me in equal parts. Half of this doctoral thesis is yours. Thanks to Mikel Izquierdo for making everything easier and making it possible.

I would like to thank all my coauthors of the articles of this thesis for everything you have contributed: Pablo Aldaz, Javier Alonso, Idoia Beobide, Álvaro Casas, Abel Cedeño, Matteo Cesari, Beatriz Contreras, Thamara Domene, Alex Ferro, Arkaitz Galbete, Belén González, Marco Inzitari, Mikel Izquierdo, Esther Lacalle, Beatriz Larráyoz, Pello Latasa, Vincenzo Malafarina, Itxaso Marín, Nicolás Martínez, and Pilar Monforte.

I also would like to thank Eli Genua for putting the seed of this doctoral thesis, and to Idoia, Alex and all the team of Matia for your support and for teaching me so much. Eskerrik asko.

To all the Navarrabiomed team, for your professionalism, availability, and your invaluable help always.

I am also grateful to all the Department of Pharmacy of the Complejo Hospitalario de Navarra for their support.

I would like to give special thanks to Matteo Tosato, Graziano Onder and all the team of the Policlinico Gemelli for those months in Rome. Grazie a tutti.

Escribiendo estos agradecimientos recuerdo a todas las personas que a lo largo de los años me han enseñado todo lo necesario para poder llegar hasta aquí (algunas ya mencionadas y otras que faltarán): desde mis profesores del colegio o universidad(es), hasta aquellos con los que trabajo cada día. Gracias a Fernando

Marcotegui y a todos los adjuntos de Virgen del Camino que me guiaron durante la residencia: Marien, Camino, Esther, Mercedes, Javier; a todas mis compañeras de residencia, que fuisteis y sois también maestras, compañeras y amigas, en especial a María, Nani, Marta y Pilar; y en general a todas las personas con las que trabajé en ese periodo de gran aprendizaje.

Gracias a todo el Servicio de Geriatría del CHN por acogerme desde el primer día, sois los mejores. Gracias especialmente a Javi y María, a todos los geriatras (Belén, Álvaro, Itziar, Agurne, Vincenzo, Bea, Abel, Jose Luis), a Itxaso, Fernanda, Ana y Nancy, a Carlos y Elena, a enfermeras, auxiliares y a todo el equipo; y a los pacientes y familiares que colaboraron. También a todo el grupo de investigación en Geriatría, de los que tengo tanto que aprender.

Gracias a toda la tropa Goofy por estar siempre ahí, no podría haberlo hecho sin vosotros.

Y finalmente gracias a mi familia, especialmente a mis padres, a Artai y Gala (la mayor alegría de estos años de tesis) y a Cris, mi espejo y mi ejemplo para todo.

A todos los que alguna vez confiaron en mí. Gracias

General Introduction

1. Medication in older adults

As a result of the increasing life expectancy and decreasing birth rates, an accelerated aging of the population has occurred. Currently, almost 19% of the Spanish population is aged over 65, which is projected to increase to 35% by 2066 [1]. In addition, the proportion of octogenarians, who now represent 6.1% of the entire population, is continuing to grow. Spain's life expectancy at birth is among the highest in the world, at 83.1 years (85.7 for women and 80.4 for men) [2], and it is expected to become over 85 for both genders by 2040 [3].

This demographic shift has huge implications for health care and health systems[4]. One of the most important issues to consider is the specific characteristics of older adults regarding the use of medications.

The aging process is characterised by relevant structural and functional modifications. The organism presents a decrease in the capacity for adaptation and internal response, and an overall reduction in the physiological reserve and defence mechanisms. These modifications determine changes in drug pharmacokinetics and pharmacodynamics. All phases of pharmacokinetic processes (absorption, distribution, metabolism, and excretion) can suffer changes [5, 6]; for example, delayed gastric emptying, reduced blood flow, absorption surface, and gastrointestinal motility can cause a decrease in absorption. Increased body fat mass and reduced body total water volume typically cause an increased volume of distribution and half-life for lipophilic drugs and an increased plasma concentrations for water-soluble drugs. First-pass and phase I metabolism can also be affected by reduced hepatic blood flow and overall liver mass. With respect to excretion, renal elimination of water-soluble drugs can be impaired due to reduced renal blood flow and glomerular filtration rate. On the other hand, ageing-associated changes in pharmacodynamic processes can be related to both differences in baseline performance and differences in sensitivity. The most studied changes in pharmacodynamics have been in relation to the central nervous

system (CNS) and cardiovascular agents, including exaggerated or paradoxical responses to drugs acting on the CNS and modified responses to calcium channel blockers (CCB) and β-adrenergic agents [5]. However, as a result of known changes in the organ functions and body composition, changes in pharmacodynamics in the elderly are less predictable than changes in pharmacokinetics. There exist several methodological issues with respect to studies concerning the effects of age on pharmacodynamics, and they depend on many different factors; thus no universal rules can be stablished [7]. Overall, all ageing-associated changes can affect drug effectiveness and toxicity, rendering the use of medications in the elderly a less predictable process.

The lack of evidence regarding the effectiveness and safety of medications in older adults is another source of uncertainty. Older people have been systematically excluded from clinical trials of drugs, not simply due to age, but as a result of other characteristics often present in these patients, such as comorbidity, polypharmacy, and cognitive or functional impairment [8, 9]. This limits the generalisability of clinical trial findings in the elderly, and forces extrapolation of results from younger populations. It would also be necessary to adapt clinical trial outcomes to those different from traditional ones in order to consider important variables in older populations. Clinical trials do not typically consider short-term objectives such as function, walking speed, or quality of life; instead, longer-term objectives, such as survival time, are the focus [10]. Moreover, clinical practice guidelines, which usually support clinical decisions regarding drug prescription, are based on the scarce evidence provided by clinical trials and are focused on individual diseases and not on the characteristic multimorbidity of older adults [11].

On the other hand, clinical practice guidelines are often unable to encompass the heterogeneity of elderly patients [11]. Different factors, such as life-expectancy, functional and cognitive abilities, social and family environment, quality of life, time to benefit from treatment, or patient preferences, priorities, and expectations, will modify therapeutic and treatment goals, affecting decision-making regarding the use of medications in older adults [12]. Medication prescription needs to be adapted to

each patient and situation throughout life, since the concepts of risk and benefit are variable, not constant.

Medication non-adherence is another issue regarding the use of medications in older adults that can compromise the effectiveness and safety of therapies. Older people may present a higher risk of non-adherence to medications as compared with younger populations, with an estimated average adherence rate of less than 45% [13]. Non-adherence to treatment is conditioned by polypharmacy and complex regimens of medications usually associated with multimorbidity, but also by other factors such as functional and cognitive abilities, social situation and family structure, dysphagia, or visual and auditory problems. Older people experience practical problems with medication use that are not common in younger patients, including problems reading or understanding instructions for use, handling packaging, preparing prior to use, or drug taking [14].

The healthcare system itself plays an important role in medication use in older adults. Health systems are yet to adapt to the new demographic and epidemiological situation, with a predominant profile of elderly patients with chronic diseases, and individual diseases still dominate health care delivery [15]. The use of many services for the management of individual diseases, including various professionals without good communication or coordination and frequent transitions between levels of care, can be duplicative and inefficient and may lead to numerous changes in treatment, overtreatment, and medication errors. In these cases, the role of the pharmacist can be an integrator and coordinator of pharmacological aspects.

Demographic transition of population aging has been accompanied by an epidemiological transition, with a modification of disease patterns towards chronic pathologies. Today, most older adults have chronic diseases, and most patients with chronic diseases have more than one chronic disorder, which is usually referred to as multimorbidity. Is has been estimated that multimorbidity in people above 65 years old is 67%, with the prevalence increasing with age and reaching 82% in people over 85 [15]. With the focus of medical care remaining on the disease, polypharmacy is the clearest consequence of multimorbidity on the treatment of elderly patients. Polypharmacy, the concurrent use of multiple drugs by an individual, is very common

in elderly patients and is considered one of the new geriatric syndromes [16]. There is not a clear consensus regarding the definition of polypharmacy, although the use of five or more medications is the most common threshold [17]. An increased number of medications have been associated with a higher cost, an increase in drug-drug and drug-disease interactions, poorer medication adherence, or prescription cascades —the prescription of a new medicine to treat an adverse drug reaction associated with another medicine—[18-20]. Therefore, polypharmacy goes beyond the high number of drugs used in quantitative terms, but is related to taking more drugs than clinically appropriate in qualitative terms. Although polypharmacy could be appropriate and necessary in some cases, it is very unlikely to happen if the treatment is not comprehensively reviewed and monitored. For this reason, as an additional concept to polypharmacy, the inappropriate prescription in the elderly is defined as: "*the use of medicines that introduce a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for treating the same condition. It also includes the use of medicines at a higher frequency and for longer than clinically indicated, the use of multiple medicines that have recognised drug–drug interactions and drug–disease interactions, and the under-use of beneficial medicines that are clinically indicated but not prescribed for ageist or irrational reasons"* [21]. Several methods have been developed for the quantitation of potentially inappropriate prescription, mainly as criteria or lists of medications to avoid; and again, polypharmacy is associated with the presence of these prescriptions [22, 23]. In observational studies, both polypharmacy and potentially inappropriate prescriptions have shown an association with adverse health outcomes such as adverse drug events, falls, delirium, malnutrition, hospital and nursing home admissions, and even mortality [24-26]. It is estimated, for example, that between 10% and 20% of hospital admissions involving elderly people in Spain are related to adverse drugs effects [27, 28], polypharmacy being one of the associated factors. In an attempt to preserve or improve the state of health in older adults, excessively or insufficiently careful use of medications may result in more harm than benefit.

2. Prevalence of polypharmacy in the older Spanish population

As a result of the aging population, it has been suggested that the prevalence of polypharmacy is increasing, and its complexity and negative consequences for patients and healthcare systems and medication use in older people is attracting great interest among the medical community and health managers. In **Chapter 1,** the prevalence of polypharmacy in non-institutionalised older adults in Spain according to the last published National Health Survey (ENSE) is estimated, and associated factors assessed. Other studies have estimated the prevalence based on previous national health surveys or European health surveys in Spain [29, 30]; however, the progressive demographic and epidemiological changes in our population necessitate an update of this information with the latest data. In addition, in the present study, a sensitivity analysis was included to reduce possible underestimation due to the methodological limitations of the ENSE for pharmacoepidemiological purposes. Analysis variables that may be relevant in elderly people, such as dependency for basic activities of daily living or geriatric syndromes, were included in the present study, which have not been included in previous studies.

3. Frailty and polypharmacy

Frailty is an age-linked concept that defines a state of vulnerability characterised by the inability to adequately respond to stressors, which could have multiple implications for medicine use in older people (Figure 1) [31].

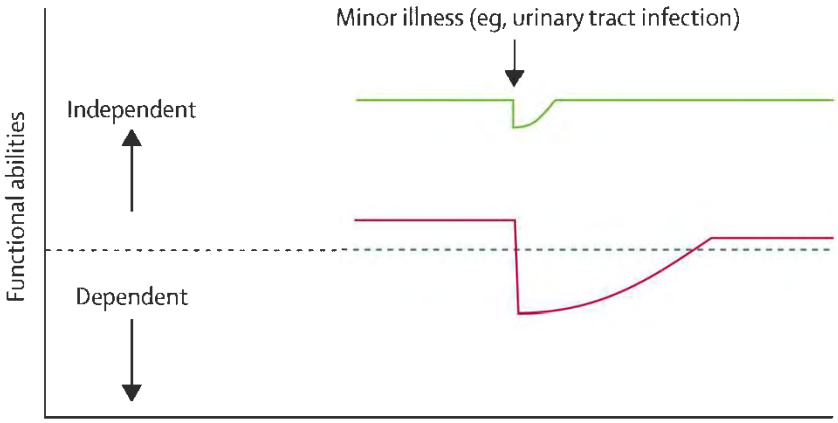


Figure 1: Vulnerability to a sudden change in health status following a minor illness (from Clegg, A, Young, J, Iliffe, S, Rikkert, MO, Rockwood, K. Frailty in elderly people. Lancet 2013;381:752-62)

The aforementioned demographic and epidemiological transitions announce a «third transition» or «clinical transition» that places the focus on functional capacity instead of on disease [32, 33]. Disability is the primary manner in which health problems manifest in the elderly and what limits patient well-being. Therefore, the new challenge for health systems is to prolong disability-free survival and provide assistance to a growing number of dependent persons. Within this context, the concept of frailty emerged, since it was observed that some people are more predisposed to losing functional capacity when presented with a health problem [34]. The term began to be used more frequently in the late 1990s, when Campbell and Buchner defined it as "*a condition or syndrome that results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure, and that is associated with an increased risk of disability and death from minor external stresses*" [35]. Since then, different definitions and measurement tools have been proposed, but two approaches or models stand out.

The frailty phenotype proposed by Fried and colleagues in 2001 [36], resulting from a prospective study, the Cardiovascular Health Study (CHS) [37], understands frailty as a clinical syndrome that is expressed in five domains: nutritional status, energy, physical activity, mobility, and strength.

There also exist the cumulative deficit model proposed by Rockwood and colleagues in 2007 [38], from the Canadian Study of Health and Aging (CSHA) [39]. This model understands frailty as the cumulative effect of individual deficits expressed as signs, symptoms, abnormal laboratory values, disease states, and disabilities; such that, a greater number of deficits corresponds to a greater degree of frailty. According to this approach, frailty is a continuous variable that does not end with disability or dependence but increases progressively until death.

Both models have shown predictive value for various adverse health outcomes and often overlap in their identification of frailty [40, 41]; however, they cannot be considered equivalent, and it has been proposed that they could be useful under different circumstances [42].

An attempt has been made to reach an operational definition of frailty through expert consensus. In 2013, a project led by Rodríguez-Mañas defined frailty as a clinical syndrome characterised by decreased reserve and diminished resistance to stresses that increases vulnerability [43]. In the same year, Morley et al. defined frailty as "*a medical syndrome with multiple causes and contributors that is characterised by diminished strength, endurance, and reduced physiological function that increase an individual's vulnerability to developing increased dependency and/or death*" [44]. Despite these attempts, different conceptual views remain, and there are difficulties in obtaining a single definition that satisfies all the experts. There appears to be consensus, however, that frailty is a state of multidimensional and multifactorial vulnerability, which is dynamic and potentially reversible and associated with functional capacity, being able to predict adverse health outcomes [45].

Many tools have been proposed for the detection or measurement of frailty [46]. Fried's phenotype translates into five criteria, considering a patient pre-frail when they meet one or two of the following conditions, and frail when they meet three or more: involuntary weight loss, exhaustion, low energy expenditure, slow gait speed, and weak strength. The cumulative deficit model is demonstrated by the frailty index (FI), which assesses the total number of deficits as a proportion of the total number of items evaluated. The deficit model also uses the Clinical Frailty Scale, which classifies individuals into seven groups based on the frailty index [39]. From these two models, various modifications have been proposed for the development of numerous frailty scales, with some designed in our environment [47], and by pharmacists [48]. Some of the most well-known tools, in addition to those already indicated, are the Groningen Frailty Indicator [49], Tilburg Frailty Indicator [50], Edmonton Frail Scale [51], different frailty indices, and physical capacity tests such as the Short Physical Performance Battery (SPPB) [52].

Although primarily associated with the field of geriatrics, frailty has now been extended to multiple medical disciplines [53]. Frailty has better predictive value for different adverse health outcomes than does chronological age, and the integration of this concept avoids ageism bias by allowing objective stratification according to needs and risks instead of exclusively by age. Although frailty conditions are not prevalent in

community-dwelling elderly people (approximately 11% of people over 65 years old) [54], it is gaining importance at a public health level due to the fact that frailty is considered a potentially detectable and reversible step prior to disability, and serves as a target for preventive interventions that contribute to successful ageing [55].

Frailty is a syndrome in which multiple interrelated physiological systems are involved. The decrease in physiological reserves is accelerated and the homeostatic processes begin to fail. The mechanisms involved in its development are complex and determined by genetic, environmental, and epigenetic factors that produce cumulative damage at both the cellular and molecular level [53]. The nervous, endocrine, and immune systems, in addition to skeletal muscle, have been best studied with respect to the development of frailty [56, 57]. One example of this implication is sarcopenia, which is considered one of the main causes of frailty [58]. Malnutrition is another condition that is considered an important risk factor for the development of frailty [59, 60].

Recent studies have found that different chronic diseases such as diabetes [61], COPD [62], or atrial fibrillation[63] may play a role in the onset of frailty. According to a recent review, frailty is also associated with the presence of multiple chronic diseases or multimorbidity [64].

The relationship between frailty and drugs is highly complex due to the physiological, cellular, or molecular processes involved in the presentation of frailty and drug activity. It seems plausible that the physiological changes that occur in frailty have an impact on drug pharmacokinetics and pharmacodynamics. In a systematic review, Corsonello et al. found that glomerular filtration rate is associated with degree of frailty [65]. Ageing has traditionally been associated with changes in drug pharmacokinetics, but this association appears to be stronger with frailty, especially for the processes of metabolism and excretion [66-70]. Older people also appear to be more sensitive to certain medications; however, evidence for the role of frailty in pharmacodynamics or drug efficacy remains underdeveloped [71-73]. Examples of altered pharmacodynamics include an increase in sedation produced by some drugs in frail patients [74], and a greater susceptibility to fall-risk-increasing drugs [75]. There are also plausible mechanisms by which the use of medications can contribute to

frailty. A relationship has been found between the number of medications taken and weight loss, impaired balance, poor nutritional status, and functional impairment, all of which are clinical features of frailty [76]. These data highlight polypharmacy as a possible mechanism that contributes to frailty.

Several observational studies have explored the association between frailty and polypharmacy in older people using different methods and objectives [77-79]. In **Chapter 2,** the available research evidence for a relationship between frailty and polypharmacy in older adults is summarised in a systematic review.

4. Frailty and underprescription in nursing homes

Other factors typically associated with polypharmacy may play a role in the development of frailty. It has been found that the use of drugs with anticholinergic properties is more frequent in frail patients, and that the risk of developing frailty increases proportionally with anticholinergic load [80-83]. The use of potentially inappropriate medications in elderly patients in relation to frailty has also been studied. Cullinan et al. found a positive association between a frailty index and the number of STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria [84]. Two studies have demonstrated an increased risk of prescribing inappropriate drugs to frail patients according to STOPP criteria [84, 85]. Maclagan et al. found a higher prevalence of Beers criteria in frail patients than in those who were not [86]. Moreover, Martinot et al. found that the presence of potentially inappropriate prescriptions increases the risk of becoming frail according to data from a three-year follow-up period [87]. Similarly, frail patients may be more exposed to underprescription of beneficial medicines that are clinically indicated, which is sometimes included in the potentially inappropriate prescription criteria. However, the association between frailty and underprescription has barely been studied [88]. In addition, although the association between polypharmacy and frailty has been studied in different settings, the evidence regarding patients in nursing homes is scarce [89]. Moreover, the heterogeneity of frailty measurement tools could have a role in the results found on this topic. To fill these three knowledge gaps, in

Chapter 3, the possible association among polypharmacy, underprescription, and frailty in older people living in nursing homes is examined according to different scales.

5. Medicine optimisation in hospitalised older adults

The data obtained in chapter 1 are very important in understanding the characteristics and trends of polypharmacy at the population level. However, in the case of polypharmacy, this view can prevent us from adequately estimating the magnitude of the problem when it is concentrated in specific population groups. An analysis in a more specific care setting can contribute complementary information, providing another approach that focusses the problem. Chapter 3 focused on older people in nursing homes, a population with high rates of frailty, polypharmacy, and inappropriate use of medications [90-92]. In **Chapter 4** attention is shifted to another population group within the elderly, which is also particularly vulnerable to the harms of medications: hospitalised patients. The profile of older inpatients is multimorbidity, polypharmacy, and drug-related problems, in addition to complexity as a result of functional, cognitive, affective or social reasons. It has been suggested that hospitalisation itself may worsen polypharmacy and drug-related problems due to concomitant acute and chronic disorders, transitions of care, and the involvement of many professionals; however, its effects on the modification of pharmacological treatments remain controversial [93-95]. This could lead to worse health outcomes during hospitalization or following discharge. In Chapter 4, the influence of hospitalisation in an acute geriatric unit on polypharmacy, potentially inappropriate prescriptions, and other medication indicators are measured. The possible impact of these characteristics on mortality, hospitalisations, and emergency room visits are also explored.

Due to the complexity of medication use in older adults, especially in some population sectors such as hospitalised patients, several strategies have been proposed to address the problems of polypharmacy and inappropriate use of medication, and their negative consequences. There have been a wide range of proposed interventions regarding the professionals involved, the tools used, or the outcomes measured, which render it difficult to clarify the best strategy for medicine

optimisation in older inpatients. For this reason, in **Chapter 5**, in a systematic review, we summarise the evidence regarding interventions aimed at optimising drug treatment in hospitalised elderly patients.

Although hospitalisation has been previously highlighted as a particularly appropriate period for the implementation of interventions to improve medication appropriateness, medication optimisation strategies in elderly people admitted to hospital are not widely extended in Spanish clinical practice. From the beginning of this research to the present moment, there have been no experiences in Navarra of strategies for medicine optimisation in hospitalised elderly people, beyond medication reconciliation in selected patients. Therefore, we intended to implement an intervention in our environment that could describe the expected benefits by patients and the health administration, and the procedures and tools necessary to make it reproducible and applicable to clinical practice.

The best results with respect to improvements in important health outcomes, such as readmissions or emergency room visits, have been shown for multifaceted multidisciplinary interventions [96-99]. As medicine experts, pharmacists could be valuable in an intervention to optimise treatment in elderly patients. Pharmacist-led medication reviews are beginning to be implemented in other countries within different health settings with a view to optimising medication in older patients with polypharmacy. However, its application is different according to the environment in which it is carried out, and it is important that the procedure is adapted to the appropriate environment and the patients to whom it is directed. As will be shown in chapter 4, the profile of the patient admitted to acute geriatric units is very specific regarding complexity and drug-related problems. Acute geriatric units (AGUs) were designed to attend to the special needs of older inpatients, and can be defined as hospital units with their own physical location and structure, run by a specialised multidisciplinary team with direct responsibility for the care of elderly people with acute medical disorders. AGUs have shown a functional benefit as compared with conventional hospital care and an increased likelihood of living at home following discharge [100]. Comprehensive geriatric assessment (CGA), as the main tool in geriatric medicine, is a multidimensional multidisciplinary diagnostic process assessing

older people's medical, psychological, and functional capability in order to develop a coordinated and integrated plan for treatment and long-term follow-up focused on the individual's needs [101]. As we have seen, not only diseases but several other factors are important for decision-making regarding the use of medications. Our approach was a specific multi-disciplinary intervention focused on drug treatment in the context of a CGA in an AGU to improve the use of medications in older inpatients from a holistic point of view. The proposal and main results are summarised in **Chapter 6**.

6. References

1. Abellán García, Antonio; Ayala García, Alba; Pérez Díaz, Julio; Pujol Rodríguez, Rogelio (2018). "Un perfil de las personas mayores en España, 2018. Indicadores estadísticos básicos". Madrid, Informes Envejecimiento en red nº 17, 34 p. [Fecha de publicación: 07/02/2018]. http://envejecimiento.csic.es/documentos/documentos/enred-indicadoresbasicos18.pdf.

2. INEbase. Indicadores demográficos básicos. Indicadores de mortalidad. Instituto Nacional de Estadística. Acceso: http://www.ine.es/jaxiT3/Tabla.htm?t=1414&L=0.

3. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet 2018; 392: 2052-90.

4. World report on Ageing and Health. World Health Organization (2015). https://www.who.int/ageing/events/world-report-2015-launch/en/.

5. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem 2010; 17: 571-84.

6. ElDesoky ES. Pharmacokinetic-pharmacodynamic crisis in the elderly. Am J Ther 2007; 14: 488-98.

7. Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. Am J Geriatr Pharmacother 2007; 5: 263-303.

8. Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasquín B, Sánchez-Castellano C, Sánchez-García E. Exclusion of older adults from ongoing clinical trials about type 2 diabetes mellitus. J Am Geriatr Soc 2013; 61: 734-8.

9. McMurdo ME, Roberts H, Parker S, et al. Age and Ageing Specialty Group, NIHR, Comprehensive Clinical Research Network. Improving recruitment of older people to research through good practice. Age Ageing 2011; 40: 659-65.

10. Martinez-Velilla N, Formiga F. Inclusion of the elderly in clinical trials: a need and an obligation. Rev Esp Geriatr Gerontol 2014; 49: 99-100.

11. Formiga F, Martinez-Velilla N, Baztan JJ. Clinical practice guidelines in geriatrics: Are they really useful? Rev Esp Geriatr Gerontol 2016; 51: 252-3.

12. Van der Linden L, Hias J, Spriet I, Walgraeve K, Flamaing J, Tournoy J. Medication review in older adults: Importance of time to benefit. Am J Health Syst Pharm 2019; 76: 247-50.

13. Giardini A, Martin MT, Cahir C, et al. Toward appropriate criteria in medication adherence assessment in older persons: Position Paper. Aging Clin Exp Res 2016; 28: 371-81.

14. Notenboom K, Beers E, van Riet-Nales DA, et al. Practical problems with medication use that older people experience: a qualitative study. J Am Geriatr Soc 2014; 62: 2339-44.

15. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012; 380: 37-43.

16. Laosa Zafra O, Tardáguila García N, Jordán Bueso J. Programas de farmacovigilancia en el anciano. In: Abizanda Soler P, Rodríguez Mañas L, editors. Tratado de medicina geriátrica. Fundamentos de la atención sanitaria a los mayores. Barcelona:Elsevier; 2015. p. 56–65.

17. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr 2017; 17: 230.

18. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother 2007; 5: 345-51.

19. Rochon PA, Gurwitz JH. The prescribing cascade revisited. Lancet 2017; 389: 1778-80.

20. Tavares NU, Bertoldi AD, Mengue SS, Arrais PS, Luiza VL, Oliveira MA, Ramos LR, Farias MR, Pizzol TD. Factors associated with low adherence to medicine treatment for chronic diseases in Brazil. Rev Saude Publica 2016; 50: 10s.

21. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther 2007; 32: 113-21.

22. Motter FR, Fritzen JS, Hilmer SN, Paniz EV, Paniz VMV. Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. Eur J Clin Pharmacol 2018; 74: 679-700.

23. Aguiar JP, Brito AM, Martins AP, Leufkens HGM, Alves da Costa F. Potentially inappropriate medications with risk of cardiovascular adverse events in the elderly: A systematic review of tools addressing inappropriate prescribing. J Clin Pharm Ther 2019. Feb 11. doi: 10.1111/jcpt.12811

24. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf 2014; 13: 57-65.

25. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc 2014; 62: 2261-72.

26. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007; 370: 173-84.

27. Cabre M, Elias L, Garcia M, Palomera E, Serra-Prat M. Avoidable hospitalizations due to adverse drug reactions in an acute geriatric unit. Analysis of 3,292 patients. Med Clin 2018; 150: 209-14.

28. Estudio Nacional de Efectos Adversos ligados a la hospitalización ENEAS, Ministerio de Sanidad y Consumo. España, 2005. Disponible en https://www.seguridaddelpaciente.es/resources/contenidos/castellano/2006/ENEAS.pdf

29. Martin-Perez M, Lopez de Andres A, Hernandez-Barrera V, Jimenez-Garcia R, Jimenez-Trujillo I, Palacios-Cena D, Carrasco-Garrido P. Prevalencia de polifarmacia en la población mayor de 65 años en España: análisis de las Encuestas Nacionales de Salud 2006 y 2011/12. Rev Esp Geriatr Gerontol 2017; 52:2-8

30. Carmona-Torres JM, Cobo-Cuenca AI, Recio-Andrade B, Laredo-Aguilera JA, Martins MM, Rodriguez-Borrego MA. Prevalence and factors associated with polypharmacy in the older people: 2006-2014. J Clin Nurs 2018; 27:2942-2952.

31. Hilmer SG, D. Prescribing for frail older people. Aust Prescr 2017: 174-8

32. Tinetti ME, Fried T. The end of the disease era. Am J Med 2004; 116: 179-85.

33. Rodriguez-Manas L, Rodriguez-Artalejo F, Sinclair AJ. The Third Transition: The Clinical Evolution Oriented to the Contemporary Older Patient. J Am Med Dir Assoc 2017; 18: 8-9.

34. Cesari M, Marzetti E, Thiem U, et al. The geriatric management of frailty as paradigm of "The end of the disease era". Eur J Intern Med 2016; 31: 11-4.

35. Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. Age Ageing 1997; 26: 315-8.

36. Fried LP, Tangen CM, Walston J, et al. Cardiovascular Health Study Collaborative Research G. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146-56.

37. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Annals Epidemiol 1991; 1: 263-76.

38. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 2007; 62: 722-7.

39. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173: 489-95.

40. Cigolle CT, Ofstedal MB, Tian Z, Blaum CS. Comparing models of frailty: the Health and Retirement Study. J Am Geriatr Soc 2009; 57: 830-9.

41. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci 2007; 62: 738-43.

42. Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. Age Ageing 2014; 43: 10-2.

43. Rodríguez-Mañas L, Féart C, Mann G, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci 2013; 68: 62-7.

44. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013; 14: 392-7.

45. Junius-Walker U, Onder G, Soleymani D, et al. The essence of frailty: A systematic review and qualitative synthesis on frailty concepts and definitions. Eur J Intern Med 2018; 56: 3-10.

46. Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev 2016; 26: 53-61.

47. Amblas-Novellas J, Martori JC, Espaulella J, et al. Frail-VIG index: a concise frailty evaluation tool for rapid geriatric assessment. BMC Geriatr 2018; 18: 29.

48. Peris-Marti JF, Parro Martin MA, Fernandez-Villalba E, Bravo Jose P. Approach to the development of a frailty index based on comprehensive geriatric assessment in nursing home. Farm Hosp 2018; 42: 159-62.

49. Steverink N. Measuring frailty : Developing and testing the GFI (Groningen Frailty Indicator). The Gerontologist 2001; 41: 236.

50. Gobbens RJ, van Assen MA, Luijkx KG, Schols JM. The predictive validity of the Tilburg Frailty Indicator: disability, health care utilization, and quality of life in a population at risk. The Gerontologist 2012; 52: 619-31.

51. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006; 35: 526-9.

52. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994; 49: M85-94.

53. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013; 381: 752-62.

54. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012; 60: 1487-92.

55. Cesari M, Prince M, Thiyagarajan JA, et al. Frailty: An Emerging Public Health Priority. J Am Med Dir Assoc 2016; 17: 188-92.

56. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, Ershler WB, Harris T, Fried LP. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc 2006; 54: 991-1001.

57. Clegg A, Hassan-Smith Z. Frailty and the endocrine system. Lancet Diabetes Endocrinol 2018; 6: 743-52.

58. Morley JE, von Haehling S, Anker SD, Vellas B. From sarcopenia to frailty: a road less traveled. J Cachexia Sarcopenia Muscle 2014; 5: 5-8.

59. Gabrovec B, Veninsek G, Samaniego LL, Carriazo AM, Antoniadou E, Jelenc M. The role of nutrition in ageing: A narrative review from the perspective of the European joint action on frailty - ADVANTAGE JA. Eur J Intern Med 2018; 56: 26-32.

60. Artaza-Artabe I, Saez-Lopez P, Sanchez-Hernandez N, Fernandez-Gutierrez N, Malafarina V. The relationship between nutrition and frailty: Effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. Maturitas 2016; 93: 89-99.

61. Assar ME, Laosa O, Rodriguez Manas L. Diabetes and frailty. Curr Opin Clin Nutr Metab Care 2019; 22: 52-57.

62. Marengoni A, Vetrano DL, Manes-Gravina E, Bernabei R, Onder G, Palmer K. The Relationship Between COPD and Frailty: A Systematic Review and Meta-Analysis of Observational Studies. Chest 2018; 154: 21-40.

63. Villani ER, Tummolo AM, Palmer K, et al. Frailty and atrial fibrillation: A systematic review. Eur J Intern Med 2018; 56: 33-38.

64. Vetrano DL, Palmer K, Marengoni A, et al. Frailty and multimorbidity: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci 2018. May 3. doi: 10.1093/gerona/gly110

65. Corsonello A, Roller-Wirnsberger R, et al. Screening for Chronic Kidney Disease among Older people across Europe Study I. Estimated glomerular filtration rate and functional status among older people: A systematic review. Eur J Intern Med 2018; 56: 39-48.

66. Ballew SH, Chen Y, Daya NR, et al. Frailty, Kidney Function, and Polypharmacy: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis 2017; 69: 228-36.

67. Hilmer SN, Tran K, Rubie P, et al. Gentamicin pharmacokinetics in old age and frailty. Br J Clin Pharmacol 2011; 71: 224-31.

68. Johnston C, Hilmer SN, McLachlan AJ, Matthews ST, Carroll PR, Kirkpatrick CM. The impact of frailty on pharmacokinetics in older people: using gentamicin population pharmacokinetic modeling to investigate changes in renal drug clearance by glomerular filtration. Eur J Clin Pharmacol 2014; 70: 549-55.

69. Williams FM, Wynne H, Woodhouse KW, Rawlins MD. Plasma aspirin esterase: the influence of old age and frailty. Age Ageing 1989; 18: 39-42.

70. Wynne HA, Cope LH, Herd B, Rawlins MD, James OF, Woodhouse KW. The association of age and frailty with paracetamol conjugation in man. Age Ageing 1990; 19: 419-24.

71. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. JAMA 2016; 315: 2673-82.

72. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. BMC Med 2015; 13: 78.

73. Nguyen TN, Pepperell D, Morel-Kopp MC, Cumming RG, Ward C, Hilmer SN. Effect of Frailty and Age on Platelet Aggregation and Response to Aspirin in Older Patients with Atrial Fibrillation: A Pilot Study. Cardiol Ther 2016; 5: 51-62.

74. Wynne HA, Yelland C, Cope LH, Boddy A, Woodhouse KW, Bateman DN. The association of age and frailty with the pharmacokinetics and pharmacodynamics of metoclopramide. Age Ageing 1993; 22: 354-9.

75. Bennett A, Gnjidic D, Gillett M, et al. Prevalence and impact of fall-risk-increasing drugs, polypharmacy, and drug-drug interactions in robust versus frail hospitalised falls patients: a prospective cohort study. Drugs Aging 2014; 31: 225-32.

76. Gnjidic D, Hilmer SN. Potential contribution of medications to frailty. J Am Geriatr Soc 2012; 60: 401.

77. Veronese N, Stubbs B, Noale M, et al. Polypharmacy Is Associated With Higher Frailty Risk in Older People: An 8-Year Longitudinal Cohort Study. J Am Med Dir Assoc 2017; 18: 624-28.

78. Saum KU, Schottker B, Meid AD, et al. Is Polypharmacy Associated with Frailty in Older People? Results From the ESTHER Cohort Study. J Am Geriatr Soc 2017; 65: e27-e32.

79. Merchant RA, Chen MZ, Tan LWL, Lim MY, Ho HK, van Dam RM. Singapore Healthy Older People Everyday (HOPE) Study: Prevalence of Frailty and Associated Factors in Older Adults. J Am Med Dir Assoc 2017; 18: 734.e9-34.e14.

80. Gnjidic D, Hilmer SN, Blyth FM, et al. High-risk prescribing and incidence of frailty among older community-dwelling men. Clin Pharmacol Ther 2012; 91: 521-8.

81. Jamsen KM, Bell JS, Hilmer SN, et al. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions Between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. J Am Geriatric Soc 2016; 64: 89-95.

82. Moulis F, Moulis G, Balardy L, et al. Exposure to atropinic drugs and frailty status. J Am Med Dir Assoc 2015; 16: 253-7.

83. Herr M, Sirven N, Grondin H, Pichetti S, Sermet C. Frailty, polypharmacy, and potentially inappropriate medications in old people: findings in a representative sample of the French population. Eur J Clin Pharmacol 2017; 73: 1165-72.

84. Cullinan S, O'Mahony D, O'Sullivan D, Byrne S. Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. Age Ageing 2016; 45: 115-20.

85. Muhlack DC, Hoppe LK, Stock C, Haefeli WE, Brenner H, Schottker B. The associations of geriatric syndromes and other patient characteristics with the current and future use of potentially inappropriate medications in a large cohort study. Eur J Clin Pharm 2018; 74: 1633-44.

86. Maclagan LC, Maxwell CJ, Gandhi S, et al. Frailty and Potentially Inappropriate Medication Use at Nursing Home Transition. J Am Geriatr Soc 2017; 65: 2205-12.

87. Martinot P, Landré B, Zins M, Goldberg M, Ankri J, Herr M. Association Between Potentially Inappropriate Medications and Frailty in the Early Old Age: A Longitudinal Study in the GAZEL Cohort. J Am Med Dir Assoc 2018; 19: 967-73.e3.

88. Meid AD, Quinzler R, Freigofas J, et al. Medication underuse in aging outpatients with cardiovascular disease: Prevalence, determinants, and outcomes in a prospective cohort study. PloS One 2015; 10.

89. Hasan SS, Chia Siang K, Verma RK, et al. An evaluation of medication appropriateness and frailty among residents of aged care homes in Malaysia: A cross-sectional study. Medicine 2017; 96: 1-7.

90. Kojima G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc 2015; 16: 940-5.

91. Cherubini A, Corsonello A, Lattanzio F. Polypharmacy in Nursing Home Residents: What Is the Way Forward? J Am Med Dir Assoc 2016; 17: 4-6.

92. García-Gollarte F, Baleriola-Júlvez J, Ferrero-López I, Cruz-Jentoft AJ. Inappropriate drug prescription at nursing home admission. J Am Med Dir Assoc 2012; 13: 83.e9-15.

93. Sganga F, Landi F, Vetrano DL, Corsonello A, Lattanzio F, Bernabei R, Onder G. Impact of hospitalization on modification of drug regimens: Results of the Criteria to Assess Appropriate Medication Use Among Elderly Complex Patients study. Geriatr Gerontol Int 2016; 16:593-9

94. Bakken MS, Ranhoff AH, Engeland A, Ruths S. Inappropriate prescribing for older people admitted to an intermediate-care nursing home unit and hospital wards. Scand J Prim Health Care 2012; 30: 169-75.

95. Laroche ML, Charmes JP, Nouaille Y, Fourrier A, Merle L. Impact of hospitalisation in an acute medical geriatric unit on potentially inappropriate medication use. Drugs Aging 2006; 23: 49-59.

96. Ravn-Nielsen LV, Duckert ML, Lund ML, Henriksen JP, Nielsen ML, Eriksen CS, Buck TC, Pottegård A, Hansen MR, Hallas J. Effect of an In-Hospital Multifaceted Clinical Pharmacist Intervention on the Risk of Readmission: A Randomized Clinical Trial. JAMA Intern Med 2018; 178: 375-82.

97. Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. Arch Intern Med 2009; 169: 894-900.

98. Skjøt-Arkil H, Lundby C, Kjeldsen LJ, et al. Multifaceted Pharmacist-led Interventions in the Hospital Setting: A Systematic Review. Basic Clin Pharmacol Toxicol 2018; 123: 363-79.

99. Van der Linden L, Hias J, Dreessen L, Milisen K, Flamaing J, Spriet I, Tournoy J. Medication review versus usual care to improve drug therapies in older inpatients not admitted to geriatric wards: a quasi-experimental study (RASP-IGCT). BMC Geriatr 2018; 18: 155.

100. Baztán JJ, Suárez-García FM, López-Arrieta J, Rodríguez-Mañas L, Rodríguez-Artalejo F. Effectiveness of acute geriatric units on functional decline, living at home, and case fatality among older patients admitted to hospital for acute medical disorders: meta-analysis. BMJ 2009; 338: b50.

101. Palmer K, Onder G. Comprehensive geriatric assessment: Benefits and limitations. Eur J Intern Med 2018; 54: e8-e9.

Aims and hypothesis

General objective

Aim: to assess the problem of polypharmacy in the elderly in different settings and its relationship with frailty and explore strategies to optimize treatments in most vulnerable sectors.

Hypothesis: polypharmacy is a growing problem in the elderly population that cannot be explained by multimorbidity alone, and is especially concentrated in vulnerable sectors, where the introduction of multidisciplinary specific strategies from a perspective not only focused on the disease can favor a more appropriate use of the medications.

Specific objectives

Chapter 1: Prevalence of polypharmacy and associated factors in older adults in Spain: Data from the National Health Survey 2017

Aim: to estimate the prevalence of polypharmacy and hyperpolypharmacy in non-institutionalized older adults in Spain and to assess the associated factors.

Hypothesis: the prevalence of polypharmacy in non-institutionalized older adults in Spain is high and could be associated to other factors than socio-demographic and comorbidities.

Chapter 2: The relationship between Frailty and Polypharmacy in older people: a Systematic Review

Aim: to analyse the available research evidence on the relationship between frailty and polypharmacy in older adults.

Hypothesis: there is a relationship between frailty and polypharmacy in older adults

Chapter 3: The Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes

Aim: to examine the possible association between polypharmacy, underprescription, and frailty in older people living in nursing homes according to different scales and explore the interaction between polypharmacy, multimorbidity, and different definitions of frailty.

Hypothesis: polypharmacy could be associated with frailty and underprescription in older adults living in nursing homes, morbidity wouldn´t be the only modulator for this association, and could differ depending on the frailty scale used.

Chapter 4: Impact of hospitalization in an acute geriatric unit on polypharmacy and potentially inappropriate prescriptions: A retrospective study

Aim: to measure the influence of hospitalization in an acute geriatric unit on polypharmacy, potentially inappropriate prescriptions, underprescription, drug interactions, anticholinergic burden and inappropriate use of drugs in patients with impaired renal function. The secondary objective was to measure the possible impact of these characteristics on mortality, hospitalizations and emergency room visits in these patients.

Hypothesis: during hospitalization in an acute geriatric unit, polypharmacy, potentially inappropriate prescriptions, underprescription, drug interactions, anticholinergic burden and inappropriate use of drugs in patients with impaired renal function do not decrease, and these measures can be associated with increased mortality, hospitalizations and emergency room visits.

Chapter 5: Interventions to optimize pharmacologic treatment in hospitalized older adults: a systematic review

Aim: to summarize the evidence on interventions aimed at optimizing the drug treatment of hospitalized elderly patients.

Hypothesis: pharmacological treatment of older inpatients can be optimized during hospitalization with a wide range of specific interventions.

Chapter 6: A medicine optimization strategy in an acute geriatric unit: the pharmacist in the geriatric team

Aim: to describe a new medicine optimization strategy in an acute geriatric unit and explore its effectiveness to reduce polypharmacy and improve medication appropriateness.

Hypothesis: a pharmacist-led medicine optimization strategy in an acute geriatric unit is feasible and can reduce polypharmacy, drug related problems and inappropriate prescribing.

Chapter 1:

Prevalence of polypharmacy and associated factors in older adults in Spain: Data from the National Health Survey 2017

1. Introduction

Over the last few decades, enormous demographic and epidemiological changes have occurred in Spain, resulting in an aging population and a greater prevalence of chronic diseases [1]. This new situation has been accompanied by an increase in chronic drug use to treat these diseases, especially in elderly people [2].

The use of medications in elderly people is complex, due to age-related changes in pharmacokinetics and pharmacodynamics, multimorbidity and other factors that condition complexity in the elderly, such as functional and cognitive impairment or geriatric syndromes. It is also due to the limited available evidence on the efficacy and safety of medicines in this population [3, 4]. Furthermore, the use of multiple drugs simultaneously, which has been called polypharmacy, despite being the logical response to the coexistence of multiple diseases, can be a problem in and of itself [5]. Polypharmacy is associated with an increase in drug-drug and drug-disease interactions, a decrease in medication adherence, an increased risk of anticholinergic effects and, in general, adverse drug effects, perhaps due to an increase in the number of potentially inappropriate prescriptions in a particularly vulnerable population [6, 7]. Probably because of all this, polypharmacy has been associated with poorer health outcomes in the elderly, increasing the risk of delirium, malnutrition, falls, hospital admissions and even mortality, among others [8, 9]. It is estimated, for example, that between 10 and 20% of the hospital admissions in older people in our country would be related to adverse drug effects, being polypharmacy one of the associated factors [10]. In an attempt to preserve or improve health conditions in older adults, excessive or not sufficiently careful use of medications can end up being more harmful than beneficial. The latest evidence suggests that a high consumption of medications can contribute to frailty, regardless of the associated comorbidities, conditioning a worse vital prognosis in the elderly [11]. In addition, excessive polypharmacy can have an

important economic impact on the public health system, both due to the increase in direct expenditure on medications and the indirect costs derived from consultations, emergency room visits, or hospital admissions. On the other hand, it must also be considered that a high consumption of medications increases the "burden of treatment" for the patient, and may affect their perceived health status, their well-being and their quality of life [12].

In order to face the causes and consequences of this problem and to improve behaviours and strategies towards a more appropriate use of medications at the individual and population level, it is essential to know the extent of polypharmacy among the elderly in our population. Other studies have been carried out in order to know the prevalence of polypharmacy in the non-institutionalized elderly in Spain, some at the local or regional level [13-15] and others based on National or European Health Surveys previously conducted in Spain [2, 16]. The demographic and epidemiological changes that occur progressively in our population make it necessary to update this data, which in recent years has shown an upward trend. The data of the National Health Survey of Spain 2017 (ENSE 2017), made by the Ministry of Health, Consumption and Social Welfare with the collaboration of the National Institute of Statistics, was published in June 2018 and it collects health information related to the population residing in Spain in 23,860 homes [17]. It is an investigation that allows us to explore numerous aspects of the health of the citizens at a national and regional level, and to plan and evaluate the actions in health services. Among others, the ENSE provides information on the consumption of medications in a representative sample of the entire population, although it requires certain adjustments to adequately estimate the prevalence of polypharmacy that have not been carried out in previous studies. Moreover, it provides essential information on the elderly population, such as functional or cognitive capacity, perception of health status or certain geriatric syndromes. The incorporation of these factors into the analysis of polypharmacy in elderly people is essential to understand the patterns of drug consumption in the elderly, so we included them for the first time in this study together with sociodemographic factors, already present in previous studies based on Health Surveys.

The aim of the present study is to estimate the prevalence of polypharmacy and hyperpolypharmacy in non-institutionalized older adults in Spain and to assess the associated factors.

2. Material and methods

2.1 Study design and population

Cross-sectional study with data obtained from the Spanish National Health Survey of 2017 (ENSE 2017), selecting participants who are 65 years old or older. The ENSE is the result of the Collaboration Agreement signed between the Spanish Ministry of Health, Social Services and Equality and the Spanish National Institute of Statistics, and the target population of the study are the people living in the main family dwellings of the Spanish territory in 2017. The information was collected through computer-assisted personal interviews in the homes of the selected participants, and carried out by specifically instructed interviewers. The interviews were conducted between October 2016 and October 2017. The ENSE, by using stratified three-stage probabilistic sampling, is rendered nationally and regionally representative. The first stage units are the census sections, the second stage units are the main family dwellings, and the third stage units are adults selected from each home to complete the Adult Questionnaire. The sample is distributed among regions assigning one portion evenly and another proportionally to the size of the region. The Adult Questionnaire had to be answered by the selected adult, except for in the cases of hospital admission, disability due to illness/disability or problems due to language. In these cases it was allowed that another person answers the questionnaire in the selected person's name.

Variables

The main outcome measures are the prevalence of polypharmacy and hyperpolypharmacy and the number of medications consumed. Sociodemographic factors (sex, age, marital status, educational level), use of the healthcare system (hospital admissions and emergency room visits in the last year, consultation with general practitioner or specialists in the last 4 weeks, health insurance modality),

comorbidity, independence for basic activities of daily living (BADL), perceived health status, cognitive impairment and body mass index (BMI) are considered as independent variables.

Polypharmacy is defined as the consumption of 5 or more medications during the last two weeks prior to the interview, and hyperpolypharmacy as the consumption of 10 or more medications. Participants were specifically asked *"which of these drugs have you consumed in the last 2 weeks?"*, considering for the present study the following categories: *"medicines for the cold, flu, throat, bronchi, for pain, to lower fever, restorative such as vitamins, minerals and tonics, laxatives, antibiotics, tranquilizers, relaxants and sleeping pills, medications for allergy, for diarrhea, for rheumatism, for the heart, for blood pressure, for the stomach and/ or digestive disorders, antidepressants or stimulants, hormones for menopause, drugs to lose weight, to lower cholesterol, for diabetes and for the thyroid"*. For the purpose of this study, this classification has been equated to the ATC therapeutic groups as much as possible. For each individual, all affirmative responses were added, thus estimating the total number of medications consumed. Although there is no consensus on the definition of polypharmacy, the threshold of 5 or more medications was chosen because it is the most commonly used [18].

A previously validated multimorbidity assessment tool was used to measure the global burden of chronic diseases or health problems of the participants [19], adapting it to the questions of the ENSE regarding whether they had ever suffered the conditions considered. This tool collects 918 ICD-10 codes and groups them into 60 categories of chronic diseases. Each of these categories has been compared to a question from the ENSE whenever possible, reflecting the most important pathologies (hypertension, hypercholesterolemia, chronic kidney disease, ischemic heart disease, other cardiac pathologies, osteoarthritis, auditory or visual impairment, obesity, thyroid pathologies, depression, malignant neoplasms, diabetes, stroke, osteoporosis, cataracts, asthma, COPD, peptic ulcer, prostatic diseases, other genitourinary pathologies, chronic anxiety, migraine, chronic allergy, mental health problems, chronic venous disease, cirrhosis, hepatic dysfunction and chronic skin conditions) (extended in **supplementary material**). The proposed methodology allows us to detect

a comprehensive set of chronic diseases that either have a long-lasting impact on older adults' autonomy and quality of life or require enduring contacts with healthcare services. This tool, therefore, is well suited to describe the burden of chronic multimorbidity in our study population. Multimorbidity is expressed as the number of chronic health problems considered by this tool. The Katz Index [20] was used to evaluate the dependency for the basic activities of daily living, adapting it from the questions of the ENSE 2017, considering these 6 categories: difficulty for daily basic activities: showering or bathing without help; getting dressed and undressed without help; going to the toilet without help; sitting down, getting up from a chair or a bed, lying down without help; partial or total incontinence; feeding themselves (description in **supplementary material**). A score of 0 was assigned as very dependent and 6 as independent. The participants were considered to have cognitive impairment when they answered that they had been limited for at least the last 6 months to perform the activities that people usually do, due to a mental problem alone or a physical and mental one together. Finally, the participants were classified according to the following BMI ranges: <18.5 kg/m^2 insufficient weight, ≥18 and <25 kg/m^2 normal weight, ≥25 and <30 kg/m^2 overweight and ≥30 kg/m^2 obesity.

2.2 Statistical analysis

First of all, a descriptive analysis was carried out showing the main characteristics of the study population using numbers and proportions in the case of qualitative variables and using means and standard deviations (SD) for quantitative variables. The prevalence of polypharmacy and hyperpolypharmacy was estimated with their corresponding 95% confidence intervals (CI). For the comparison of means, the Student test was used and for the comparison of proportions, the Pearson Chi-square test. The association between the consumption of the most frequent medications and the most common pathologies registered in the ENSE for which they are indicated was analyzed using the Chi-square test.

One of the major limitations of the ENSE to estimate the prevalence of polypharmacy is that, as it only allows dichotomous yes/no responses to the consumption of different types of drugs, it does not contemplate the use of combination therapies for the same pathology (it always considers monotherapy). In

order to obtain an estimate closer to reality, a sensitivity analysis was carried out in which the fact that a proportion of the participants would be receiving combination therapy for two of the most frequent chronic health problems such as hypertension and diabetes in which this situation is common was contemplated. The average number of drugs consumed and the prevalence of polypharmacy and hyperpolypharmacy were calculated assuming that patients taking antihypertensive drugs consumed 1.8 antihypertensive drugs per patient (one antihypertensive drug alone in 38.3% of cases, two antihypertensive drugs in 43.5% of patients, three antihypertensive drugs in 15% of cases and four antihypertensive drugs in 3.2% of cases, based on previous literature[21, 22]); and that patients who used drugs for diabetes took an average of 1.5 antidiabetic agents (monotherapy in 54.2% of cases and two antidiabetic drugs in 45.8% of cases[23]). A homogeneous distribution for all participants in all polypharmacy categories was assumed.

To identify factors associated with polypharmacy and hyperpolypharmacy, a multivariate logistic regression analysis was performed with all the variables included in Table 1. A limit for statistical significance of alpha <0.05 was established. All statistical analyses were performed with the IBM SPSS Statistics version 20 software (IBM Corp, Armonk, NY, USA).

2.3 Ethical considerations

This study respects the fundamental principles established in the Declaration of Helsinki and its updates, and meets the requirements established in the legislation in the field of biomedical research, the protection of personal data and bioethics. According to the Methodology of the National Health Survey of Spain (ENSE) *"the microdata files are anonymized. The microdata files of the ENSE are apt for public consumption and non-identifiable, and therefore do not require agreements for their use. The files apt for public consumption are not considered confidential, in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council, of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and the free movement of such data. It is not necessary to apply the principles of data protection to anonymous information, that is, information that does not relate to an identified or identifiable natural person, nor to data that has been*

converted into anonymous so that the interested party is not identifiable, or is no longer identifiable. Consequently, the Regulation does not affect the treatment of the information published by the ENSE. Even for statistical or research purposes, its use does not require the approval of an accredited ethics committee."

3. Results

3.1 Main Characteristics

The total sample of the ENSE 2017 comprises 29,195 individuals, of whom 7023 who were 65 years old or older were selected. The mean age was 76.0 years (Standard deviation, SD 7.6), and 59.4% were women. The main characteristics of the participants are described in **Table 1**. 92.5% declared having a chronic or long-term health problem at the time of the interview (chronic meaning it has lasted or is expected to last at least 6 months). The most frequent chronic health problems were hypertension (56.0%), osteoarthritis (51.8%), hypercholesterolemia (43.3%), diabetes (22.4%), depression (18.0%), osteoporosis (13.0%), prostatic diseases (12.2%), chronic anxiety (11.3%), COPD (10.2%) and thyroid diseases (10.2%). Women had a higher mean number of chronic health problems than men (4.7 (SD 2.9) vs 3.8 (SD 2.6)), as well as older people compared to the youngest: 5.1 (SD 2.9) in the case of the older than 85, 4.8 (SD 2.9) in those 76 to 85 years old and 3.8 (SD 2.7) in those 65 to 75 years old. In the same way, people with higher levels of education suffered fewer chronic health problems than those with a lower level of education: without studies: 5.6 (SD 3.2), primary studies: 4.6 (SD 2.8), secondary studies 3.8 (SD 2.6) and university studies 3.5 (SD 2.5). Men rated their health status in the last 12 months as good or very good in 52.6% of cases compared to 40.4% in women, as medium in 34.2% of cases compared to 38.7% in women, and as bad or very bad in 13.1% of cases compared to 20.9% in women ($p < 0.001$). Men rated the pain suffered in the last 4 weeks as none (48.4%), very mild (10.7%), mild (15.1%), moderate (17.5%), severe (6.7%), and extreme (1.5%), women rating this value as 26.6%, 9.8%, 16.4%, 27.7%, 16.3% and 3.2% respectively.

Table 1. Characteristics of study participants

Characteristic	Total (n=7023) N (%)	With polypharmacy (n=1914) N (%)	Without polypharmacy (n=5109) N (%)	p-value*
Sex				
Male	2850 (40,6)	607 (21,3)	2243 (78,7)	<0,001
Female	4173 (59,4)	1307 (31,3)	2866 (68,7)	
Age (years), mean (SD)	76,0 (7,6)	77,6 (7,3)	75,4 (7,6)	<0,001
65-75	3652 (59,1)	786 (21,6)	2856 (78,4)	<0,001
76-85	2502 (35,6)	838 (33,5)	1664 (66,5)	
>85	879 (12,5)	290 (33,0)	589 (67,0)	
Marital status (n=7012)				
Single	752 (8,1)	120 (21,0)	452 (79,0)	<0,001
Married	3567 (50,8)	865 (24,3)	2702 (75,7)	
Widower	2567 (36,6)	867 (33,8)	1700 (66,2)	
Divorced/separated	306 (4,4)	61 (19,9)	245 (80,1)	
Educational level				
Without studies	339 (4,8)	148 (43,7)	191 (56,3)	<0,001
Primary education	4411 (62,8)	1301 (29,5)	3110 (70,5)	
Secondary education, baccalaureate or professional education	1638 (23,3)	348 (21,2)	1290 (78,8)	
University studies or equivalent	635 (9,0)	117 (18,4)	518 (81,6)	
Nationality				
Spanish	6924 (98,6)	1896 (27,4)	5028 (72,6)	0,024
Others	99 (1,4)	18 (18,2)	81 (81,8)	
Katz Index, mean (SD)	5,5 (1,2)	5,1 (1,5)	5,7 (0,9)	<0,001
6	5519 (78,6)	1155 (20,9)	4364 (79,1)	<0,001
4-5	1057 (15,1)	508 (48,1)	549 (51,9)	
2-3	203 (2,9)	122 (60,1)	81 (39,9)	
0-1	244 (3,5)	129 (52,9)	115 (47,1)	
Number of chronic health problems, mean (SD)	4,3 (2,8)	7,0 (2,7)	3,3 (2,2)	<0,001
Cognitive impairment				
No	6501 (92,6)	1677 (25,8)	48,24 (74,2)	<0,001
Yes	522 (7,4)	237 (45,4)	285 (54,6)	
Sensory deficits				
Auditory deficit				
No	6708 (95,5)	1789 (26,7)	4919 (73,3)	<0,001
Yes	315 (4,5)	125 (39,7)	190 (60,3)	
Visual deficit				
No	6652 (94,7)	1719 (25,8)	4933 (74,2)	<0,001
Yes	371 (5,3)	195 (52,6)	176 (47,4)	
Urinary incontinence				
No	5909 (84,1)	1347 (22,8)	4562 (77,2)	<0,001
Yes	1114 (15,9)	567 (50,9)	547 (49,1)	
Perceived health status				
Very good	441 (6,3)	18 (4,1)	423 (95,9)	<0,001
Good	2745 (39,1)	288 (10,5)	2457 (89,5)	
Medium	2593 (36,9)	918 (35,4)	1675 (64,6)	
Bad	997 (13,9)	529 (54,1)	448 (45,9)	
Very bad	267 (3,8)	161 (60,3)	106 (39,7)	
Health insurance modality				
Public healthcare	6222 (88,6)	1741 (28,0)	4481 (72,0)	<0,001
State mutualities	283 (4,0)	52 (18,4)	231 (81,6)	
Private insurance	518 (7,4)	121 (23,4)	397 (76,6)	
Hospital admission in the last year				
No	5992 (85,3)	1460 (24,4)	4532 (75,6)	<0,001
Yes	1031 (14,7)	454 (44,0)	577 (56,0)	
Emergency service in the last year				
No	4826 (68,7)	996 (20,6)	3830 (79,4)	<0,001
Yes	2197 (31,3)	918 (41,8)	1279 (58,2)	
Consultation with general practitioner in the last month				
No	3971 (56,5)	811 (20,4)	3160 (79,6)	<0,001
Yes	3052 (43,5)	1103 (36,1)	1949 (63,9)	
Consultation with medical specialist in the last month				
No	5911 (84,2)	1472 (24,9)	4439 (75,1)	<0,001
Yes	1112 (15,8)	442 (39,7)	670 (60,3)	
BMI, mean (SD)				
Insufficient weight	72 (1,0)	18 (25,0)	54 (75,0)	<0,001
Normal weight	1978 (28,2)	449 (22,7)	1529 (77,3)	
Overweight	2841 (40,5)	729 (25,7)	2112 (74,3)	
Obesity	1487 (21,2)	532 (35,8)	955 (64,2)	
Do not know, no answer	645 (9,2)	186 (28,8)	459 (71,2)	

SD: standard deviation, BMI: body mass index

* Comparison between groups with polypharmacy and without polypharmacy

3.2 Polypharmacy

Out of all the participants, 91.9% reported having consumed some medication prescribed by a doctor in the last two weeks, and 11.2% some medication not prescribed by a doctor. Overall, 91.9% had used some medication in the last two weeks; 1914 individuals presented polypharmacy (27.3%, 95% CI 26.2-28.3) and 65 presented hyperpolypharmacy (0.9%, 95% CI 0.7-1.1). Women presented polypharmacy and hyperpolypharmacy more frequently than men (31.3% vs 21.3%, p <0.001 and 1.3% vs 0.3%, p <0.001 respectively). Polypharmacy was more frequent in individuals between 76 and 85 years old (65-75 years: 21.6%, 76-85: 33.5% and> 85: 33.0%). The differences between men and women were maintained in the different age groups, although they were not statistically significant in those older than 85 (**Figure 1**).

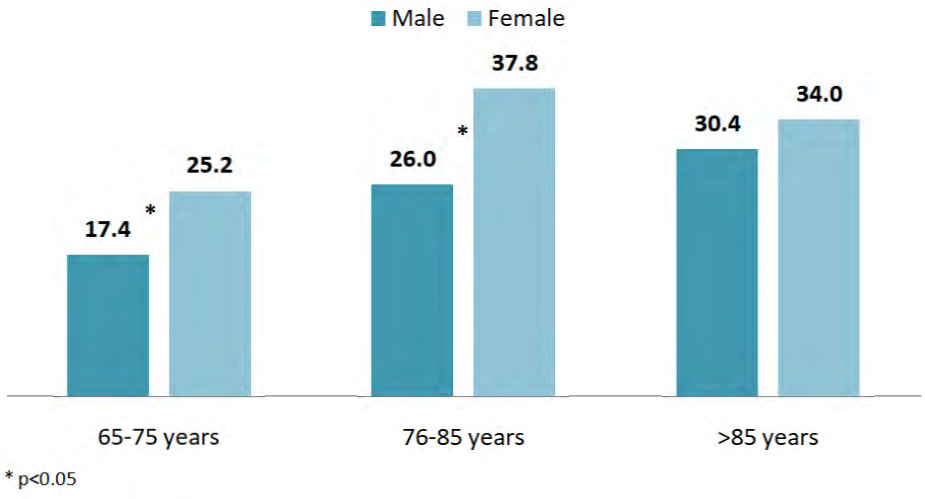


Figure 1. Prevalence of polypharmacy (%) by age group and sex

Differences were found in the prevalence of polypharmacy among the different regions (**Figure 2**). Ceuta, Cantabria and La Rioja presented the lowest polypharmacy rates, while Andalusia, Galicia and Navarra presented the highest. Regarding the most consumed drugs, the most used groups were antihypertensive drugs (56.4%), analgesics (47.0%), lipid modifying agents (38.2%), drugs for the alimentary tract (32.2%), anxiolytics, hypnotics and sedatives (26.8%), drugs used in diabetes (20.2%) and drugs for the heart (19.4%).

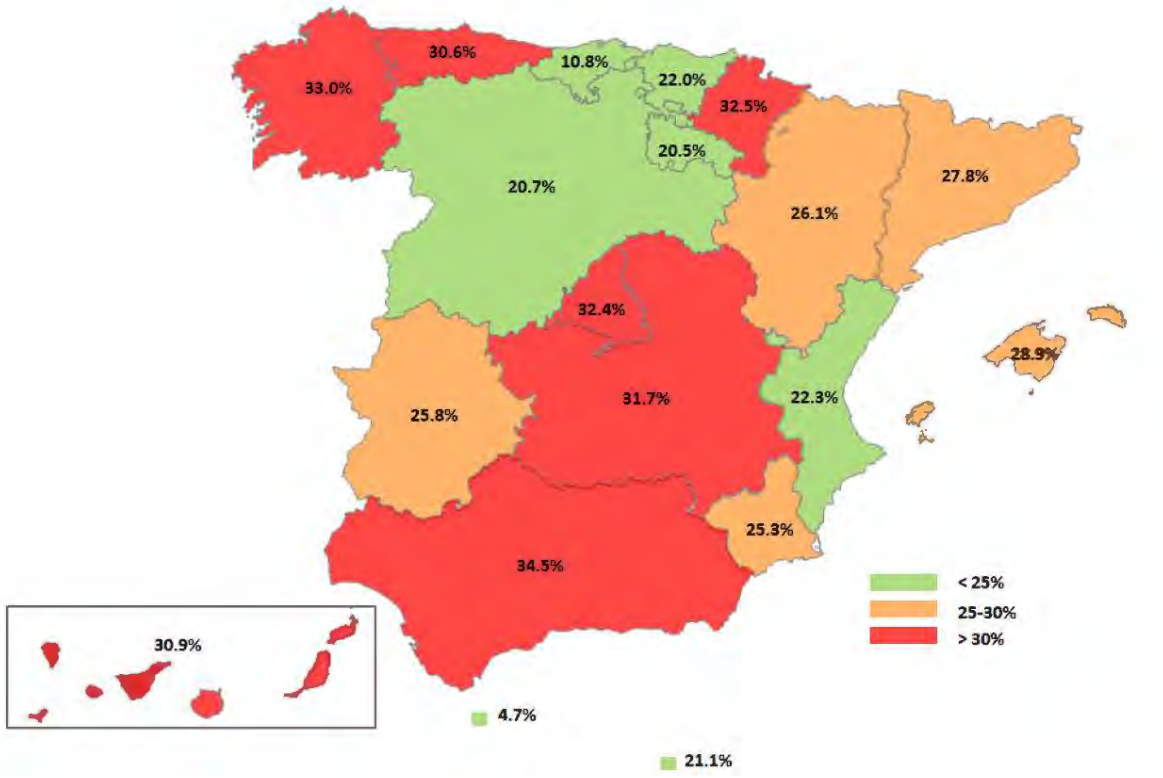


Figure 2. Prevalence of polypharmacy by region

Figure 3 shows the differences in the consumption of different drugs according to sex and age group.

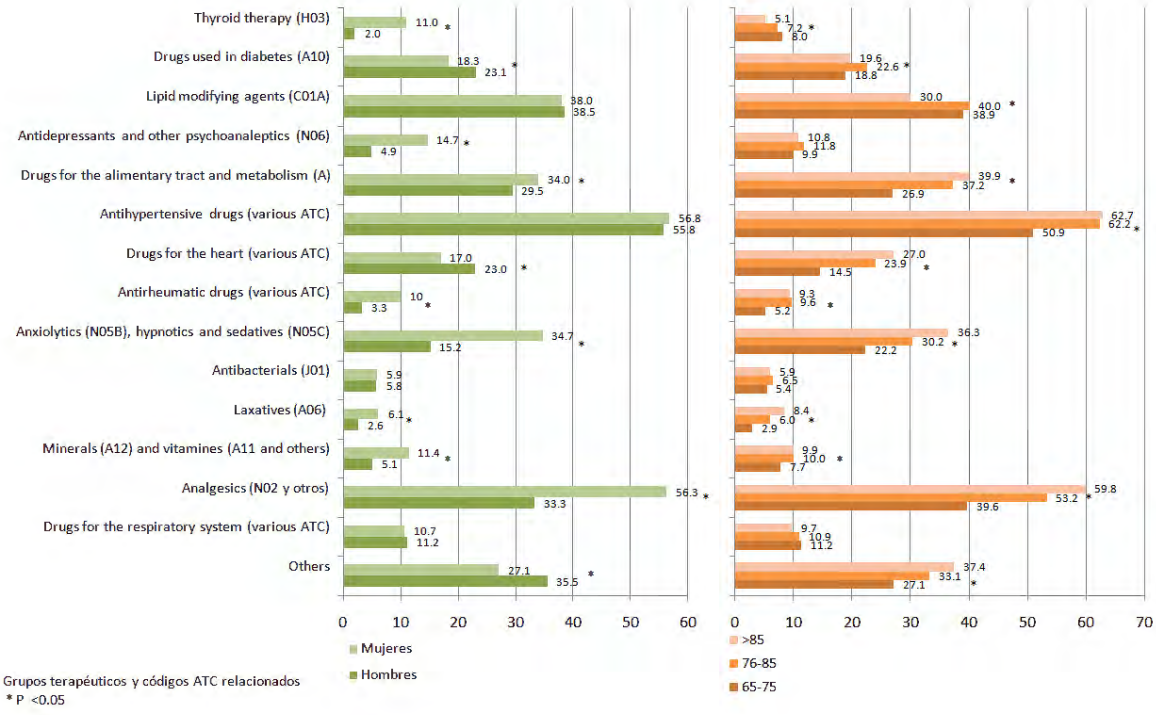


Figure 3. Consumption of different drugs by sex and age group

Figure 4 shows the association between the consumption of the most frequent medications and the most common pathologies recorded for which they are indicated.

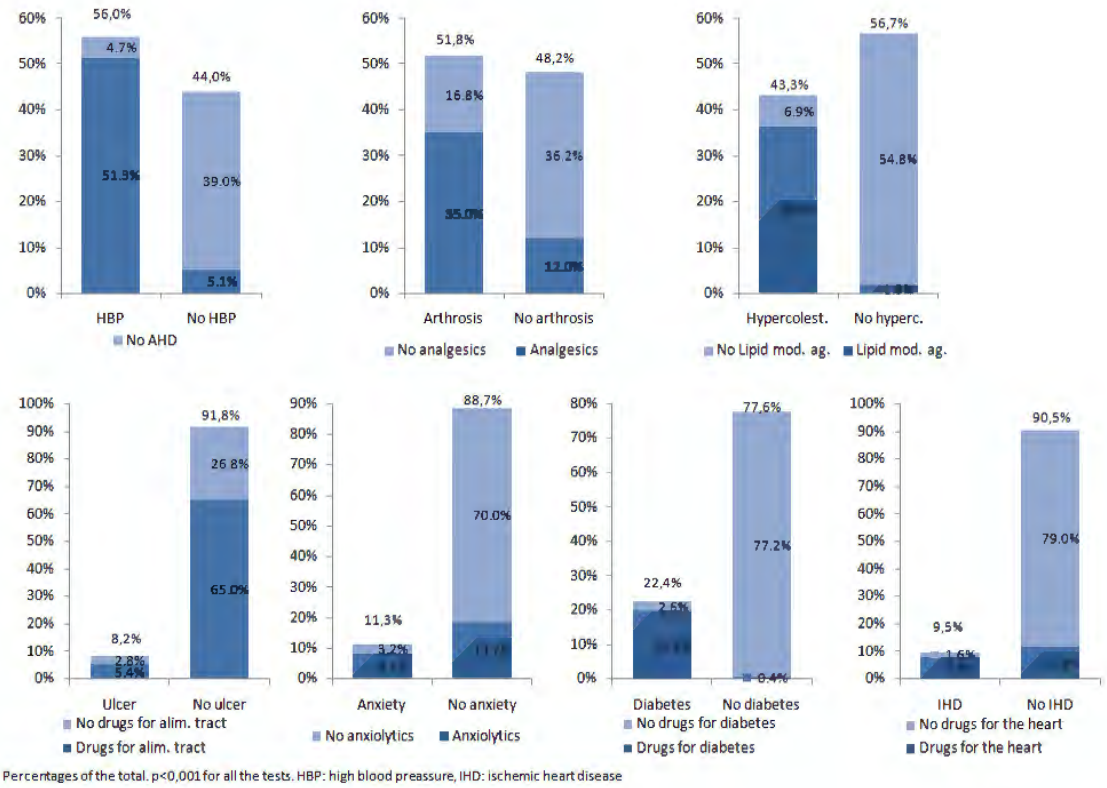


Figure 4. Prevalence of common drugs and diseases with common indications

Participants consumed a mean of 3.3 (SD 2.2) medications, 2.9 (SD 2.0) in men and 3.6 (SD 2.3) in women (p <0.001).

Sensitivity analysis considering the possible combination therapy for hypertension and diabetes showed that the mean number of medications consumed amounted to 3.9 (SD 2.5) drugs per person, and that the prevalence of polypharmacy and hyperpolypharmacy amounted to 37.5% and 2.5% respectively.

The multivariate analysis showed that polypharmacy was positively associated with the number of chronic health problems, the dependence for BADL, a worse perceived health status, hospital admissions or emergency room visits in the last year, consultations in the last month with a general practitioner and medical specialist, obesity and widowhood; but not with sex or with being older. Furthermore, it was negatively associated with visual and auditory impairment and with urinary incontinence. The adjusted odds ratios (OR) for the presence of polypharmacy are shown in **table 2**.

Table 2.Number of medications and factors associated with polypharmacy

	No. medications	Polypharmacy (≥5)
	Mean (SD)	Adjusted OR (CI95%)
Sex		
Male	2,9 (2,0)	1
Female	3,6 (2,3)	1,04 (0,89-1,21)
Age (years)		
65-75	2,9 (2,1)	1
76-85	3,7 (2,2)	1,12 (0,96-1,31)
>85	3,8 (2,2)	1,00 (0,79-1,27)
Marital status (n=7012)		
Single	2,9 (2,1)	1
Married	3,1 (2,1)	1,16 (0,88-1,53)
Widower	3,7 (2,3)	1,46 (1,10-1,93)
Divorced/separated	2,8 (2,2)	0,92 (0,60-1,43)
Educational level		
Without studies	4,3 (2,4)	1
Primary education	3,5 (2,2)	0,82 (0,61-1,10)
Secondary education, baccalaureate or professional education	2,9 (2,1)	0,87 (0,63-1,22)
University studies or equivalent	2,6 (2,1)	0,91 (0,61-1,37)
Nationality		
Spanish	3,3 (2,2)	1
Others	2,6 (2,4)	0,87 (0,45-1,70)
Katz Index		
6	2,9 (2,0)	1
4-5	4,6 (2,3)	1,39 (1,06-1,83)
2-3	5,3 (2,5)	1,78 (1,19-2,65)
0-1	4,6 (2,5)	1,67 (1,09-2,56)
Number of chronic health problems	-	1,73 (1,67-1,79)
Cognitive impairment		
No	3,2 (2,2)	1
Yes	4,5 (2,3)	0,85 (0,66-1,09)
Sensory deficits		
Auditory deficit		
No	3,3 (2,2)	1
Yes	4,2 (2,3)	0,44 (0,32-0,61)
Visual deficit		
No	3,3 (2,2)	1
Yes	4,8 (2,4)	0,73 (0,55-0,97)
Urinary Incontinence		
No	3,0 (2,1)	1
Yes	4,8 (2,4)	0,51 (0,39-0,68)
Perceived health status		
Very good	1,5 (1,5)	1
Good	2,3 (1,7)	1,66 (0,97-2,85)
Medium	3,9 (2,0)	3,28 (1,92-5,59)
Bad	4,9 (2,3)	4,43 (2,55-7,70)
Very bad	5,4 (2,5)	3,76 (2,01-7,03)
Health insurance modality		
Public healthcare	3,4 (2,3)	1
State mutualities	2,8 (2,0)	0,76 (0,51-1,13)
Private insurance	3,0 (2,1)	1,22 (0,93-1,62)
Hospital admission in the last year		
No	3,1 (2,1)	1
Yes	4,4 (2,3)	1,24 (1,03-1,50)
Emergency service in the last year		
No	2,9 (2,1)	1
Yes	4,2 (2,3)	1,32 (1,14-1,54)
Consultation with general practitioner in the last month		
No	2,8 (2,1)	1
Yes	3,9 (2,2)	1,37 (1,20-1,57)
Consultation with medical specialist in the last month		
No	3,2 (2,2)	1
Yes	4,1 (2,3)	1,20 (1,01-1,43)
BMI		
Insufficient weight	2,9 (4,6)	1
Normal weight	3,1 (2,1)	0,86 (0,44-1,66)
Overweight	3,2 (2,1)	1,11 (0,94-1,32)
Obesity	3,9 (2,3)	1,28 (1,06-1,55)
Do not know, no answer	3,4 (2,3)	1,12 (0,86-1,46)

SD: standard deviation, BMI: body mass index. OR: odds ratio

* Due to the lost values for marital status (n = 11), odds ratios and confidence intervals were calculated for a sample of 7012 individuals (99.8% of the total).

4. Discussion

In this study that assess the prevalence of polypharmacy and hyperpolypharmacy in the non-institutionalized elderly population of Spain, frequent drug use was found (up to 91.9% of respondents), and it was estimated that 27.3% of the elderly population presents polypharmacy (95% CI 26.2-28.3) and only 0.9% hyperpolypharmacy (95% CI 0.7-1.1). Important differences were found in the prevalence of polypharmacy among the different regions, with values ranging between 4.7% and 32.4%. These variations could be due to differences in socio-demographic determinants and in health systems between different regions. There were also notable differences between both sexes in the pattern of drug consumption. Globally, women consumed more drugs than men, especially when considering analgesics, anxiolytics, hypnotics and sedatives, antidepressants, laxatives, and drugs for thyroid and antirheumatic pathologies. Men, however, consumed more drugs used in diabetes and drugs for the heart. There was also an increase in the consumption of drugs related to the increase in age, except for the case of women older than 85, who had a lower prevalence of polypharmacy than those who were between 76 and 85 years old. Some drug groups showed an increase in use with age (such as analgesics, laxatives, anxiolytics, hypnotics and sedatives, drugs for the heart, for the alimentary tract, and other medicines), but this trend was not present for other pharmacological groups such as lipid modifying agents, thyroid therapy or drugs for the respiratory system. Despite the differences found in the prevalence of polypharmacy in different sexes and age groups, the multivariate analysis including several factors found no association between the presence of polypharmacy and age or sex. There was also no association between polypharmacy and other characteristics in which a higher prevalence was found, such as a lower level of education or the presence of cognitive impairment. However, there was a positive association with the number of chronic health problems, dependence for basic activities of daily living, perceived health status or contacts with the health system; and a negative association with sensory deficits and incontinence. This data indicates that the increase in the prevalence of polypharmacy in women, older individuals or those with less educational level is probably due to the greater presence of other explanatory factors in these population groups (for example,

the greater number of chronic health problems in women and older people, a worse perceived health status, or a greater dependence for the basic activities of daily living). The differences in the baseline characteristics of the different population sectors could also explain the different patterns in the consumption of certain groups of medicines. For example, the greater degree of pain and dependence and the worse perceived health status in women may be related to the greater consumption of analgesics, antidepressants and anxiolytics, hypnotics and sedatives in this population sector. Furthermore, the multivariate analysis also suggests that certain characteristics such as sensory deficits and incontinence could lead to a lower prescription of drugs regardless of the number of diseases, which could be understood either as a sign of underprescription in these people or as an adapted prescription to the characteristics of the patient (in terms of prognosis, therapeutic objective, etc.). In any case, it is shown that drug prescription does not depend only on the number of diseases, it also depends on how they affect health status and daily life of the individuals, and on the interaction with the health system.

The prevalence of polypharmacy found in previous studies has a great variability depending on the place and the methodology of each study. Some population studies performed in other countries in patients over 65 in primary care, estimated that the prevalence of polypharmacy reached 44% in Sweden [24], 39% in the United States [25], 41.2% in Switzerland [26] and up to 70.3% in France [27]. Other studies carried out at the regional level in Spain in elderly people in primary care, which recorded each drug individually, show prevalences between 45% and 83.1% [13-15]. A recent study carried out across Europe estimates a prevalence of polypharmacy between 26.3 and 39.9%, reaching 31.6% in Spain [28], according to our same definition and taking data from surveys. There are also studies that estimated the prevalence of polypharmacy in non-institutionalized Spanish elderly population with previous National Health Surveys or European Health Surveys in Spain [2, 16]. Martín-Pérez et al. [2] showed a prevalence of polypharmacy of 19.7% and 24.5% in the ENSE of 2006 and 2012, respectively, using our same definition of polypharmacy, and the mean of drugs consumed estimated in these surveys was 2.87 and 2.93 medications per individual respectively, compared to the estimate of 3.3 in our study. Likewise,

Carmona-Torres et al. [16] estimated that the prevalence of polypharmacy was 21.9% and hyperpolypharmacy 0.6%, taking 4 surveys carried out between 2006 and 2014 into account. It should be noted that in the study carried out by Carmona-Torres et al. they included homeopathic and naturist products in the calculation of the number of medicines consumed, which we have not included here since they cannot be considered medicines, which could have slightly overestimated the figures in their study. From all this data we can derive the conclusion that there is a tendency to increase the consumption of drugs, polypharmacy and hyperpolypharmacy in the elderly population in Spain over recent years. This may be due to several factors, such as the increase in multimorbidity, the appearance of new drugs in the market or the medicalization of life [29]. Regarding the most consumed type of drugs, we found similar results to other studies, predominantly antihypertensive drugs, analgesics, lipid modifying agents and drugs for the alimentary tract [16], coinciding with the more frequent chronic health problems in this population.

Regarding the implications of the results of this study, we must highlight the consequences that the increase of polypharmacy in the elderly population in our country may pose, beyond the direct increase in cost. Polypharmacy entails a greater therapeutic complexity when associated with an increase in medication-medication and drug-disease interactions, adverse reactions, therapeutic cascades or worse therapeutic adherence [9]. But besides being a quantitative issue, it is a qualitative change, since polypharmacy is closely linked to the inappropriate use of medications, which refers to treatments in which the risk is higher than the expected clinical benefit, especially when there are safer or more effective therapeutic alternatives [30]. Polypharmacy and the inappropriate use of medications are going to pose a growing challenge for the clinician, who will find more patients with polypharmacy and with greater complexity, so it is essential to know the most common potentially inappropriate medications in our environment (such as the use of benzodiazepines with a long half-life) [31], as well as certain tools that help detect and address this problem [32].

The fact that we have used the official data of the Spanish National Health Survey has the advantage of knowing it has been obtained through a careful

methodology, including sampling, the design of the forms, the preparation of the interviewers, the supervision in the execution, or the data cleansing, which guarantees that we obtain a representative sample of the population and highly reliable data. In addition, by asking specifically about drugs consumed, the problem of overestimation that can occur in studies based on prescription or drug dispensing records –which ignore the degree of adherence to treatment –is avoided; and by asking about the last two weeks the risk of memory bias that occurs if you ask for longer periods of time is reduced. It also allows us to obtain data from individuals using different types of health insurance (up to 11.4% of participants in this study could use systems other than Public Health), something that may bias the results in studies based on medication records in public administrations or private insurers alone. In addition to the ENSE methodology itself, this study has other strengths, such as evaluating different factors associated with polypharmacy through a multivariate analysis that includes very relevant variables in elderly people such as dependence for basic activities of daily living or geriatric syndromes. This type of variables had not been included in previous studies conducted with national health surveys in Spain to study the use of medications, and show in this study that they are key factors that modulate the consumption of drugs in the elderly population.

On the other hand, the use of Health Surveys for the estimation of pharmacoepidemiological data also has certain limitations. When dealing with self-reported data, it must be taken into account that the degree of knowledge of the medication consumed and specifically its indication is not always optimal, especially in elderly people [33] with marked polypharmacy, which could lead to an underestimation in the prevalence. This could explain the low prevalence found for hyperpolypharmacy. Moreover, the ENSE does not include institutionalized people, who are precisely those who show higher levels of polypharmacy as reported by other studies [34, 35], which may also lead to an underestimation of polypharmacy in the elderly, taking into account that more than 4% of the Spanish population aged 65 or over is institutionalized [36]. In addition, the survey methodology itself does not allow us to know exactly which therapeutic groups are used, or whether polypharmacy is associated with specific pathologies and their severity. Finally, given that the survey has not been designed for the purpose of this study, it can only identify the use of

medications for each indication, always considering said medications to be used in monotherapy. For some of the most common health problems such as hypertension, pain or diabetes, the use of several drugs for the same indication is common, whereby this may be the most important cause of underestimation of polypharmacy, and part of the reason why the polypharmacy prevalence rates are notably lower than in other countries around us, where they record each medication individually, such as those cited above [24-27]. The sensitivity analysis proposed to try to correct this bias, although it only makes the correction for hypertension and diabetes, estimates a prevalence of polypharmacy up to 10 points higher (from 27.3% to 37.5%), thus approaching the figures obtained in studies carried out in other countries. In fact, the studies carried out at a regional level in Spain in elderly people in primary care that register each drug individually find rather higher prevalences [13-15], which also seems to suggest the underestimation that can occur due to the methodology of the ENSE.

In conclusion, there is a significant consumption of drugs in the elderly population not institutionalized in Spain, and the trend observed in recent years to increase the prevalence of polypharmacy over time continues. The factors that are most associated with polypharmacy are the number of chronic health problems, dependence for basic activities of daily life, perceived health status or contacts with the health system; sensory deficits and incontinence being negatively associated. Knowing the patterns of drug use in our population and the associated factors is essential to understand the phenomenon of polypharmacy in the elderly and the extent of its consequences for the population, professionals and health systems.

5. References

1. Abellán García A, Ayala García A, Pérez Díaz J, Pujol Rodríguez R (2018).Un perfil de las personas mayores en España, 2018. Indicadores esta-dísticos básicos. Madrid, Informes Envejecimiento en red n.◦17. p. 34.Disponible en: http://envejecimiento.csic.es/documentos/documentos/enred-indicadoresbasicos18.pdf.

2. Martin-Perez M, Lopez de Andres A, Hernandez-Barrera V, Jiménez-García R, Jiménez-Trujillo I, Palacios-Ceña D, et al. Prevalencia de polifarmacia en la pobla-ción mayor de 65 años en España: análisis de las Encuestas Nacionales de Salud2006 y 2011/12. Rev Esp Geriatr Gerontol. 2017;52:2–8.

3. Cho S, Lau SW, Tandon V, Kumi K, Pfuma E, Abernethy DR. Geriatric drug evaluation: Where are we now and where should we be in the future? Arch InternMed. 2011;171:937–40.

4. Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasquín B, Sánchez-Castellano C,Sánchez-García E. Exclusion of older adults from ongoing clinical trials abouttype 2 diabetes mellitus. J Am Geriatr Soc. 2013;61:734–8.

5. Gutierrez-Valencia M, Izquierdo M, Malafarina V, Alonso-Renedo J, Gonzáñez-Glaría B, Larrayoz-Sola B, et al. Impact of hospitalization in an acute geriatric uniton polypharmacy and potentially inappropriate prescriptions: A retrospectivestudy. Geriatr Gerontol Int. 2017;17:2354–60.

6. Chang CB, Chen JH, Wen CJ, Kuo HK, Lu IS, Chiu LS, et al. Potentially inappropriatemedications in geriatric outpatients with polypharmacy: Application of six setsof published explicit criteria. Br J Clin Pharmacol. 2011;72:482–9.

7. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt PMLA, JanssenMJA, Karapinar-Carkit F. Prevalence and preventability of drug-related hospital readmissions: A systematic review. J Am Geriatr Soc. 2018;66:602–8.

8. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: A systematic review. J Am Geriatr Soc. 2014;62:2261–72.

9. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13:57–65.

10. Cabre M, Elias L, Garcia M, Palomera E, Serra-Prat M. Avoidable hospitalizations due to adverse drug reactions in an acute geriatric unit. Analysis of 3,292 patients. Med Clin (Barc). 2018;150:209–14.

11. Gutierrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero A, Inzitari M, Martinez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. Br J Clin Pharmacol. 2018;84:1432–44.

12. Dobler CC, Harb N, Maguire CA, Armour CL, Coleman C, Murad MH. Treatment burden should be included in clinical practice guidelines. BMJ. 2018;363, k4065.

13. Blanco-Reina E, Ariza-Zafra G, Ocana-Riola R, Leon-Ortiz M, Bellido-Estevez I. Optimizing elderly pharmacotherapy: polypharmacy vs. undertreatment. Are these two concepts related? Eur J Clin Pharmacol. 2015;71:199–207.

14. Blanco-Reina E, Garcia-Merino MR, Ocana-Riola R, Aguilar-Cano L, ValdellósJ, Bellido-Estévez I, et al. Assessing potentially inappropriate prescribing incommunity-dwelling older patients using the updated version of STOPP-START criteria: A comparison of profiles and prevalences with respect to the original version. PloS One. 2016;11, e0167586.

15. Cruz-Esteve I, Marsal-Mora JR, Galindo-Ortego G, Galván-Santiago L, Serrano-Godoy M, Ribes-Murillo E, et al. Análisis poblacional de la prescripción potencialmente inadecuada en ancianos según criterios STOPP/START (estudio STARTREC). Aten Primaria. 2017;49:166–76.

16. Carmona-Torres JM, Cobo-Cuenca AI, Recio-Andrade B, Laredo-Aguilera JA, Martins MM, Rodriguez-Borrego MA. Prevalence and factors associated with polypharmacy in the older people: 2006-2014. J Clin Nurs. 2018;27:2942–52.

17. Encuesta Nacional de Salud de España 2017 (ENSE 2017). Ministerio de Sanidad, Consumo y Bienestar Social e Instituto Nacional de Estadística, 2018. Disponible en: https://www.msssi.gob.es/estadEstudios/estadisticas/encuestaNacional/encuesta2017.htm.

18. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17:230.

19. Calderon-Larranaga A, Vetrano DL, Onder G, Gimeno-Feliu LA, Coscollar-Santaliestra C, Carfí A, et al. Assessing and measuring chronic multimorbidity in the

older population: A proposal for its operationalization. J Gerontol A BiolSci Med Sci. 2017;72:1417–23.

20. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of Adl: A standardized measure of biological and psychosocial function. JAMA. 1963;185:914–9.

21. Rodríguez-Roca GC, Valls-Roca F, Pallarés-Carratalá V, Llisterri JL, Barrios V, Alonso-Moreno FJ, et al. Control de la presión arterial en una población hipertensa española ≥ 65 años asistida en Atención Primaria. Datos del estudio PRESCAP 2006. SEMERGEN. 2009;35:426–34.

22. Barrios V, Escobar C, Alonso-Moreno FJ, Prieto MA, Pallares V, Rodríguez-Roca G, et al. Evolution of clinical profile, treatment and blood pressure control in treated hypertensive patients according to the sex from 2002 to 2010 in Spain. J Hypertens. 2015;33:1098–107.

23. Orlando V, Guerriero F, Putignano D, Monetti VM, Tari DU, Farina G, et al. Prescription patterns of antidiabetic treatment in the elderly. Results from Southern Italy. Curr Diabetes Rev. 2015;12:100–6.

24. Morin L, Johnell K, Laroche ML, Fastbom J, Wastesson JW. The epidemiologyof polypharmacy in older adults: Register-based prospective cohort study. ClinEpidemiol. 2018;10:289–98.

25. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. JAMA.2015;314:1818–31.

26. Blozik E, Rapold R, Von Overbeck J, Reich O. Polypharmacy and potentially inappropriate medication in the adult, community-dwelling population in Switzerland. Drugs Aging. 2013;30:561–8.

27. Herr M, Sirven N, Grondin H, Pichetti S, Sermet C. Frailty, polypharmacy, and potentially inappropriate medications in old people: Findings in a representative sample of the French population. Eur J Clin Pharmacol. 2017;73:1165–72.

28. Midao L, Giardini A, Menditto E, Kardas P, Costa E. Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. Arch Gerontol Geriatr. 2018;78:213–20.

29. Cerecedo Pérez MJ, Tovar Bobo M, Rozadilla Arias A. Medicalización de la vida.«Etiquetas de enfermedad: todo un negocio». Aten Primaria. 2013;45:434–8.

30. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther. 2007;32:113–21.

31. Salgueiro E, Elizarde BC, Elola AI, Garcia-Pulido B, Nicieza-Garcia ML, Manso G. Los criterios STOPP/START más frecuentes en España. Una revisión de la literatura. Rev Esp Geriatr Gerontol. 2018;53:274–8.

32. Delgado Silveira E, Montero Errasquin B, Munoz Garcia M, Vélez-Díaz-Pallarés M, Lozano-Montoya I, Sánchez-Castellano C, et al. Mejorando la prescripción de medicamentos en las personas mayores: una nueva edición de los criterios STOPP-START. Rev Esp Geriatr Gerontol. 2015;50:89–96.

33. Modig S, Kristensson J, Ekwall AK, Hallberg IR, Midlov P. Frail elderly patients in primary care–their medication knowledge and beliefs about prescribed medicines. Eur J Clin Pharmacol. 2009;65:151–5.

34. Onder G, Liperoti R, Fialova D, Topinkova E, Tosato M, Danese P, et al. Polypharmacy in nursing home in Europe: Results from the SHELTER study. J Gerontol ABiol Sci Med Sci. 2012;67:698–704.

35. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: A systematic review. J Am Med Dir Assoc. 2015;16:e1–12.

36. Envejecimiento en Red (2014). Estadísticas sobre residencias: distribución de centros y plazas residenciales por provincia. Madrid, Informes en Red, n.◦7. Disponible en: http://envejecimiento.csic.es/documentos/documentos/ enred-estadisticasresidencias2013.pdf

6. Supplementary material

Table S1. Chronic health problems

Chronic health problems considered by Calderón-Larrañaga et al.[19]	Equivalent chronic health problems in National Health Survey of Spain (ENSE)
Hypertension	Hypertension
Dyslipidemia	High cholesterol
Chronic kidney diseases	Kidney problems
Ischemic heart disease	Ischemic heart disease (infarction or angina pectoris, coronary heart disease)
Anemia	-
Osteoarthritis and other degenerative joint diseases	Arthrosis
Colitis and related diseases	-
Deafness, hearing impairment	Difficulty hearing in a quiet place: Yes much difficulty or I cannot do it at all
Heart failure	Other heart diseases
Obesity	BMI of the adult: obesity
Thyroid diseases	Thyroid problems
Dementia	
Atrial fibrillation	-
Depression and mood diseases	Depression
Solid neoplasms	Malignant tumors
Diabetes	Diabetes
Cerebrovascular disease	Stroke
Osteoporosis	Osteoporosis
Other musculoskeletal and joint diseases	-
Dorsopathies	-
Glaucoma	-
Cataract and other lens diseases	Cataract
Asthma	Asthma
Other eye diseases	-
COPD, emphysema, chronic bronchitis	chronic bronchitis, emphysema, COPD
Autoimmune diseases	-
Blindness, visual impairment	Difficulty to see: Yes, a lot of difficulty or I cannot see at all
Esophagus, stomach, and duodenum diseases	Stomach or duodenal ulcer
Prostate diseases	Prostate problems
Inflammatory arthropathies	-
Other cardiovascular diseases	-
Neurotic, stress-related and somatoform diseases	Chronic anxiety
Other genitourinary diseases	Urinary incontinence or problems of urine control
Cardiac valve diseases	-
Migraine and facial pain syndromes	Migraine or frequent headache
Other psychiatric and behavioral diseases	Other mental problems
Other neurological diseases	-
Sleep disorders	-
Bradycardias and conduction diseases	-
Peripheral vascular disease	-
Other metabolic diseases	-
Peripheral neuropathy	-
Chronic pancreas, biliary tract and gallbladder diseases	-
Allergy	Chronic allergy
Parkinson and parkinsonism	-
Other respiratory diseases	-
Chronic ulcer of the skin	-
Epilepsy	-
Ear, nose, throat diseases	-
Inflammatory bowel diseases	-
Hematological neoplasms	-
Venous and lymphatic diseases	Varicose veins
Schizophrenia and delusional diseases	-
Blood and blood forming organ diseases	-
Other digestive diseases	-
Chronic infectious diseases	-
Chronic liver diseases	Cirrhosis, liver dysfunction
Multiple sclerosis	-
Other skin diseases	Chronic skin problems
Chromosomal abnormalities	-

Table S2. Basic activities of daily living (Katz Index)[2]

Katz Index of Independence in Activities of Daily Living		**Equivalent question in the ENSE**	**Equivalent answer in the ENSE**
BATHING	Independence (1): Bathes self completely or needs help in bathing only a single part of the body such as the back, or disabled extremity	Difficulty for basic daily activities: Showering or bathing without help	No, any difficulty Yes, some difficulty
	Dependence (0): Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing		Yes, a lot of difficulty I can not do it by myself
DRESSING	Independence (1): Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	Difficulty for daily basic activities: Dress and undress without help	No, any difficulty Yes, some difficulty
	Dependence (0): Needs help with dressing self or needs to be completely dressed.		Yes, a lot of difficulty I can not do it by myself
TOILETING	Independence (1): Goes to toilet, gets on and off, arranges clothes, Cleans genital area without help.	Difficulty for daily basic activities: Go to the toilet without help	No, any difficulty Yes, some difficulty
	Dependence (0): Needs help transferring to the toilet, cleaning self or uses bedpan or commode		Yes, a lot of difficulty I can not do it by myself
TRANSFERRING	Independence e (1): Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable	Difficulty for daily basic activities: Sit, get up from a chair or a bed, lie down without help	No, any difficulty Yes, some difficulty
	Dependence (0): Needs help in moving from bed to chair or requires a complete transfer.		Yes, a lot of difficulty I can not do it by myself
CONTINENCE	Independence (1): Exercises complete self control over urination and defecation	Have suffered in the past 12 months: Urinary incontinence or problems with urine control	No/missing
	Dependence (0): Is partially or totally incontinent of bowel or bladder		Yes
FEEDING	Independence (1): Gets food from plate into mouth without help. Preparation of food may be done by another person	Difficulty for basic daily activities: Feeding without help	No, any difficulty Yes, some difficulty
	Dependence (0): Needs partial or total help with feeding or requires parenteral feeding.		Yes, a lot of difficulty I can not do it by myself

Chapter 2:

The relationship between Frailty and Polypharmacy in older people: a Systematic Review

Capítulo eliminado por restricciones de derechos de autor

Publicado en:
Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. *Br J Clin Pharmacol*. 2018;84(7):1432–1444. doi:10.1111/bcp.13590

Chapter 3:

The Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes

Capítulo eliminado por restricciones de derechos de autor

Publicado en:
Gutiérrez-Valencia M, Izquierdo M, Lacalle-Fabo E, et al. Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes. *Eur J Clin Pharmacol.* 2018;74(7):961-970. doi:10.1007/s00228-018-2452-2.

Chapter 4:

Impact of hospitalization in an acute geriatric unit on polypharmacy and potentially inappropriate prescriptions: A retrospective study

Capítulo eliminado por restricciones de derechos de autor

Publicado en:
Gutiérrez-Valencia, M. , Izquierdo, M. , Malafarina, V. , Alonso-Renedo, J. , González-Glaría, B. , Larrayoz-Sola, B. , Monforte-Gasque, M. P., Latasa-Zamalloa, P. and Martínez-Velilla, N. (2017), Impact of hospitalization in an acute geriatric unit on polypharmacy and potentially inappropriate prescriptions: A retrospective study. *Geriatr Gerontol Int*, 17: 2354-2360. doi:10.1111/ggi.13073

Chapter 5:

Interventions to optimize pharmacologic treatment in hospitalized older adults: a systematic review

1. Background

Drug therapy is one of the most important tools available for preserving and improving health; however, the use of medications is not without risk. The high prevalence of adverse events due to medication [1] is a significant public health problem, due to the significant morbidity and mortality they cause [2,3], which entail a significant consumption of resources and high healthcare costs [4,5]. This problem is especially relevant for the elderly, who have numerous factors that contribute to a greater risk of drug iatrogenesis. These factors include age-related changes in pharmacokinetics and pharmacodynamics [6,7] and the combination of chronic diseases that inevitably lead to polypharmacy.

A number of studies in Spain have shown that the prevalence of polypharmacy (defined as the consumption of more than 5 drugs a day) in patients older than 65 years is approximately 50% [8,9] and that polymedicated patients consume a mean of almost 9 medications a day [8]. Polypharmacy is strongly linked to drug-related adverse events, interactions and interferences between the drugs and the disease itself [10,11], to lack of treatment adherence [12] and, ultimately, to mortality [13]. Other patient-related factors, such as frailty, geriatric syndromes, dependence and cognitive impairment, frequently overlap, increasing the complexity of medication use, which ultimately leads to poorer health outcomes. For example, it is estimated that between 10% and 20% of hospital admissions for elderly patients in Spain are associated with medication-related adverse events [14,15], which quadruple the risk when compared with younger patients [16].

All of these problems gain special relevance in elderly hospitalized patients. Hospitalization is an especially delicate situation for the elderly and is associated with higher morbidity, mortality and cognitive and functional impairment [17,18]. The

incorporation of new prescribers and the increase in the number of drugs during hospitalization contribute to the risk of iatrogenesis and the complexity of administering drugs [19,20].

The progressive aging of the population predicts that medication-related problems in the elderly will be increasingly common. Fortunately, most medication-related adverse events are considered preventable [21]. Improving therapeutic appropriateness could therefore help minimize the problem. The issue of prescription quality in the elderly has generated significant interest in the scientific community, which, in an attempt to define it, has coined terms such as ‘‘therapeutic appropriateness’’ and has led to the development of numerous tools to quantify it (Appendix A).

Considering the complexity of administering drugs to elderly hospitalized patients and the high prevalence of inappropriate prescriptions [19,22], it seems that we need to incorporate strategies aimed at optimizing drug treatment. Although it has been previously mentioned that hospitalization is an especially appropriate period for implementing strategies for improving the quality of the use of medications [23], most studies have been implemented in other healthcare settings.

The aim of this review is to summarize the evidence on interventions aimed at optimizing the drug treatment of hospitalized elderly patients.

2. Materials and methods

2.1 Search strategy

In August 2015, we conducted a search in the following scientific literature databases to locate primary studies, without setting any date restrictions: MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and the Cochrane Library. The search was designed with MeSH terms (Medical Subject Headings) for MEDLINE and was adapted to the other databases according to its descriptors or through keywords. We combined the following search terms: ‘‘Aged’’ and (‘‘Hospitalization’’, ‘‘Inpatients’’ or ‘‘Hospitals’’); and (‘‘Drug utilization review’’, ‘‘Polypharmacy’’, ‘‘Inappropriate prescribing’’ or ‘‘Medication therapy management’’).

A manual search was also conducted, reviewing the references cited in the selected studies and in relevant systematic reviews.

2.2 Study selection

We included studies that met the following criteria: (a) prospective studies (not necessarily controlled or randomized), (b) inclusion of interventions aimed at optimizing the drug treatment in terms of the prescription, (c) inclusion of at least 80% of the sample composed of hospitalized patients 65 years of age or older, and (d) measurement of quantifiable process variables (change in therapeutic appropriateness measured by validated tools or polypharmacy) or endpoints (clinical, use of healthcare resources, financial, humanistic, etc.).

We excluded studies with the following criteria: (a) systematic reviews and meta-analyses, presentations at congresses or scientific meetings and study protocols; (b) published in languages other than English and Spanish; (c) focus on a single disease or medical condition or regarding a certain medication or therapeutic group; and (d) inclusion of interventions directed exclusively to improving treatment adherence or decreasing reconciliation errors.

2.3 Data collection and analysis

To select the studies, 2 reviewers examined the titles and abstracts of those studies identified in the search and then examined the full text of those studies that were not excluded, ultimately evaluating the ones that met the inclusion criteria. The relevant data were extracted from the selected articles, including the study design, number of participants, demographic characteristics, type of intervention and practitioner who performed it, follow-up time, degree of therapeutic appropriateness, polypharmacy, mortality, adverse reactions to medications, falls, changes in Barthel index, hospital readmissions, emergency department visits, time of admission, financial savings per patient and health-related quality of life. The main characteristics of the measurement methods for therapeutic appropriateness employed in the studies are shown in Table 1.

Table 1 Methods for assessing medication appropriateness.

Criterion (year of publication)	Years of updates	Country	Study population	Main characteristics
Explicit criteria				
Beers criteria (1991)	1997, 2003, 2007, 2012, 2015	USA	>65 years	• List of medicinal products to avoid • List of medicinal product or therapeutic groups to avoid in certain diseases (since 1997) • List of medicinal products to use with caution (since 2012) • Inappropriate prescription due to drug interactions and renal function (since 2015)
STOPP–START criteria (2008)	2014	Ireland	>65 years	• STOPP: list of potentially inappropriate medications, organized by physiological system • START: underprescription criteria (health condition – indicated drug)
PRISCUS list (2010)		Germany	>65 years	• List of potentially inappropriate medications. Classified by therapeutic group. • Proposes therapeutic alternatives and precautions if used
National quality indicators in the use of drug therapy for the elderly (2004)	2010	Sweden	>75 years	• Specific medicinal product indicators: selection, indication, dosage, polypharmacy, drug interactions, use of medicinal products with altered renal function and in the presence of certain symptoms • Specific indicators of diagnosis: rational, irrational and dangerous use
ACOVE (1999)	2001, 2007	USA	>65 years frail	• Quality indicators for improving the quality of care in various chronic conditions. Not focused exclusively on drug treatment. 35% of indicators for treatment
Criterios implícitos				
MAI (1992)		USA	All	• Ten questions are assigned to each medicinal product regarding the indication, effectiveness, dosage, instructions, regimen, drug–drug interactions, drug–disease interactions, duplication, duration and cost • Responses based on a 3-point Likert scale (A: appropriate, C: inappropriate). Each inappropriate item scores between 1 and 3 points based on its importance. The sum of all items creates a weighted score for each drug between 0 and 18. By adding up the scores for the drugs, we can obtain an overall index • Higher scores mean lower therapeutic suitability
FORTA (2008)	2014	Germany	>65 years	• Records inappropriate prescriptions and omissions for indicated medicinal products • Drugs are classified into 4 categories: A (Indispensable), B (Beneficial), C (Questionable), D (To be avoided). Based on the evidence of safety, efficacy and suitability for the age
AOU (1999)		USA	All	• Measures underprescription. Requires the clinical discretion of a healthcare practitioner who compares the medical history and the list of medicinal products to establish treatment omissions

Abbreviations: ACOVE, Assessing Care of Vulnerable Elders; AOU, Assessment of Underutilization of Medication tool; FORTA, Fit for the Aged; MAI, Medication Appropriateness Index; START, Screening Tool to Alert Doctors to Right Treatment; STOPP, Screening Tool of Older Persons' Potentially Inappropriate Prescriptions.

The quality of the prescription can be assessed using process variables (see whether the prescription coincides with the accepted standards) or results (consequences for the patient, the healthcare system and society) [24].

Ultimately, 2 reviewers separately assessed the included studies according to the risk of bias criteria developed by the Cochrane Effective Practice and Organization of Care group [25] for the main variables.

3. Results

3.1 Search results

A total of 794 references were identified, among which were 41 duplicates. After reviewing the titles and abstracts of 753 publications, 677 were excluded for not meeting the inclusion criteria or meeting exclusion criteria. The remaining 76 publications were assessed. Ultimately, 19 publications were selected for this review. These publications referred to 18 studies [26-44] that met all the defined criteria (2 studies referred to the same publication) (Fig. 1) [37,38].

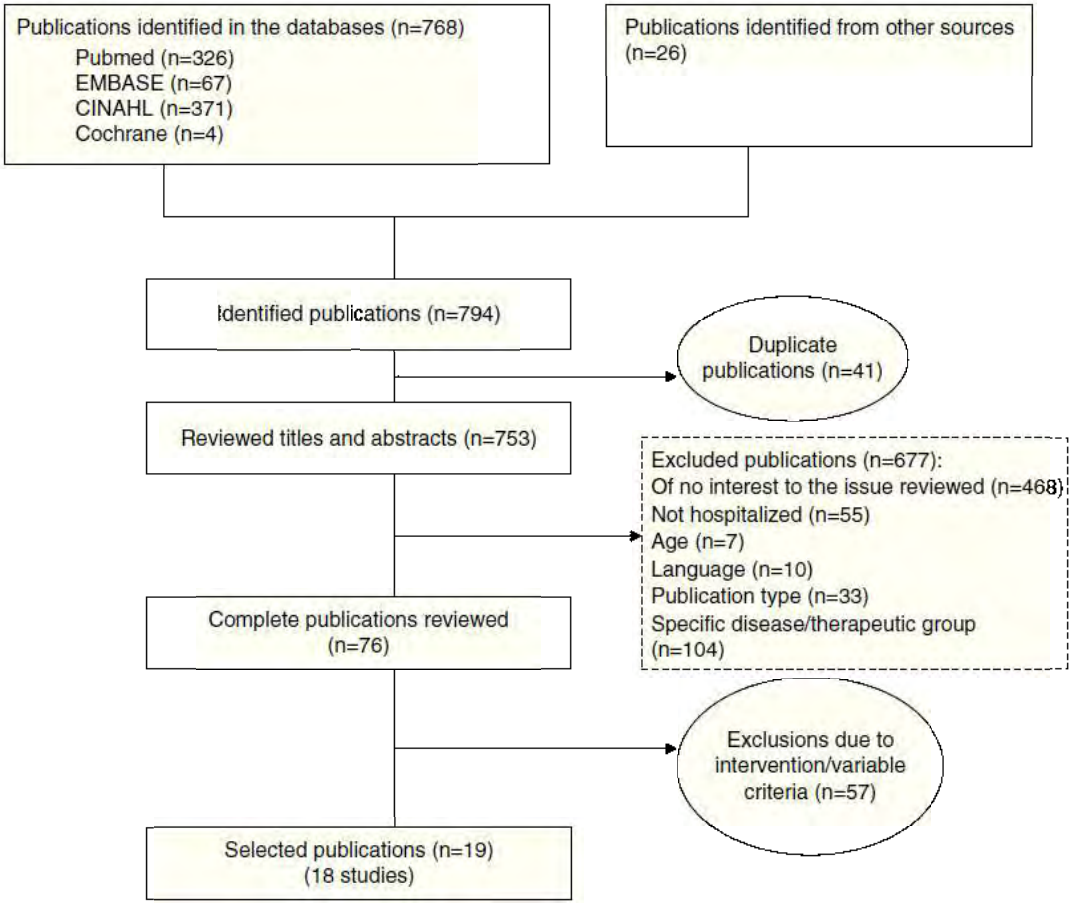


Figure 1 Database search.

3.2 Study characteristics

The number of participants in the studies varied from 43 to 3974, with a mean of 518 patients and a median of 316. Fifteen studies were conducted in Europe and the remaining 3 in the United States. Most studies had a control group, except for 2 [46,47], and 12 were also randomized. The followup time varied between the hospitalization period itself [40,42-44] and 12 months [29,32,41].

3.3 Participant characteristics

The mean age of the participants ranged from 74.5 [35] to 86.6 years [32]; 2 of the studies did not provide this datum [27,28]. The proportion of women ranged from 3% [28] to 71% [26]; 1 study did not provide this information [42]. The age inclusion criteria in the studies were an age greater than 65 years in 9 studies [27,28,30,31,35,36,40,43,44], greater than 70 in 4 [29,33,37,42], greater than 75 in 2 [26,41], and greater than 80 in another [32]. Two studies did not have age criteria for inclusion [34,39], but more than 80% of the participants were older than 65 years. A number of studies also required other inclusion criteria, such as multiple diseases [44], frailty [28,41], and the consumption of more than 3 medications [27,41].

3. 4 Intervention characteristics

The intervention was performed by pharmacists in 9 studies, by a multidisciplinary team in 3 [28,36,41] by pharmacists and clinical pharmacologists in 1 [33], by geriatricians in 1 [37], by nurses in 1 [31], and by physicians other than the prescriber (without specifying specialty) in 2 [35,43]. One intervention consisted of a software application used by the prescribing physician [40].

In terms of type of intervention, most of the studies (13, 72%) conducted medication reviews with subsequent recommendations by or discussions with the prescribing physician. The intervention in 2 studies was based on detecting explicit criteria such as the Screening Tool of Older Person's Potentially Inappropriate Prescriptions (STOPP) [35,41] and the Screening Tool to Alert Doctors to Right Treatment (START) [35]. In another study, the intervention consisted of advising a team of geriatric medicine specialists [28] We also included a study with an educational approach, based on training nurses on clinical pharmacology and tools for detecting medication-related problems.31 A number of studies performed other types of intervention, such as patient information, counseling and education [27,29,32-34,37] and medication reconciliation [36,37,39], which are beyond the scope of this review.

3.5 Variables analyzed

3.5.1 Process variables

Among the 14 studies that measured therapeutic appropriateness, 13 achieved an improvement in at least one of the parameters due to the intervention. The most widely used measurement tool was the Medication Appropriateness Index (MAI) [45,46], which was employed in 6 studies [28-30,35,36,43]. All 6 studies showed significant improvements in this scale after the intervention. The study by Michelek et al [42]. used the Fit for the Aged (FORTA) system [47], achieving an increase in the prescription of category A drugs (indispensable) compared with the control group, but without reaching statistical significance. Two studies [28,35] measured medication underutilization through the Assessment of Underutilization of Medication index [48], both of which achieved improvements in this criterion compared with the control group.

In terms of the explicit methods (see Appendix A in the supplementary material), the Beers criteria were employed in 4 studies [28,29,40,43], in its updated versions of 1997 [49] and 2003 [50], but only 2 of them [28,40] achieved improvements after the intervention. The STOPP and START criteria [51] were employed to quantify therapeutic appropriateness after the intervention in 2 studies. A statistically significant improvement was observed with the STOPP criteria [41,43] but not in the study that applied the START criteria [43] Only one study measured appropriateness using the Priscus criteria [43] but could not demonstrate clear improvement attributable to the intervention (42.4-40.6%) (p = .421). Two interventions reported in Swedish studies attempted to decrease the prevalence of inappropriate medications based on quality indicators described in Sweden [52] one successfully [34], the other without achieving significant differences compared with the control group [31]. Two studies included the Assessing Care Of Vulnerable Elders (ACOVE) criteria [53] to measure underprescription. While Spinewine et al. [29] showed a marked improvement with the intervention (OR, 6.1; 95% CI 2.2-17), the improvement did not achieve statistical significance (p = .739) in the study by O'Sullivan et al. [43]. The studies by Delgado-Silveira et al. [44] and Lipton et al. [27] reported a reduction in medication-related problems due to the intervention.

Among the 8 studies that measured the effect of the intervention on polypharmacy [26,31,36-38,40,42,43], only 1 showed better results than those of the control group [26].

3.5.2 Outcome variables

Seven of the studies analyzed the effect of the interventions on mortality after a follow-up period of 3 [31,33], 6 [35,38,39] or 12 months [29,32] without conclusive results. The study by Michalek et al. [42] achieved a significant reduction in the number of falls in the intervention group (3.4% vs. 21.4%, $p < .001$) and an improved Barthel index, although that did not achieve statistical significance. In the study by Gallagher et al. [35], the reduction in the prevalence of falls 6 months after the intervention did not reach statistical significance ($p = .332$).

Among the 6 studies that analyzed the influence on hospital readmissions at 3 [31,33,37], 6 [35], or 12 months of admission [29,32], only the study by Legrain et al. [37] achieved a statistically significant reduction (20.2% vs. 28.4%, $p = .01$). Among the 4 studies that quantified emergency department visits [29,32,33,39], only the study by Gillespie et al. [32] achieved a 47% reduction at 1 year compared with the control group. None of the interventions achieved a significant reduction in hospital stays [33,35,36,40].

In terms of the analysis of secondary costs, Gillespie et al. [32] showed a reduction of $400 (USD) per patient when compared with the control group. This savings was due to the reduction in expenses associated with readmissions and emergency department visits ($230 less per patient when taking into account the intervention costs). Legrain et al. [37] showed a reduction of € 797; € 519 per patient if the intervention cost was discounted.

Two studies measured the health-related quality of life using the EuroQol-5D questionnaire at 3 [33] and 6 months [34]. Although the first study achieved no significant differences, the second showed an improvement in overall health, although not in the other parameters.

The main characteristics and results of the studies are listed in Table 2, which also shows the potential sources of bias.

Table 2 Main characteristics and results of the studies.

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Owens 1990[26] USA	Controlled randomized	>75 years *n* = 436 (221/215) Women: 71% Mean age: 83.5/83	Medication review and recommendation to responsible team	3 months	Drug	No. of medications at day 3: 5.3 (I) vs. 5.9 (C) ($p < .05$). No differences at 6 weeks and 3 months Increase in the number of medications at day 3: 18% (I) vs. 40% (C) ($p < .005$) Medications with no apparent indication: 11% (I) vs. 19% (C) ($p < .025$) Inappropriate medications (potential adverse effects and availability of an alternative): 20% (I) vs. 37% (C) ($p < .005$)	
Owens 1992[27] USA	Controlled randomized	>65 years, 3 or more medications *n* = 236 (123/113) Women: 51%	Medication review and pharmacist counseling at discharge and for 3 months	3 months	Clinical pharmacists	Patients with MRP: 82% (I) vs. 93% (C) ($p = .05$) Patients with suboptimal or nonindicated medication: 51 (I) vs. 68 (C) ($p = .01$). Other categories (dosage or regimen problems, M–M interactions, duplication, allergies): ns Mean score differences for: prescription appropriateness: 0.59 (I) vs. 0.76 (C) ($p = .01$). Dosage: 0.09 (I) vs. 0.13 (C) ($p = .02$). Suboptimal or nonindicated: 0.17 (I) vs. 0.24 (C) ($p = .03$). Other categories: ns	
Schmader 2004[28] USA	Controlled randomized	>65 years and frailty criteria *n* = 834 Women: 3/2%	Geriatric assessment and intervention	12 months	Multidisciplinary team: geriatrician, social worker, nurse, pharmacist	(P) ADRs (events per 1000 days): 206 (I) vs. 64 (C). RR = 1.85 ($p = .0001$) Severe ADRs (events per 1000 days): 27 (I) vs. 15 (C) ($p = .93$) (S) Difference in change of: Unnecessary medications: −0.5 ($p < .0001$) MAI score: −5.4 ($p < .0001$) IM (Beers): −0.1 ($p = .03$) Medication underutilization (AOU): −0.3 ($p < .0001$)	

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Spinewine 2007[29] Belgium	Controlled randomized	>70 years *n* = 203(103/100) Women: 71.9/66.7% Mean age: 82.4/81.9	Medication review and recommendation to attending physician Patient interview and information	12 months	Clinical pharmacist	(P) Prescription appropriateness (at admission, at discharge and at 3 months): Change in mean MAI score per patient: decreases more in intervention group: 24.1–7.1 ($p < .001$), OR = 9.1 (95% CI 4.2–21.6) IM reduction (Beers): similar I–C, OR = 0.6 (95% CI 0.3–1.1) Mean change ACOVE criteria underutilization per patient: I decreases more; OR = 6.1 (95% CI 2.2–17) (S) Prevalence of unnecessary medications (MAI): decreases from 87.4% to 37.5% (I) and 77.8% (C) Mortality at 1 year: 22.5% (I) vs. 30.1% (C) ($p < .30$) Readmissions at 1 year: 32.6% (I) vs. 33.7% (C) ($p = 1.0$) Emergency department visits at 1 year: 7.9% (I) vs. 12% (C) ($p = .45$) Satisfied with information on medications received at 1 month: 80% vs. 60.9% ($p = .1$)	Blinding of evaluators to the results: unblinded evaluator Contamination: physicians who treated patients in the 2 groups
Bergkvist 2009[30] Sweden	Controlled nonrandomized	>65 years *n* = 43 (28/25) Women: 61/64% Mean age: 82/84	Medication review and discussion with multidisciplinary team	2 weeks after discharge	Drug	Change in MAI score (admission–discharge-after 2 weeks): ns Reduction in the no. of medications with inappropriate characteristics according to MAI: less in the intervention group ($p = .049$)	Random sequence generation: nonrandomized Hiding of the assignment: historical control Initial imbalance: control group was older and had more inappropriate drugs at the start

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Bergqvist 2009[31] Sweden	Controlled nonrandomized	>65 years *n* = 460(250/210) Women: 56/53% Mean age: 80.3	Nurse training in clinical pharmacology for MRP detection. Tools: SYM (Symptoms Assessment Form) and JWA (Janus Web Application)	3 months	Nurses	(P) Readmissions at 3 months: 38% (I) vs. 36% (C) (p = .86) (S) Proportion of inappropriate medications at discharge: ns Medication-related readmissions: ns Deaths: 24% (I) vs. 23.3% (C) (p = .91)	Random sequence generation: nonrandomized Hiding of the assignment: historical control Blinding of evaluators to the results: unblinded evaluator
Gillespie 2009[32] Sweden	Controlled randomized	>80 years *n* = 400 (199/201) Women: 58.7% Mean age: 86.6	Medication review and recommendation to responsible physician Patient counseling	12 months	Drug	Readmissions: 217 (I) vs. 223 (C) (Estimate = 0.97) Medication-related readmissions: 9 (I) vs. 45 (C) (estimate = 0.2) Reduction in emergency department visits: 47%; 49 (I) vs. 93 (C) (Estimate = 0.53) Difference readmissions + emergency department visits: 16%; 266 (I) vs. 316 (C) (Estimate = 0.84) Mortality at 1 year: 57 (I) vs. 61 (C) (p = .82) Overall cost reduction: $400/patient (I–C) Cost reduction by emergency department visits: $100/patient (I–C) Cost reduction by readmissions: $300/patient (I–C) Savings counting the cost of the intervention: $230/patient (I–C)	Contamination: I and C same ward

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Lisby 2010[33] Denmark	Controlled randomized	>70 years *n* = 99 (50/49) Women: 60/61% Mean age: 80.2/78.2	Systematic review of medication, with recommendations to the responsible physician and patient counseling	3 months	Pharmacist and clinical pharmacologist	(P) Hospital stay: 239.9 (I) vs. 238.6 (C) h ($p > .05$) (S) Time to readmission, no. of readmissions, emergency department and PC visits, death, health-related quality of life (EQ-5D): ns	Contamination: I and C same ward
Bladh 2011[34] Sweden	Controlled randomized	>80% participants > 65 years *n* = 345 Women: 61% Mean age: 82	Medication review (with MiniQ tool) and feedback with physicians Information at discharge	6 months	Clinical pharmacist	Change in health-related quality of life (EQ-5D) at 6 months: greater in overall health 3.14 (I) vs. 2.77 (C); $p = .02$, but not in other parameters PIP: decreases in intervention group 0.39 (admission) vs. 0.26 (discharge) ($p = .039$)	Blinding of evaluators to the results: unblinded evaluator Contamination: I and C same ward
Gallagher 2011[35] Ireland	Controlled randomized	>65 years *n* = 382: 190/192 Women: 53.2/53.1% Mean age: 74.5/77	STOPP/START detection and recommendation to attending physician	6 months	Medical researcher	(P) Patients with reduction in MAI admission–discharge score: 71.1% (I) vs. 35.4% (C) (ARR = 35.7%) Rate of unnecessary polypharmacy at discharge: 5.4% (I) vs. 19.8% (C) ($p < .001$) All MAI criteria differ significantly between I–C at discharge and at 6 months Mean MAI score decreases from 10 to 3 (I) ($p < .001$) and remains after 6 months ($p < .001$) Patients with AOU admission–discharge reduction: 31.6% (I) vs. 10.4% (C) (ARR = 21.2%) (S) Prevalence decreases after 6 months: 5.8% (I) vs. 8.4% (C) ($p = .332$) Mortality after 6 months: 5.3% (I) vs. 7.3% (C) ($p = .414$) Hospital stay: 8 (I) vs. 8.5 days (C) ($p = .471$) Readmission rate: 67 (I) vs. 64 (C) ($p = .691$) Fewer visits to PC physician ($p = .063$)	Blinding of evaluators to the results: unblinded evaluator

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Hellstrom 2011[36] Sweden	Controlled nonrandomized	>65 years (*n* = 210) Women: 60/51% Mean age: 83/81.8	Reconciliation, medication review and monitoring	3 months	Multidisciplinary team (includes clinical pharmacist)	Reduction in medicines with inappropriate characteristics (MAI): 51% vs. 39% ($p = .0446$) ITT; 60% vs. 44% ($p = .01$) PP Differences in mean MAI score per patient or drug at discharge: ns Medication-related readmissions or emergency department visits: 6 (I) vs. 12 (C) ($p = .0469$) Hospital stay: 16 vs. 13 days ($p = .09$)	Random sequence generation: nonrandomized Hiding of the assignment: historical control
Legrain 2011[37] France	Controlled randomized	>70 years *n* = 665 (317/348) Women: 69.7/62.6% Mean age: 86.1	Review of long-term therapy, patient education, reconciliation at discharge	6 months	Geriatrician researcher (different from regular medical team)	(P) Readmissions or emergency department visits at 3 months: 23% (I) vs. 30.5% (C) ($p = .03$) and 6 months: 35.3% (I) vs. 40.8% (C) ($p = .15$) Event-free survival at 3 months: longer in intervention group HR = 0.72 ($p = .03$); and at 6 months: HR = 0.81 ($p = .10$) (S) Readmissions at 3 months: 20.2% (I) vs. 28.4% (C) ($p = .01$); and at 6 months: 32.5 (I) vs. 38.2 (C) ($p = .12$). Mortality at 3 months: 12% (I) vs. 13.2% (C) ($p = .63$); and at 6 months: 17.7% (I) vs. 18.7% (C) ($p = .74$) Difference in cost at 6 months (I–C): €797/patient Savings including intervention cost: €519/patient	Incomplete data from results: 380 excluded after randomization
Bonnet-Zamponi 2012[38]						Medication-related readmissions: 34.7% vs. 40.4% ($p = .54$). No. of medications, polypharmacy, mean daily dose: ns Difference in cost due to medication-related readmissions: €392 vs. €953.5 per patient ($p = .13$)	Incomplete data from results: 380 excluded after randomization

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Hellstrom 2012[39] Sweden	Controlled nonrandomized	85% > 65 years *n* = 3974 (1216/2758) Women: 54.2/55.5% Mean age: 78.3/79.5	Reconciliation, medication review and monitoring	6 months	Clinical pharmacist	(P) Duration of emergency department visits/readmission: HR 0.95 ($p = .266$) (S) Event-free survival: HR = 0.96 ($p = .305$) Mean number of emergency department visits at 6 months: 1.02 (I) vs. 1.03 (C) ($p = .89$) Mortality at 6 months: 18.2% (I) vs. 17.3% (C) ($p = .55$) Mean number of PC visits: 1.58 (I) vs. 1.71 (C) ($p = .057$) Patients who visited PC: 68.5% (I) vs. 70.3% (C) ($p = .34$)	Random sequence generation: nonrandomized Hiding of the assignment: historical control Initial imbalance: intervention group younger than control group
Ghibelli 2013[40] Italy	Controlled nonrandomized	>65 years *n* = 134 (60/74) Women: 58.3/64.8% Mean age: 81.1/81.3	Intercheck® (computer support system for prescriptions)	Admission	Computer system	Reduction in number of patients with PIM (Beers) admission–discharge: 41.7–11.6% ($p < .001$) Mean reduction in PIM by patient admission–discharge: 0.5–0.1 ($p < .001$) Reduction in number of patients with potentially severe M–M interaction admission–discharge: 45–33.3% ($p = .703$) Reduction in new potentially severe M–M interactions: 59–33% ($p < .001$) Hospital stay: 10.4 (I) vs. 10.1 (C) days ($p = .84$)	Random sequence generation: nonrandomized Hiding of the assignment: historical control
Dalleur 2014[41] Belgium	Controlled randomized	>75 years Frail patients according to the ISAR scale and more than 3 medicines *n* = 146 (74/72) Women: 63% Mean age: 85	STOPP recommendations to responsible physician	12 months	Multidisciplinary team specialized in geriatric medicine	Reduction in PIM by STOPP criteria at discharge: 39.7% (I) vs. 19.3% (C) ($p = .013$)	

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Michalek 2014[42] Germany	Controlled randomized	>70 years *n* = 114: 58/56 Mean age: 84/83	FORTA instrument and recommendations to attending physician	Admission	Physicians other than the one responsible	Patients with polypharmacy (>5 medications) at discharge: 84% (I) vs. 84% (C) ($p = .935$) Increases in control and intervention Category A FORTA medications at discharge: 4 vs. 3 ($p = .051$). Increases in both Over and underprescription: less in intervention group ($p = .03$ and $p = .025$) Patients with an increased Barthel index at discharge: 76% (I) vs. 71% (C) ($p < .226$) Patients with falls: 3.4% (I) vs. 21.4% (C) ($p < .001$) Proportion of falls/1000 patients/year: 1.5 (I) vs. 10.6 (C) days ($p = .004$)	
O'Sullivan 2014[43] Ireland	Uncontrolled	>65 years (*n* = 361) Women: 50.1% Median age: 77 years	Structured review of medication and computer support system for decision making	Admission	Drug	Reduction in MAI score from admission to discharge: 15–12 ($p < .001$). 59.3% patients with lower scores Change in underprescription by ACOVE criteria admission–discharge: 28.3–26.9% ($p = .739$) Median no. of medications: 9 at admission 12 at discharge Patients with 5 or more medications: 84.5% at admission and 95.8% at discharge 10 or more medications: 43.5% at admission and 66.8% at discharge Change in STOPP criteria admission–discharge: 62.4–55.5% patients ($p < .001$) Change in Beers CD criteria admission–discharge: 31.8–31.6% patients ($p = .282$) Change in Priscus criteria admission–discharge: 42.4–40.6% patients ($p = .421$) Change in START criteria admission–discharge: 31–31.5% patients ($p = .512$) Potential M–M interactions: 57.7% patients at admission and 63.9% at discharge ($p = .50$) Incorrect dosage in RF: 9.7% patients at admission and 7.2% at discharge ($p < .05$)	Blinding of evaluators from results: the evaluator is the same individual who performs the intervention

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Delgado-Silveira 2015[44] Spain	Uncontrolled	>65 years, multiple diseases [85% hospitalized] *n* = 287 53.3% women (hospitalized) Mean age (hospitalized): 85	Pharmaceutical intervention (clinical judgment and Checkthemeds®) and attending physician's recommendation	Admission	Drug	MRP: 96.4% patients PI resolved 58.9% of the MRP (association PI-resolution; $p < .001$) PIP for START/STOPP: 65%	Blinding of evaluators from results: the individual who assesses the resolution of MRP is the one who performed the intervention

Abbreviations: AOU, assessment of underutilization of medication index; Beers CD, Beers criteria considering diagnosis; C, control group; HR, hazard ratio; I, intervention group; CI, confidence interval; PI, pharmaceutical intervention; M-M interactions, medication-medication interactions; RF, renal failure; ITT, intent-to-treat analysis; MAI, medical appropriateness index; IM, inappropriate medication; PC, primary care; PIM, potentially inappropriate medication; ns, not statistically significant; PP, per protocol analysis; PIP, potentially inappropriate prescriptions; MRP, medication-related problems; ADR, adverse drug reactions; RR, relative risk.

4. Discussion

This review provides a summary of the evidence on various strategies for optimizing treatments for elderly hospitalized patients, aimed at reducing polypharmacy and improving therapeutic appropriateness, health results and the use of the healthcare system.

Among the analyzed variables, it is worth noting the good results regarding the improvement in therapeutic appropriateness, which appears to be independent of the personnel who perform the intervention and the type of intervention (except in the Bergqvist et al. Study [31], which used an educational approach).

Although the majority of studies managed to improve therapeutic appropriateness in one or more of the parameters, the results differed depending on the measurement method. While all of the studies that used the MAI scale or STOPP criteria achieved an improvement, the same was not true for studies using Beers, Priscus or ACOVE criteria. These results provide an introduction to the debate on the applicability and validity of measurement tools for appropriateness. The difficulty in applying these tools in settings other than those from where the tools originate (healthcare levels, countries) has been widely commented in the literature [54-56]. An example of this challenge is the use of the Beers criteria in the studies by Spinewine et al. [29] (Belgium) and O'Sullivan et al. (Ireland) [43], which were not able to detect positive results in terms of therapeutic appropriateness. The usefulness of the Beers criteria in the European setting is questionable [57]; however, the criteria are still widely used for being one of the first tools developed. The validity of the measurement methods for appropriateness has also been the subject of controversy, given that the process variables should be related to relevant health outcomes (mortality, morbidity, medication-related adverse events and quality of life) to be valid [58]. Although there are studies that show a significant association between the use of inappropriate medications (according to the Beers criteria) and the health outcomes in certain healthcare settings (residence and outpatient) [59-61], the use of inappropriate medications for hospitalized patients is not associated with a significant increase in the risk of adverse events [62], the hospital stay or mortality [63,64]. The degree of therapeutic appropriateness measured with the MAI scale has been shown to be

related to health outcomes in the primary care setting [65,66]. The use of inappropriate medications, according to the STOPP criteria, has been associated with the onset of adverse events in elderly hospitalized patients [67]. However, a study [68] showed that most medication-related problems in elderly patients who live in the community are not detected using STOPP or START criteria. A number of studies that compared the Beers and STOPP criteria seem to show a lower sensitivity for the former in detecting potentially inappropriate medications [69,70] or for preventing hospitalizations due to medication-related adverse events [67].

In light of the fact that the available evidence on the predictive validity of explicit criteria is not definitive or the fact that the results can differ depending on the method of analysis employed, it is worth questioning the suitability of the measurement systems for therapeutic appropriateness being used and thus their published results. Given that the tools are employed both to measure results and to perform interventions, we should consider that the health endpoints can also be affected by this validity, especially if the intervention is based exclusively on detecting explicit criteria, as in the study by Gallagher et al. [35].

The use of explicit methods has numerous practical advantages (Appendix A), but interventions based on implicit methods (standardized or not) provide a broader vision on the patient's situation, their preferences, life expectancy and the fixed therapeutic objectives. A recent study [71] showed that a number of more significant causes for prescribers not modifying the treatment (according to the recommendations included in the STOPP/START criteria) are patient disability, dependence and risk of adverse events, variables that, in the elderly, can be much more important than survival itself. Regardless of the method employed, this type of information is important for adapting the intervention to each patient's needs. However, only 6 [26,29,37,40-42] studies conducted a comprehensive geriatric assessment, and 8 studies did not record any information on the functional, cognitive and nutritional condition or on the presence of geriatric syndromes [27,30,31,33,34,36,39,44]. Only the study by Legrain et al. [37] recorded the patients' preferences regarding their health. If the practitioners who conduct the intervention do not know these data, the recommendations for modifying

the treatment will not correctly fit the patient's characteristics and will probably not be accepted by the prescriber.

Acceptance of these recommendations is essential to interpreting the endpoints, because the interventions need to result in treatment changes in order to affect the patient's health. Consequently, a low degree of acceptance of the recommendations can lead to a lack of improvement in the endpoints. The study by Lisby et al. [33], for example, had a degree of acceptance of the recommendations of 39% and achieved no benefits in any of the study variables (hospital stay, readmissions, emergency department visits, mortality and quality of life). In contrast, those studies with a higher proportion of accepted recommendations achieved more noticeable improvements. The study by Gillespie et al. [32], in which 77% of the recommendations were accepted, showed a reduction in emergency department visits. The study by Legrain et al. [37], with an acceptance of 70.9%, hospital readmissions decreased significantly.

Other factors that could have affected the health outcomes are methodological, such as the low number of participants in a number of the studies and the studies' low power for detecting significant differences. The studies that had no statistically significant results in terms of mortality, readmissions or emergency department visits had not defined these variables as primary objectives [29,33,35,39]. Age is another factor worth considering. The studies with better health outcomes were those whose participants had a higher mean age [32,37], which suggests that patients with greatest risk and frailty are the ones most likely to benefit from strategies that optimize the drug therapy.

In terms of the impact of interventions on other significant variables such as quality of life and financial savings, it is difficult to make relevant conclusions, given the little evidence provided by the analyzed studies.

The results of this review are similar to those of other published studies. Various reviews have been conducted on the drug treatment optimization in elderly patients, not focused on the hospital setting. Two of these studies concluded that some interventions with different approaches (educational, treatment reviews, geriatric services, multidisciplinary teams, computer support systems, etc.) can improve the degree of therapeutic appropriateness [72,73]. In the review by Patterson et al. [74],

the impact of these interventions on clinical outcomes was uncertain, although benefits were demonstrated in terms of reducing inappropriate prescriptions. In the study by Holland et al. [75], which examined the impact of treatment reviews performed by pharmacists on hospitalizations and mortality, also found no positive effect on these parameters. On the other hand, we found reviews on hospitalized patients, although not specifically elderly, such as the study by Christensen et al. [76] focusing on medical reviews, which show a reduction in emergency department visits, with no influence on mortality or hospital readmissions. Similarly, Graabaek et al. [77], in a recent systematic review of medication reviews performed by clinical pharmacists, indicated a positive effect in the use and cost of medications and a number of improvements in the use of healthcare resources, which was not statistically significant.

In terms of the bias of the included studies, the fact that the evaluator of the results knew which group each patient belonged to was a high risk of bias. Given the presence of several nonrandomized studies, the risks of associated bias were also frequent.

Future research should be aimed at checking the validity of the tools for measuring and improving therapeutic appropriateness, which confer a greater reliability to the studies and a greater impact of interventions for optimizing therapeutic appropriateness on health outcomes. Moreover, quality controlled clinical trials need to be developed, with sufficient sample sizes and with the necessary methodological quality to detect the expected impact on clinical variables such as hospital readmissions, emergency department visits and quality of life.

5. Conclusions

The analyzed studies show that the therapeutic appropriateness of elderly hospitalized patients can be improved by interventions with various approaches (systematic treatment reviews, support software for decision making and detection of explicit criteria of inappropriate prescription), implemented by various practitioners (clinical pharmacists, geriatricians, multidisciplinary teams, etc.). However, there is

significant variability in the endpoints. The role of these interventions in health outcomes (the consequences for patients, healthcare system and society) is uncertain.

We need to address the applicability and validity of the tools that assess therapeutic appropriateness to obtain more reliable results with greater impact on health. Explicit criteria for optimizing treatments should not be considered the gold standard, and their implementation should preferably be combined with implicit methods so as to address especially important issues for elderly patients, such as the sociofamiliar context, functional and cognitive conditions and life expectancy.

The clinical variables for elderly patients should be properly selected, given that the therapeutic objectives are often different, and the functional aspects or those related to quality of life can be more important in this population than others, such as mortality. The selection of objectives can benefit from consensus in multidisciplinary teams that include a comprehensive geriatric assessment.

6. References

1. Thomsen LA, Winterstein AG, Sondergaard B, Haugbolle LS, Melander A. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. Ann Pharmacother. 2007;41:1411-26.

2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200-5.

3. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1997;277: 301-6.

4. Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. J Am Pharm Assoc (Wash). 2001;41:192-9.

5. Field TS, Gilman BH, Subramanian S, Fuller JC, Bates DW, Gurwitz JH. The costs associated with adverse drug events among older adults in the ambulatory setting. Med Care. 2005;43:1171-6.

6. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57:6-14.

7. ElDesoky ES. Pharmacokinetic-pharmacodynamic crisis in the elderly. Am J Ther. 2007;14:488-98.

8. Molina Lopez T, Caraballo Camacho ML, Palma Morgado D, Lopez Rubio S, Dominguez Camacho JC, Morales Serna JC. Prevalencia de polimedicación y riesgo vascular en la población mayor de 65 años. Aten Primaria. 2012;44:216-22.

9. Proupín Vázquez N, Aparicio Ruiz M, Garea Sarandeses P, Segade Buceta X, Arceo Túñez A, López Rodríguez L. Resumen de polimedicación en pacientes adultos con dolencias crónicas en un centro de salud. Cad Aten Primaria. 2008;15:275-9.

10. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother. 2007;5:345-51.

11. Goldberg RM, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. Am J Emerg Med. 1996;14:447-50.

12. Leal Hernandez M, Abellan Aleman J, Casa Pina MT, Martinez Crespo J. Paciente polimedicado: ¿conoce la posología de la medicación?, ¿afirma tomarla correctamente? Aten Primaria. 2004;33:451-6.

13. Gomez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-Leon J. Polypharmacy in the elderly: a marker of increased risk of mortality in a population-based prospective study (NEDICES). Gerontology. 2015;61:301-9.

14. Perez Menendez-Conde C, Bermejo Vicedo T, Delgado Silveira E, Carretero Accame E. Resultados negativos asociados al uso de medicamentos que motivan ingreso hospitalario. Farm Hosp. 2011;35:236-43.

15. Ministerio de Sanidad y Consumo. Estudio Nacional de Efectos Adversos ligados a la hospitalización ENEAS 2005.

16. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci. 2002;24:46-54.

17. Krumholz HM. Post-hospital syndrome - an acquired, transient condition of generalized risk. N Engl J Med. 2013;368:100-2.

18. Lafont C, Gerard S, Voisin T, Pahor M, Vellas B. Reducing «iatrogenic disability» in the hospitalized frail elderly. J Nutr Health Aging. 2011;15:645-60.

19. Tosato M, Landi F, Martone AM, Cherubini A, Corsonello A, Volpato S, et al. Potentially inappropriate drug use among hospitalised older adults: results from the CRIME study. Age Ageing. 2014;43:767-73.

20. Sganga F, Landi F, Vetrano DL, Corsonello A, Lattanzio F, Bernabei R, et al. Impact of hospitalization on modification of drug regimens: results of the criteria to assess appropriate medication use among elderly complex patients study. Geriatr Gerontol Int. 2015, doi:10.1111/ggi.12517 [in press].

21. Martin MT, Codina C, Tuset M, Carne X, Nogue S, Ribas J. Problemas relacionados con la medicación como causa de ingreso hospitalario. Med Clin (Barc). 2002;118:205-10.

22. Gallagher P, Lang PO, Cherubini A, Topinková E, Cruz-Jentoft A, Montero Errasquín B, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. Eur J Clin Pharmacol. 2011;67:1175-88.

23. Hortal Carmona J, Aguilar Cruz I, Parrilla Ruiz F. Un modelo de deprescripción prudente. Med Clin (Barc). 2015;144:362-9.

24. Brook RH. Quality - can we measure it. N Engl J Med. 1977;296:170-2.

25. EPOC. Cochrane effective practice and organisation of care review group. Oslo: Norwegian Knowledge Centre for the Health Services; 2015.

26. Owens NJ, Sherburne NJ, Silliman RA, Fretwell MD, The Senior Care Study. The optimal use of medications in acutely ill older patients. J Am Geriatr Soc. 1990;38:1082-7.

27. Lipton HL, Bero LA, Bird JA, McPhee SJ. The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing. A randomized controlled trial. Med Care. 1992;30:646-58.

28. Schmader KE, Hanlon JT, Pieper CF, Sloane R, Ruby CM, Twersky J, et al. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. Am J Med. 2004;116:394-401.

29. Spinewine A, Swine C, Dhillon S, Lambert P, Nachega JB, Wilmotte L, et al. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. J Am Geriatr Soc. 2007;55:658-65.

30. Bergkvist A, Midlöv P, Höglund P, Larsson L, Eriksson T. A multiintervention approach on drug therapy can lead to a more appropriate drug use in the elderly. LIMM-Landskrona Integrated Medicines Management. J Eval Clin Pract. 2009;15:660-7.

31. Bergqvist M, Ulfvarson J, Karlsson EA. Nurse-led medication reviews and the quality of drug treatment of elderly hospitalized patients. Eur J Clin Pharmacol. 2009;65:1089-96.

32. Gillespie U, Alassaad A, Henrohn D, Garmo H, Hammarlund- Udenaes M, Toss H, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. Arch Intern Med. 2009;169:894-900.

33. Lisby M, Thomsen A, Nielsen LP, Lyhne NM, Breum-Leer C, Fredberg U, et al. The effect of systematic medication review in elderly patients admitted to an acute ward of internal medicine. Basic Clin Pharmacol Toxicol. 2010;106:422-7.

34. Bladh L, Ottosson E, Karlsson J, Klintberg L, Wallerstedt SM. Effects of a clinical pharmacist service on health-related quality of life and prescribing of drugs: a randomised controlled trial. BMJ Qual Saf. 2011;20:738-46.

35. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clin Pharmacol Ther. 2011;89:845-54.

36. Hellström LM, Bondesson A, Höglund P, Midlöv P, Holmdahl L, Rickhag E, et al. Impact of the Lund Integrated Medicines Management (LIMM) model on medication appropriateness and drug-related hospital revisits. Eur J Clin Pharmacol. 2011;67:741-52.

37. Legrain S, Tubach F, Bonnet-Zamponi D, Lemaire A, Aquino JP, Paillaud E, et al. A new multimodal geriatric discharge-planning intervention to prevent emergency visits and rehospitalizations of older adults: the optimization of medication in AGEd multicenter randomized controlled trial. J Am Geriatr Soc. 2011;59:2017-28.

38. Bonnet-Zamponi D, d'Arailh L, Konrat C, Delpierre S, Lieberherr D, Lemaire A, et al. Drug-related readmissions to medical units of older adults discharged from acute

geriatric units: results of the optimization of medication in AGEd multicenter randomized controlled trial. J Am Geriatr Soc. 2013;61:113-21.

39. Hellstrom LM, Hoglund P, Bondesson A, Petersson G, Eriksson T. Clinical implementation of systematic medication reconciliation and review as part of the Lund Integrated Medicines Management model - impact on all-cause emergency department revisits. J Clin Pharm Ther. 2012;37:686-92.

40. Ghibelli S, Marengoni A, Djade CD, Nobili A, Tettamanti M, Franchi C, et al. Prevention of inappropriate prescribing in hospitalized older patients using a computerized prescription support system (INTERcheck (R)). Drugs Aging. 2013;30:821-8.

41. Dalleur O, Boland B, Losseau C, Henrard S, Wouters D, Speybroeck N, et al. Reduction of potentially inappropriate medications using the STOPP criteria in frail older inpatients: a randomised controlled study. Drugs Aging. 2014;31:291-8.

42. Michalek C, Wehling M, Schlitzer J, Frohnhofen H. Effects of «Fit fOR The Aged» (FORTA) on pharmacotherapy and clinical endpoints - a pilot randomized controlled study. Eur J Clin Pharmacol. 2014;70:1261-7.

43. O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, Cullinan S, O'Sullivan R, et al. The impact of a structured pharmacist intervention on the appropriateness of prescribing in older hospitalized patients. Drugs Aging. 2014;31:471-81.

44. Delgado Silveira E, Fernandez-Villalba EM, García-Mina Freire M, Albi˜nana Pérez MS, Casajús Lagranja MP, Peris Martí JF. Impacto de la intervención farmacéutica en el tratamiento del paciente mayor pluripatológico. Farm Hosp. 2015;39:192-202.

45. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992;45:1045-51.

46. Samsa GP, Hanlon JT, Schmader KE, Weinberger M, Clipp EC, Uttech KM, et al. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. J Clin Epidemiol. 1994;47:891-6.

47. Kuhn-Thiel AM, Weiss C, Wehling M. Consensus validation of the FORTA (Fit fOR The Aged) List: a clinical tool for increasing the appropriateness of pharmacotherapy in the elderly. Drugs Aging. 2014;31:131-40.

48. Jeffery S, Ruby C, Twersky J, Hanlon J. Effect of an interdisciplinary team on suboptimal prescribing in a long-term care facility. Consult Pharm. 1999;14:1386-91.

49. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. Arch Intern Med. 1997;157:1531-6.

50. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163:2716-24.

51. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46:72-83.

52. Swedish National Board of Health and Welfare (Socialstyrelsen). Indikatorer för utvärdering av kvaliteten i äldres läkemedelsterapi [*Indicators for evaluation of the quality of drug yse in the elderly*]; 2003.

53. Wenger NS, Shekelle PG. Assessing care of vulnerable elders: ACOVE project overview. Ann Intern Med. 2001;135:642-6.

54. Budnitz DS. Inappropriate medication use in hospitalized older adults - is it time for interventions? J Hosp Med. 2008;3: 87-90.

55. Page RL, Linnebur SA, Bryant LL, Ruscin JM. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. Clin Interv Aging. 2010;5:75-87.

56. Lam MP, Cheung BM. The use of STOPP/START criteria as a screening tool for assessing the appropriateness of medications in the elderly population. Expert Rev Clin Pharmacol. 2012;5:187-97.

57. O'Connor MN, Gallagher P, O'Mahony D. Inappropriate prescribing: criteria, detection and prevention. Drugs Aging. 2012;29:437-52.

58. Pronovost PJ, Nolan T, Zeger S, Miller M, Rubin H. How can clinicians measure safety and quality in acute care? Lancet. 2004;363:1061-7.

59. Perri M, Menon AM, Deshpande AD, Shinde SB, Jiang R, Cooper JW, et al. Adverse outcomes associated with inappropriate drug use in nursing homes. Ann Pharmacother. 2005;39:405-11.

60. Chang CM, Liu PY, Yang YH, Yang YC, Wu CF, Lu FH. Use of the Beers criteria to predict adverse drug reactions among first-visit elderly outpatients. Pharmacotherapy. 2005;25:831-8.

61. Lau DT, Kasper JD, Potter DE, Lyles A, Bennett RG. Hospitalization and death associated with potentially inappropriate medication prescriptions among elderly nursing home residents. Arch Intern Med. 2005;165:68-74.

62. Laroche ML, Charmes JP, Nouaille Y, Fourrier A, Merle L. Impact of hospitalisation in an acute medical geriatric unit on potentially inappropriate medication use. Drugs Aging. 2006;23:49-59.

63. Onder G, Landi F, Liperoti R, Fialova D, Gambassi G, Bernabei R. Impact of inappropriate drug use among hospitalized older adults. Eur J Clin Pharmacol. 2005;61:453-9.

64. Page RL, Ruscin JM. The risk of adverse drug events and hospital-related morbidity and mortality among older adults with potentially inappropriate medication use. Am J Geriatr Pharmacother. 2006;4:297-305.

65. Lund BC, Carnahan RM, Egge JA, Chrischilles EA, Kaboli PJ. Inappropriate prescribing predicts adverse drug events in older adults. Ann Pharmacother. 2010;44:957-63.

66. Schmader KE, Hanlon JT, Landsman PB, Samsa GP, Lewis IK, Weinberger M. Inappropriate prescribing and health outcomes in elderly veteran outpatients. Ann Pharmacother. 1997;31:529-33.

67. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med. 2011;171:1013-9.

68. Verdoorn S, Kwint HF, Faber A, Gussekloo J, Bouvy ML. Majority of drug-related problems identified during medication review are not associated with STOPP/START criteria. Eur J Clin Pharmacol. 2015;71:1255-62.

69. Ryan C, O'Mahony D, Kennedy J, Weedle P, Byrne S. Potentially inappropriate prescribing in an Irish elderly population in primary care. Br J Clin Pharmacol. 2009;68:936-47.

70. Conejos Miquel MD, Sánchez Cuervo M, Delgado Silveira E, Sevilla Machuca I, González-Blazquez S, Montero Errasquin B, et al. Potentially inappropriate drug prescription in older subjects across health care settings. Eur Geriatr Med. 2010;1:9-14.

71. Lozano-Montoya I, Velez-Diaz-Pallares M, Delgado-Silveira E, Montero-Errasquin B, Cruz Jentoft AJ. Potentially inappropriate prescribing detected by STOPP-START criteria: are they really inappropriate? Age Ageing. 2015;44:861-6.

72. Kaur S, Mitchell G, Vitetta L, Roberts MS. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. Drugs Aging. 2009;26:1013-28.

73. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;370:173-84.

74. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2014;10:CD008165.

75. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. Br J Clin Pharmacol. 2008;65:303-16.

76. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev. 2013;2:Cd008986.

77. Graabaek T, Kjeldsen LJ. Medication reviews by clinical pharmacists at hospitals lead to improved patient outcomes: a systematic review. Basic Clin Pharmacol Toxicol. 2013;112: 359-73.

7. Appendix

The concept of "medication appropriateness" has been described in different ways. Villafaina and Gavilán [1] define it as the process of choosing the therapy of the patient in which, by indication, prescription, dispensation, administration and monitoring, the professional can achieve appropriate results to the conditions and

circumstances of the patient and of the whole community. Perhaps, the simplest definition is that which says that a prescription is appropriate when there is clear evidence for its use in that indication, it is well tolerated and cost-effective [2]. Shortly, it is a term that speaks about the quality of prescription, and questions whether a treatment will provide the greatest expected benefit in a patient.

In contrast, the terms "inappropriate prescription" or "potentially inappropriate medication" refer to treatments in which the risk is greater than the expected clinical benefit, especially when there are safer or more effective therapeutic alternatives. It also includes the use of drugs at higher doses or duration of the indicated, the use of drugs with high risk of interactions, duplicity and the omission of a clinically indicated drug [3].

Over the years, different tools have been developed to evaluate whether a certain treatment or medication is appropriate or not. These tools can be used both in clinical practice during the process of prescription or medication review, and for quantifying medication appropriateness (eg in the field of research, measuring results after an intervention). Classically, methods for measuring medication appropriateness have been divided into implicit systems (based on clinical judgments) and explicit systems (based on criteria centered on the drug) [4].

Explicit methods are focused on drugs and diseases, usually consist of lists of medications or therapeutic groups that should be avoided in elderly people, and are made by panels of experts through reviews and consensus. On the other hand, implicit methods are centered on the patient and are based on open questions, which require the knowledge and interpretation by the clinician of patient's characteristics and circumstances.

Both systems have strengths and limitations. Explicit methods have the advantage of being quick and easy to apply, have greater reliability, require little preparation and resources and can be systematized or incorporated into computerized systems easily; but they have less validity, and do not consider the particularity of each patient. The implicit methods have a broader perspective on the patient's situation and are more sensitive, but they consume more time and resources, they require a more complex preparation and are less reproducible.

Some of the most commonly used explicit methods are the Beers criteria, STOPP/START (Screening Tool of Older Persons´ potentially inappropriate Prescriptions/ Screening Tool to Alert doctors to Right Treatment), PRISCUS, NORGEP or McLeod. The most common implicit methods include the MAI (Medication Appropriateness Index), and the AOU (Assessment Of Underutilization of medication tool). Table 1 describes the most important characteristics of the methods used in the studies included in this review.

7.1 References

1. Villafaina A, Gavilán E. Polimedicación e inadecuación farmacológica: ¿dos caras de la misma moneda? Pharm Care Esp. 2011;13:23-9.

2. Lu CY, Ross-Degnan D, Soumerai SB, Pearson SA. Interventions designed to improve the quality and efficiency of medication use in managed care: a critical review of the literature - 2001-2007. BMC Health Serv Res. 2008;8:75.

3. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther. 2007;32:113-21.

4. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;370:173-84.

Chapter 6:

A medicine optimization strategy in an acute geriatric unit: the pharmacist in the geriatric team

Capítulo eliminado por restricciones de derechos de autor

Publicado en:
Gutiérrez-Valencia, M, Izquierdo, M, Beobide-Telleria, I, et al. Medicine optimization strategy in an acute geriatric unit: The pharmacist in the geriatric team. *Geriatr. Gerontol. Int.* 2019; 19: 530– 536. https://doi.org/10.1111/ggi.13659

Chapter 7:

General Discussion

The aim of the present doctoral thesis was to assess the problem of polypharmacy in the elderly within different settings and its relationship with frailty, and to explore strategies to optimise treatments in the most vulnerable sectors.

In the study based on the National Health Survey 2017 (**Chapter 1**), we found that polypharmacy is a growing situation in our population when comparing the results with those shown in previous studies carried out using the same methodology based on data from previous national or European surveys in Spain [1, 2]. However, from this study, we can also infer that polypharmacy is not distributed equally among the entire older population, and that it is particularly concentrated in certain sectors. Higher rates of polypharmacy will be found in older people with multimorbidity and functional and cognitive impairment, among others. In our different studies conducted in various settings, different consumption of drugs and characteristics were found: in non-institutionalised older people in Spain, the average number of medications consumed was 3.3 (3.9 according to sensitivity analysis) according to the ENSE 2017, 7.2 in institutionalised elderly people according to our results, and 9.1 in older people admitted to our acute geriatric unit (AGU); and the prevalence of polypharmacy was 27.3% (37.5% with sensitivity analysis), 73.6%, and 86.5% respectively. The non-institutionalised elderly had 4.3 chronic health problems per person, and both patients in nursing homes and those in the AGU had high rates of comorbidities, although they were measured using different tools (3.2 geriatric syndromes per patient in nursing homes, age-adjusted Charlson comorbidity index: 8.1 in patients admitted to the AGU). A total of 80% of the non-institutionalised population was completely independent with respect to basic activities of daily living, while in nursing homes this was 13.6%, and in the AGU, 20.5%. In addition, among the non-institutionalised population in Spain, only 7.4% had cognitive impairment, while this was 64.2% in nursing homes and 43.5% in hospitalised older patients in the AGU.

It seems clear that polypharmacy can be a particularly relevant problem in people with certain characteristics, and therefore in specific settings such as nursing homes or certain areas of hospitalisation, due to the high prevalence of polypharmacy and associated factors in these settings and the complexity and vulnerability of this type of patients, in addition to the possible negative consequences that can result from excessive polypharmacy.

The elderly living in nursing homes have many peculiarities in relation to the use of medicines. Some studies have suggested that polypharmacy rates in nursing homes are the highest in older populations [3], as well as the use of potentially inappropriate medications. This is likely due to the profile of older adults admitted to nursing homes: very old age, multimorbidity, and high prevalence of cognitive impairment and advanced disability [4]. A recent study has shown that although the prevalence of polypharmacy is higher in nursing homes than in the community, when adjusting for confounders, living in nursing homes is associated with a lower risk of the prevalence and incidence of polypharmacy [5]. Due to the particularities in this population, the same rules can not be applied as those to the rest of the elderly population. Health and polypharmacy determinants in older nursing home residents depart from those usually accounted for in the general population [6, 7]. In the study shown in Chapter 3, no relationship was found between the prevalence of polypharmacy and frailty status according to any of the proposed definitions. In fact, in our sample, frail participants generally consumed fewer medications than non-frail participants. This is the opposite behaviour to that expected when considering most of the studies investigating the association between frailty and polypharmacy, as was shown in Chapter 2.

This may be related to the short life expectancy in this population [6, 8]. In nursing homes, advanced disability, severe cognitive impairment, and frailty may be perceived as end of life markers, which may influence decision-making regarding medications. In the same study (Chapter 3), we examined the prevalence of underprescription as described by the START criteria and found a high prevalence, which is in accordance with that reported by other studies [9, 10]. The drugs and characteristics described in explicit criteriam such as the STOPP-START, have been considered potentially inappropriate in older patients, since frequently or in most

cases, the risks to which they are exposed exceed the expected benefits [11]. However, these risks and benefits are not constant, but variable (among different people or in the same person over time), and must be defined individually for each patient considering all their characteristics and complexity. We must remember that it is the drug-patient binomial that leads us to consider the use of a drug (or the omission of a drug) as inappropriate. Some studies have described the causes that lead to not applying this type of criteria in certain patients, especially the START criteria [12]. From this perspective, in many nursing home residents, the START criteria would not be considered an inappropriate prescription when taking into account the individual characteristics. The results of the study (Chapter 3) also show that the prevalence of underprescription was higher in frail subjects, which is in accordance with those reported by Meid et al., when studying cardiovascular START criteria [13]. Considering the association of frailty with an increased risk of adverse drug reactions [14] and its prognostic value for different adverse health outcomes [15], it seems reasonable to modify the type of drugs used to avoid high risk drugs with little expected benefit. This is why we propose that underprescription in frail older adults should be redefined, and new measurement strategies should be developed. Presumably, the START criteria are not very useful for frail patients, and specific criteria or tools should be developed for this population.

From a global perspective, the significant demographic and epidemiological changes that we face represent a great challenge for the administrations and health systems and institutions, which, for several years, have been projecting different strategies to face these challenges based on diverse conceptual models of the management of chronic diseases. Numerous international, national, and regional initiatives have emerged, which attempt to create new health care models that adapt to the new realities of the population.

One of the axes commonly present in these initiatives is the stratification of the population according to their health-related needs. This is based on population models for the care of chronic patients, such as the so-called Kaiser Pyramid of the Kaiser Permanente model, which identifies different levels of intervention according to the

level of complexity of the chronic patient. In regard to medicines and the possible risks derived from their inappropriate use, it is also important to identify patients according to their risk of medication use, to be able to carry out treatment interventions adapted to patient needs.

Pharmacists, as members of the healthcare system and medicine professionals, are also striving to adapt to new healthcare environments and the needs of chronic patients in their areas of competence. Accordingly, in 2012, the Spanish Society of Hospital Pharmacy (SEFH) published its own "*Strategic Plan of the SEFH on Pharmaceutical Care for the Chronic Patient*". This document highlights the importance of promoting the identification and stratification of chronic patients in accordance with the systems developed in various regions of Spain, and developing a pharmaceutical care model that includes specific actions for each patient type identified. With the intention of addressing this strategic axis, in 2013, SEFH published the "*Model of Selection and Pharmaceutical Care of Chronic Patients of the Spanish Society of Hospital Pharmacy*". This document establishes a model for the stratification of patients according to their risk of medication use, and proposes different interventions according to their needs. Classification considers demographic and social factors, cognitive and functional status, clinical and health service utilisation variables, and medication-related aspects. Four risk groups have been proposed: level 3 basic risk; level 2a, drug risk; level 2b, socio-health risk; and level 1, global risk. Level 1 patients would receive the greatest benefit from the most comprehensive pharmacist interventions. Although these data have not been published, 91% of patients admitted to the AGU of the Complejo Hospitalario de Navarra were classified as level 1 (overall risk), and greater than 97% as level 1 or 2a (medication risk), the two groups in which a systematic medication review would be recommended. Therefore, the AGU is an area of already selected patients regarding medication risk; and directing more comprehensive interventions towards this population avoids the need for developing strategies to select and identify these patients.

There are two reasons that come together in the justification of performing a medicine optimisation strategy in the setting of an acute care hospital, specifically in an acute geriatric unit.

Firstly, we found a **need** to optimise the pharmacological treatment of these patients. They are complex patients with a high prevalence of drug related problems or indicators that could be related, as the study of patients admitted to this unit shows (Chapter 4). At the time of admission, these patients are also in a particularly vulnerable situation, since chronic and acute treatment can be conflicting, and they can present medication reconciliation problems associated with changes in the level of care and the multiple prescribers involved (general practitioners, emergency physicians, geriatricians, on-call physicians), perhaps also being exposed to high-risk medications associated with hospital use.

On the other hand, interventions focused on pharmacological treatment in this setting can be a great **opportunity** for several reasons.

The first reason is the aforementioned presentation of highly selected patients without the need for a population screening. In addition, the hospital setting provides all the necessary tools for a comprehensive and patient-centred intervention regarding drug treatment: complete access to patients' clinical information, both in their history of primary care and specialised care (background, laboratory tests, constants, anthropometric data, etc.), and medication history, including updated electronic prescription and dispensing registries from all settings. The continued presence of the patient during admission is an advantage for obtaining or providing information on medications, health problems, etc., facilitates shared decision-making and provides the possibility to monitor changes that are made in order to prevent or detect possible negative effects. In this setting, the pharmacist can interview patients and caregivers, and extend the intervention not only to the prescription but also to other medication processes, including those at the level of the patient.

Moreover, the AGU allows the clinical pharmacist to work within a specialised and interdisciplinary team, contributing to the improvement of the quality of pharmaceutical care. This enables integration of the medicine optimisation strategy into the comprehensive geriatric assessment (CGA), making it a real multi-disciplinary

process. The CGA, which encompasses all aspects of the patient in their current situation, from its holistic approach, provides information of special value for tailored interventions. The work of the clinical pharmacist is enriched by the CGA, since it can be supplemented with the vision provided by the pharmacist using a clinical interview and a systematic medication review. The appropriate use of medications in older adults should consider all their circumstances and complexity; thus, we must go beyond the sum of single conditions and medication indications. This approach reframes the pharmacist's role as a professional providing care as part of a team, rather than simply as a medication technician.

For the design of our intervention, we considered the patient characteristics that we observed in our previous study (Chapter 4), the operation and characteristics of the AGU and the Complejo Hospitalario de Navarra, and the conclusions of our previous systematic review regarding medication optimisation strategies in hospitalised older adults. Therefore, we proposed pharmacist-led intervention based on the CGA and clinical interview, combining medication reconciliation and review, implicit and explicit methods with a computerised decision support system to assist the review process. This approach was properly implemented in the AGU, and was well accepted by patients and geriatricians, in addition to showing good results in terms of the proposed objectives. This type of intervention focusing on hospitalised older adults should be considered a complementary strategy that is coordinated with other strategies to optimise treatment at the population level or in other settings such as primary care or nursing homes. All these are necessary and should ideally coexist to respond in the most appropriate way to the problem of polypharmacy depending on the situation and the needs of each population group. In line with the above, this strategy responds to the need to introduce more complex interventions in patients with more complex needs, also regarding the use of medications.

Moreover, ideally, frailty in older people should also be considered when making decisions regarding medications and planning strategies to improve treatment. Our systematic review on the relationship between polypharmacy and frailty concluded that there is an association between these factors, and that polypharmacy can be an important contributor to frailty. Further longitudinal cohort studies are needed, but it

suggests that a reduction in polypharmacy could be a cautious strategy to prevent and manage frailty. Frailty, as a risk predictor and prognostic measure, can help to more precisely define the risk-benefit of drugs in each patient, adapting it to individual needs. Therefore, frailty screening could also contribute to a more appropriate use of medications, or to design therapeutic optimisation strategies in different settings and levels of care (at an epidemiological level, in hospitals, nursing homes, etc.). Some clinical practice guidelines are beginning to incorporate specific recommendations for frail older patients[16], and the European Medicines Agency has recommended baseline characterisation of frailty in patients older than 65 years who participate in clinical trials or other clinical investigations, in addition to the incorporation of this variable into subgroup analysis [17]. Frailty is a complex concept that is gaining increasing interest in research and is progressively moving to clinical practice in many disciplines, not only in geriatrics. For this reason, and due to the important relationship between frailty and medicines at many levels, the pharmacist must know and properly handle the basic notions regarding frailty in elderly patients, and gradually integrate these in our professional practice.

Practical applications and future perspectives

The present thesis aimed to advance the knowledge of polypharmacy as a growing phenomenon in older people in different areas of our society. From this point, it has also sought to promote the implementation of new roles and integrated multidisciplinary care models orientated to patient needs and based on reliable evidence from clinical research applied to our environment. It proposes strategies to improve the organisation and efficiency of health services in one of the most vulnerable sectors of our population, such as the elderly. Our proposal opens new avenues for the role of the clinical pharmacist as a professional integrated into health teams and gives some preliminary information regarding the benefits that can be obtained from this collaboration.

Given the satisfactory results in terms of feasibility and improvement of medication appropriateness, the new work methodologies and multidisciplinary

collaboration models described here could serve as a model for the future implementation of new services in clinical practice.

The present project was also intended to advance clinical research within the Navarra Health Service and create proposals for innovation in clinical practice that can respond to the challenges of ageing, chronicity, and sustainability of the health system.

New approaches are needed for the development of population-based studies on polypharmacy using different methodologies. Moreover, further research is required to explore the role of a reduction in polypharmacy in the development, reversion, or delay of frailty, and the possible benefits of screening frailty in older people to lead interventions on excessive polypharmacy.

We must also advance in the optimisation of medications in elderly people living in nursing homes through specific strategies, given the particularities of this population.

References

1. Martin-Perez M, Lopez de Andres A, Hernandez-Barrera V, et al. Prevalencia de polifarmacia en la población mayor de 65 años en España: análisis de las Encuestas Nacionales de Salud 2006 y 2011/12. Rev Esp Geriatr Gerontol 2017; Feb;52:2-8

2. Carmona-Torres JM, Cobo-Cuenca AI, Recio-Andrade B, Laredo-Aguilera JA, Martins MM, Rodríguez-Borrego MA. Prevalence and factors associated with polypharmacy in the older people: 2006-2014. J Clin Nurs 2018; 27(15-16):2942-2952

3. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. J Am Med Dir Assoc 2015; 16: 535 e1-12.

4. Rolland Y, Abellan van Kan G, Hermabessiere S, Gerard S, Guyonnet Gillette S, Vellas B. Descriptive study of nursing home residents from the REHPA network. J Nutr Health Aging 2009; 13: 679-83.

5. Morin L, Johnell K, Laroche ML, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. Clin Epidemiol 2018; 10: 289-98.

6. Vetrano DL, Collamati A, Magnavita N, et al. Health determinants and survival in nursing home residents in Europe: Results from the SHELTER study. Maturitas 2018; 107: 19-25.

7. Onder G, Liperoti R, Fialova D, et al. Polypharmacy in nursing home in Europe: results from the SHELTER study. J Gerontol A Biol Sci Med Sci 2012; 67: 698-704.

8. Kelly A, Conell-Price J, Covinsky K, et al. Length of stay for older adults residing in nursing homes at the end of life. J Am Geriatr Soc 2010; 58: 1701-6.

9. Sloane PD, Gruber-Baldini AL, Zimmerman S, Roth M, Watson L, Boustani M, Magaziner J, Hebel JR. Medication undertreatment in assisted living settings. Arch Intern Med 2004; 164: 2031-7.

10. Parsons C, Lapane K, Kerse N, Hughes C. Prescribing for older people in nursing homes: a review of the key issues. Int J Older People Nurs 2011; 6: 45-54.

11. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther 2008; 46: 72-83.

12. Lozano-Montoya I, Velez-Diaz-Pallares M, Delgado-Silveira E, Montero-Errasquin B, Jentoft AJC. Potentially inappropriate prescribing detected by STOPP-START criteria: are they really inappropriate? Age Ageing 2015; 44: 861-66.

13. Meid AD, Quinzler R, Freigofas J, et al. Medication underuse in aging outpatients with cardiovascular disease: Prevalence, determinants, and outcomes in a prospective cohort study. PloS One 2015; 10.e0136339. doi: 10.1371/journal.pone.0136339. eCollection 2015

14. Poudel A, Peel NM, Nissen LM, Mitchell CA, Gray LC, Hubbard RE. Adverse Outcomes in Relation to Polypharmacy in Robust and Frail Older Hospital Patients. J Am Med Dir Assoc 2016; 17: 767.e9-67.e13.

15. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013; 381: 752-62.

16. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38: 140-9.

17. Physical frailty: instruments for baseline characterisation of older populations in clinical trials. European Medicines Agency. 9 January 2018 EMA/CHMP/778709/2015. Committee for Medicinal Products for Human Use. Available in: https://www.ema.europa.eu/en/physical-frailty-instruments-baseline-characterisation-older-populations-clinical-trials

Chapter 8:

Conclusions

1. There is a significant consumption of drugs in non-institutionalized elderly population in Spain, and the trend observed in recent years to increase the prevalence of polypharmacy over time continues. Population-based studies carried out so far in Spain have probably underestimated the prevalence of polypharmacy in non-institutionalized older adults, which may be at least a third greater than previously estimated. The factors that are most associated with polypharmacy are the number of chronic health problems, dependence for basic activities of daily living, perceived health status or contacts with the health system; and inversely, sensory deficits and incontinence. It is important to contemplate variables such as function or geriatric syndromes, essential in elderly people, to consider the consumption habits and prescription of medications in this population. Knowing the patterns of drug use in our population and the associated factors is essential to understand the phenomenon of polypharmacy in the elderly and the extent of its consequences for the population, professionals and health systems.

2. Results from the systematic review suggest that polypharmacy is associated with frailty in older people, although the causal relationship is unclear and, in fact, appears to be bidirectional. The lack of standardized definitions for frailty and polypharmacy hinders research in this area and leads to a wide range of outcomes. There is still scarce evidence of the mechanisms involved, and it is difficult to form conclusions on clinical practice based on the observational studies available at the moment. However, polypharmacy may be recognized as a major contributor to the development of frailty. It seems clear that frailty is an important issue that must be taken into account for decision-making in drug prescribing to older patients, and that polypharmacy should be assessed with special caution in frail older adults. Therefore, it has been suggested that a

reduction of polypharmacy could be a strategy to prevent and manage frailty. Further research is needed to confirm the possible benefits of reducing polypharmacy.

3. There is no clear relationship between the prevalence of polypharmacy and frailty status based on different proposed definitions of frailty, and frailty status is associated with a lower number of medications among people living in nursing homes. Accordingly, the positive association found in previous studies between frailty and polypharmacy cannot be extrapolated to institutionalized populations. There is a trend of a greater prevalence of underprescription according to the START criteria in frail subjects compared with robust ones. To promote the appropriate use of drugs in frail patients without falling into ageism, we should redefine underprescription in frail older adults and develop new strategies to measure it. The Fried criteria could be one of the best indicators of medication-related clinical outcomes, but has important limitations for the application in nursing homes, while the FRAIL-NH could be more useful for disabled people.

4. After hospitalization in an acute geriatric unit, the prevalence of polypharmacy, Potentially Inappropriate Prescriptions, Potentially Prescription Omissions, drug-drug interactions or drugs with anticholinergic effect continues to be very high, which can have important consequences on the health of elderly patients. Regarding medication use, polypharmacy is the most important risk factor for readmission and emergency room visits in complex elderly hospitalized patients. Although it has been suggested that a better quality of prescription is seen with hospitalizations in geriatric units, there is still a need to implement specific strategies to improve pharmacotherapy in hospitalized older adults.

5. The systematic review concluded that the medication appropriateness in elderly hospitalized patients can be improved by interventions with various approaches (systematic medication reviews, decision-making support softwares, and detection of explicit criteria of inappropriate prescription),

implemented by various professionals (clinical pharmacists, geriatricians, multidisciplinary teams, etc.). However, there is significant variability in the endpoints. The role of these interventions in health outcomes (the consequences for patients, healthcare system and society) is uncertain. We need to address the applicability and validity of the tools that assess medication appropriateness to obtain more reliable results with greater impact on health. Explicit criteria for optimizing treatments should not be considered the gold standard, and their implementation should preferably be combined with implicit methods so as to address especially important issues for elderly patients, such as the sociofamiliar context, functional and cognitive status and life expectancy. The clinical variables for elderly patients should be properly selected, and the selection of objectives can benefit from consensus in multidisciplinary teams that include a comprehensive geriatric assessment.

6. There is a need to implement medication optimization strategies in very old and complex patients; a systematic pharmacist-led intervention within a Comprehensive Geriatric Assessment in the context of an Acute Geriatric Unit is a great opportunity to reduce polypharmacy and improve medication appropriateness. We propose a strategy with a multidisciplinary team that can improve the care of elderly patients.

Conclusiones

1. Se encuentra un importante consumo de medicamentos en la población mayor no institucionalizada en España, y continúa la tendencia observada en los últimos años a aumentar la prevalencia de polifarmacia en el tiempo. Los estudios a nivel poblacional realizados hasta ahora en España han infraestimado probablemente la prevalencia de polifarmacia en mayores no institucionalizados, que puede ser al menos un tercio mayor de los que se había estimado previamente. Los factores que más se asocian a la polifarmacia son el número de problemas de salud crónicos, la dependencia para las actividades básicas de la vida diaria, el estado de salud percibido o los contactos con el sistema sanitario; y de forma inversa los déficits sensoriales y la incontinencia. Es importante contemplar variables como la función o los síndromes geriátricos, fundamentales en personas mayores, para entender los hábitos de consumo y prescripción de medicamentos en esta población. Conocer los patrones de consumo de medicamentos en nuestra población y los factores asociados es fundamental para comprender el fenómeno de la polifarmacia en las personas mayores y el alcance de sus consecuencias para la población, los profesionales y los sistemas sanitarios.

2. Los resultados de la revisión sistemática sugieren que existe asociación entre la polifarmacia y la fragilidad en las personas mayores, aunque la relación causal no está clara y, de hecho, parece ser bidireccional. La falta de definiciones estandarizadas de fragilidad y polifarmacia dificulta la investigación en esta área y conduce a una amplia variabilidad de resultados. Todavía hay poca evidencia sobre los mecanismos involucrados, y es difícil llegar a conclusiones aplicables en la práctica clínica en base a los estudios observacionales disponibles en este momento. Sin embargo, la polifarmacia puede ser reconocida como un importante contribuyente al desarrollo de la fragilidad. Parece claro que la fragilidad es un tema importante que debe tenerse en

cuenta para la toma de decisiones en la prescripción de medicamentos en pacientes mayores, y que la polifarmacia debe evaluarse con especial precaución en adultos mayores frágiles. Por lo tanto, se ha sugerido que una reducción de la polifarmacia podría ser una estrategia para prevenir y manejar la fragilidad. Se necesita más investigación para confirmar los posibles beneficios de la reducción de la polifarmacia.

3. En personas mayores que viven en residencias, no existe una relación clara entre la prevalencia de la polifarmacia y el estado de fragilidad según las diferentes definiciones propuestas de fragilidad, y el estado de fragilidad se asocia con un número menor de medicamentos. En consecuencia, la asociación positiva encontrada en estudios previos entre fragilidad y polifarmacia no puede extrapolarse a poblaciones institucionalizadas. Existe una tendencia a una mayor prevalencia de infraprescripción según los criterios START en sujetos frágiles en comparación con los robustos. Para promover el uso apropiado de medicamentos en pacientes frágiles sin caer en la discriminación por edad, debemos redefinir la infraprescripción en adultos mayores frágiles y desarrollar nuevas estrategias para medirla. Los criterios de Fried podrían ser uno de los mejores indicadores de resultados clínicos relacionados con la medicación, pero tienen importantes limitaciones para la aplicación en residencias de ancianos, mientras que el FRAIL-NH podría ser más útil para las personas con discapacidad.

4. Después de la hospitalización en una unidad de agudos de geriatría, la prevalencia de polifarmacia, prescripciones potencialmente inadecuadas, prescripciones potencialmente omitidas, interacciones farmacológicas o fármacos con efecto anticolinérgico sigue siendo muy alta, lo que puede tener importantes consecuencias en la salud de los pacientes ancianos. Con respecto al uso de medicamentos, la polifarmacia es el factor de riesgo más importante para el reingreso y las visitas a urgencias en pacientes ancianos complejos hospitalizados. Aunque se ha sugerido que se observa una mejor calidad de la prescripción con las hospitalizaciones en unidades geriátricas, todavía existe la

necesidad de implementar estrategias específicas para mejorar la farmacoterapia en adultos mayores hospitalizados.

5. Los estudios analizados en la revisión sistemática muestran que se puede mejorar la adecuación terapéutica de los ancianos hospitalizados mediante intervenciones con distintos enfoques (revisiones sistemáticas de tratamiento, programas informáticos de apoyo a la toma de decisiones, o detección de criterios explícitos de prescripción inadecuada), desarrolladas por distintos profesionales (farmacéuticos clínicos, geriatras, equipos multidisciplinares, etc.). Sin embargo, hay mucha variabilidad en las variables de resultado, por lo que el papel de estas intervenciones sobre los resultados en salud (consecuencias para el paciente, el sistema sanitario o la sociedad) es incierto. Es necesario atender a la aplicabilidad y validez de las herramientas que evalúan la adecuación terapéutica, para obtener resultados más fiables y con mayor impacto sobre la salud. Los criterios explícitos para optimizar los tratamientos no deben considerarse el «patrón oro», y su aplicación debería combinarse preferentemente con métodos implícitos, para abarcar cuestiones especialmente importantes en el paciente anciano como el contexto sociofamiliar, la situación funcional o cognitiva o la expectativa de vida del paciente. La selección de objetivos puede beneficiarse del consenso en equipos multidisciplinares que incluyan una valoración geriátrica integral.

6. Existe la necesidad de implementar estrategias de optimización de medicamentos en pacientes complejos muy ancianos. Una intervención sistemática dirigida por un farmacéutico dentro de una valoración geriátrica integral en el contexto de una unidad de geriatría de agudos es una gran oportunidad para reducir la polifarmacia y mejorar la adecuación de la medicación. Proponemos una estrategia con un equipo multidisciplinar que puede mejorar la atención de los pacientes ancianos.

Med Clin (Barc). 2019;xxx(xx):xxx–xxx

ELSEVIER

www.elsevier.es/medicinaclinica

Original

Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017

Marta Gutiérrez-Valencia[a,*], Pablo Aldaz Herce[b], Esther Lacalle-Fabo[c], Beatriz Contreras Escámez[d], Bernardo Cedeno-Veloz[e] y Nicolás Martínez-Velilla[d]

[a] *Servicio de Farmacia, Navarrabiomed, Universidad Pública de Navarra (UPNA), Complejo Hospitalario de Navarra (CHN), IdiSNA, Pamplona, Navarra, España*
[b] *Centro de Salud de San Juan, Pamplona, Navarra, España*
[c] *Servicio de Farmacia, Complejo Hospitalario de Navarra, Pamplona, Navarra, España*
[d] *Servicio de Geriatría, Navarrabiomed, Universidad Pública de Navarra (UPNA), Complejo Hospitalario de Navarra (CHN), IdiSNA, Pamplona, Navarra, España*
[e] *Servicio de Geriatría, Complejo Hospitalario de Navarra, Pamplona, Navarra, España*

INFORMACIÓN DEL ARTÍCULO

Historia del artículo:
Recibido el 10 de septiembre de 2018
Aceptado el 13 de diciembre de 2018
On-line el xxx

Palabras clave:
Polifarmacia
Encuesta Nacional de Salud
Adultos mayores
Atención primaria

RESUMEN

Fundamento y objetivo: Estimar la prevalencia de polifarmacia e hiperpolifarmacia en adultos mayores no institucionalizados en España y analizar los factores asociados.
Material y métodos: Estudio transversal a partir de datos de la Encuesta Nacional de Salud de España 2017, con participantes de 65 años o más. Se estimó la prevalencia de polifarmacia (≥ 5 medicamentos) e hiperpolifarmacia (≥ 10), y la asociación con diversos factores mediante regresión logística multivariante. Se realizó un análisis de sensibilidad considerando el posible consumo de más de un fármaco para la misma indicación (politerapia).
Resultados: Se incluyeron 7.023 participantes, con edad media de 76,0 (desviación estándar [DE] 7,6) años, 59,4% mujeres y consumo medio de 3,3 (DE 2,2) medicamentos por persona. La prevalencia de polifarmacia fue de 27,3% (intervalo de confianza del 95%: 26,2-28,3) y la de hiperpolifarmacia de 0,9% (intervalo de confianza del 95%: 0,7-1,1). El análisis de sensibilidad estimó que la prevalencia podría ascender al menos a un 37,5% y la media a 3,9 (DE 2,5) al considerar la politerapia. Los factores que más se asocian a la polifarmacia fueron el número de enfermedades crónicas, el grado de dependencia para las actividades básicas de la vida diaria, el estado de salud percibido o los contactos con el sistema sanitario; y de forma inversa los déficits sensoriales y la incontinencia.
Conclusiones: La prevalencia de polifarmacia en adultos mayores en atención primaria continúa aumentando, y podría estar ampliamente infraestimada. Además de la pluripatología, factores como la capacidad funcional o los síndromes geriátricos, fundamentales en personas mayores, modulan los hábitos de consumo y prescripción de medicamentos en esta población.

Prevalence of polypharmacy and associated factors in older adults in Spain: Data from the National Health Survey 2017

Keywords:
Polypharmacy
National Health Survey
Older adults
Primary care

ABSTRACT

Background and objective: to estimate the prevalence of polypharmacy and hyperpolypharmacy in non-institutionalised older adults in Spain and assess the associated factors.
Material and methods: a cross-sectional study based on data from the National Health Survey of Spain 2017, with participants aged 65 and over. The prevalence of polypharmacy (≥ 5 medications) and hyperpolypharmacy (≥ 10) were estimated, as well as the association with several factors through multivariate logistic regression. A sensitivity analysis was carried out considering the possible consumption of more than one drug for the same indication (polytherapy).

* Autor para correspondencia.
Correo electrónico: marta.guva@gmail.com (M. Gutiérrez-Valencia).

https://doi.org/10.1016/j.medcli.2018.12.013

Results: 7023 participants were included, with a mean age of 76.0 (SD 7.6), 59.4% female and average consumption of 3.3 (SD 2.2) drugs per person. The prevalence of polypharmacy was 27.3% (95% CI 26.2-28.3) and of hyperpolypharmacy 0.9% (95% CI 0.7-1.1). The sensitivity analysis showed that the prevalence could be at least 37.5% and the average 3.9 (SD 2.5) when considering polytherapy. The factors most associated with polypharmacy were the number of chronic diseases, degree of dependence for the basic activities of daily living, self-perceived health or contacts with the health system; and negatively, sensory deficits and incontinence.
Conclusions: the prevalence of polypharmacy in the elderly in primary care continues to increase and could be widely underestimated. In addition to multimorbidity, factors such as functional capacity or geriatric syndromes, fundamental in elderly people, modulate the habits of consumption and prescription of drugs in this population.

Introducción

A lo largo de las últimas décadas se han producido en España enormes cambios demográficos y epidemiológicos, cuyos resultados son el envejecimiento de la población y la mayor prevalencia de enfermedades crónicas[1]. Esta nueva situación se ha acompañado de un aumento del consumo de medicamentos de forma crónica para tratar esas enfermedades, especialmente en personas mayores[2].

El uso de medicamentos en personas mayores es de por sí complejo, debido a los cambios en la farmacocinética y la farmacodinamia asociados al envejecimiento, a la multimorbilidad y a otros factores que condicionan la complejidad en los mayores, como el deterioro funcional y cognitivo o los síndromes geriátricos. También a la escasa evidencia disponible sobre la eficacia y la seguridad de los medicamentos en esta población[3,4]. Pero además, el empleo de múltiples medicamentos simultáneamente, lo que se ha llamado polifarmacia, a pesar de ser la respuesta lógica a la coexistencia de múltiples enfermedades, puede resultar un problema por sí mismo[5]. La polifarmacia se asocia a un aumento de interacciones entre medicamentos y entre medicamento y enfermedad, a una disminución de la adherencia al tratamiento, a un mayor riesgo de efectos anticolinérgicos y, en general, a efectos adversos a medicamentos, tal vez por aumentar el número de prescripciones potencialmente inadecuadas en una población especialmente vulnerable[6,7]. Probablemente por todo ello la polifarmacia se ha asociado a peores resultados en salud en los mayores, aumentando el riesgo de delirium, malnutrición, caídas, ingresos hospitalarios e incluso de mortalidad, entre otros[8,9]. Se estima, por ejemplo, que entre un 10% y un 20% de los ingresos hospitalarios de personas mayores en nuestro país tendrían relación con efectos adversos a medicamentos, siendo la polifarmacia uno de los factores asociados[10]. En un intento de preservar o mejorar el estado de salud en los adultos mayores, un uso excesivo o no suficientemente cuidadoso de los medicamentos puede acabar siendo más perjudicial que beneficioso. Comienza a haber evidencias de que un elevado consumo de medicamentos puede contribuir a la fragilidad, independientemente de las comorbilidades asociadas, condicionando un peor pronóstico vital en las personas mayores[11]. Además, la polifarmacia excesiva puede tener un importante impacto económico para el sistema sanitario público, tanto por el incremento del gasto directo en medicamentos, como por los gastos indirectos derivados de las consultas, visitas a urgencias o ingresos hospitalarios resultantes. Por otra parte, hay que tener en cuenta también que un elevado consumo de medicamentos aumenta la «carga del tratamiento» para el paciente, y puede afectar a su percepción del estado de salud, a su bienestar y a su calidad de vida[12].

Para poder afrontar las causas y las consecuencias de este problema y mejorar las conductas y estrategias hacia un uso más adecuado de los medicamentos en las esferas individual y poblacional, es fundamental conocer el alcance de la polifarmacia en las personas mayores en nuestra población. Se han realizado previamente estudios con el fin de conocer la prevalencia de polifarmacia en mayores no institucionalizados en España, algunos de ámbito local o regional[13–15] y otros basados en encuestas nacionales o europeas de salud realizadas previamente en España[2,16]. Los cambios demográficos y epidemiológicos que se producen progresivamente en nuestra población hacen necesaria la actualización de estos datos, que en los últimos años han tenido una tendencia ascendente. En junio de 2018 se hicieron públicos los datos de la Encuesta Nacional de Salud de España 2017 (ENSE 2017), realizada por el Ministerio de Sanidad, Consumo y Bienestar Social con la colaboración del Instituto Nacional de Estadística, y que recoge información sanitaria relativa a la población residente en España en 23.860 hogares[17]. Es una investigación que permite conocer numerosos aspectos de la salud de los ciudadanos en el ámbito nacional y autonómico, y planificar y evaluar las actuaciones en materia sanitaria. Entre ellos, la ENSE aporta información sobre el consumo de medicamentos en una muestra representativa de toda la población, aunque requiere ciertos ajustes para estimar adecuadamente la prevalencia de polifarmacia que no han sido realizados en estudios previos. Además, proporciona información de vital interés en la población de edad avanzada, como la capacidad funcional o cognitiva, la percepción del estado de salud o determinados síndromes geriátricos. La incorporación de estos factores al análisis sobre la polifarmacia en personas mayores es fundamental para comprender los patrones de consumo de medicamentos en ancianos, por lo que los incluimos por primera vez en este estudio junto con factores sociodemográficos, ya presentes en estudios previos con encuestas de salud.

El objetivo del presente estudio es estimar la prevalencia de polifarmacia e hiperpolifarmacia en adultos mayores no institucionalizados en España y analizar los factores asociados.

Material y métodos

Diseño del estudio y población

Estudio transversal con datos obtenidos de la ENSE 2017, seleccionando los participantes con 65 años o más. La ENSE es el resultado del convenio de colaboración suscrito entre el Ministerio de Sanidad, Servicios Sociales e Igualdad y el Instituto Nacional de Estadística españoles, y la población objeto del estudio son las personas residentes en viviendas familiares principales del territorio español en 2017. La información se recogió a través de entrevistas personales asistidas por ordenador en los hogares de los participantes seleccionados, y se llevaron a cabo por entrevistadores específicamente instruidos. Las entrevistas se realizaron entre octubre de 2016 y octubre de 2017. La ENSE tiene representatividad nacional y autonómica, utilizando un muestreo probabilístico trietápico estratificado, siendo las unidades de primera etapa las

Cómo citar este artículo: M. Gutiérrez-Valencia, P. Aldaz Herce, E. Lacalle-Fabo, et al.. Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017. Med Clin (Barc). 2019. https://doi.org/10.1016/j.medcli.2018.12.013

secciones censales, las unidades de segunda etapa las viviendas familiares principales y las unidades de tercera etapa un adulto seleccionado de cada vivienda para cumplimentar el cuestionario de adultos. La muestra se distribuye entre comunidades autónomas asignando una parte uniformemente y otra de forma proporcional al tamaño de la comunidad. El cuestionario de adultos debía ser respondido por el adulto seleccionado, salvo por ingreso hospitalario, incapacidad por enfermedad/discapacidad o impedimento por el idioma. En estos casos se admitía que respondiera al cuestionario otra persona en su nombre.

Variables

Las variables de resultado principales son la prevalencia de polifarmacia e hiperpolifarmacia y el número de medicamentos consumidos. Se consideran como variables independientes factores sociodemográficos (sexo, edad, estado civil, nivel de estudios), de utilización del sistema sanitario (ingreso hospitalario y visita a urgencias en el último año, consulta con el médico de familia y especialista en las últimas 4 semanas, modalidad de seguro sanitario), comorbilidad, independencia para las actividades básicas de la vida diaria (ABVD), estado de salud percibido, deterioro cognitivo e índice de masa corporal (IMC).

Se define la polifarmacia como el consumo de 5 o más medicamentos durante las últimas 2 semanas previas a la entrevista, y la hiperpolifarmacia como el consumo de 10 o más medicamentos. Se preguntaba específicamente «¿cuál o cuáles de estos medicamentos ha consumido en las últimas 2 semanas?», considerando para el presente estudio las siguientes: «medicinas para el catarro, gripe, garganta, bronquios, para el dolor, para bajar la fiebre, reconstituyentes como vitaminas, minerales y tónicos, laxantes, antibióticos, tranquilizantes, relajantes y pastillas para dormir, medicamentos para la alergia, para la diarrea, para el reuma, para el corazón, para la tensión arterial, para el estómago y/o las alteraciones digestivas, antidepresivos o estimulantes, hormonas para la menopausia, medicamentos para adelgazar, para bajar el colesterol, para la diabetes y para el tiroides». Para la redacción de este artículo se ha equiparado en lo posible esta clasificación a los grupos terapéuticos ATC. Para cada individuo se sumaron todas las respuestas afirmativas, estimando así el número total de medicamentos consumidos. Pese a no existir un consenso en la definición de polifarmacia, se escogió el umbral de 5 o más medicamentos al ser la fórmula más utilizada[18].

Se empleó una herramienta previamente validada de evaluación de multimorbilidad para medir la carga global de enfermedades crónicas o problemas de salud de los participantes[19], adaptándola a las preguntas de la ENSE respecto a si ha padecido alguna vez las condiciones consideradas. Esta herramienta recoge 918 códigos CIE-10 y los agrupa en 60 categorías de enfermedades crónicas. Se ha equiparado cada una de estas categorías a una pregunta de la ENSE siempre que ha sido posible, reflejando las enfermedades más importantes (hipertensión, hipercolesterolemia, enfermedad renal crónica, cardiopatía isquémica, otras afecciones cardiacas, artrosis, déficit auditivo o visual, obesidad, enfermedades tiroideas, depresión, neoplasias malignas, diabetes, ictus, osteoporosis, cataratas, asma, enfermedad pulmonar obstructiva crónica [EPOC], úlcera péptica, procesos patológicos prostáticos, otras enfermedades genitourinarias, ansiedad crónica, migraña, alergia crónica, problemas de salud mental, enfermedad venosa crónica, cirrosis, disfunción hepática y afecciones crónicas de la piel) (Anexo en material suplementario disponible en la Web). La metodología propuesta permite capturar un conjunto completo de problemas de salud crónicos que tienen un impacto duradero en la autonomía y calidad de vida de los adultos mayores, o requieren contactos frecuentes con los servicios de salud. Este instrumento, por lo tanto, es adecuado para describir la carga de la enfermedad crónica en nuestra población de estudio. Se expresa la multimorbilidad como el número de problemas de salud crónicos contemplados por esta herramienta. Se utilizó el Índice de Katz[20] para evaluar la dependencia para las actividades básicas de la vida diaria, adaptándolo a partir de las preguntas de la ENSE 2017, considerando estas 6 categorías: dificultad para actividades básicas diarias —ducharse o bañarse sin ayuda, vestirse y desvestirse sin ayuda, ir al servicio sin ayuda, sentarse, levantarse de una silla o de una cama, acostarse sin ayuda, incontinencia parcial o total; alimentarse sin ayuda (descripción en el ANEXO del material suplementario disponible en la Web)—. Se asignó una puntuación de 0 como muy dependiente y 6 como independiente. Se consideró que los participantes presentaban deterioro cognitivo al responder que se habían visto limitados durante al menos los últimos 6 meses para realizar las actividades que la gente habitualmente hace, debido a un problema de tipo mental, o físico y mental conjuntamente. Finalmente se clasificó a los participantes según los siguientes rangos de IMC: $< 18{,}5\ kg/m^2$ peso insuficiente, ≥ 18 y $< 25\ kg/m^2$ normopeso, ≥ 25 y $< 30\ kg/m^2$ sobrepeso y $\geq 30\ kg/m^2$ obesidad.

Análisis estadístico

Se realizó en primer lugar un análisis descriptivo mostrando las principales características de la población de estudio mediante número y proporción para variables cualitativas, y mediante medias y desviación estándar (DE) para variables cuantitativas. Se estimó la prevalencia de polifarmacia e hiperpolifarmacia con sus correspondientes intervalos de confianza del 95% (IC). Para la comparación de medias se empleó el test de Student y para las proporciones el test de Chi-cuadrado de Pearson. Se analizó la asociación entre el consumo de los medicamentos más frecuentes y las enfermedades más comunes registradas en la ENSE para las que están indicados mediante el test Chi-cuadrado.

Una de las mayores limitaciones de la ENSE para estimar la prevalencia de polifarmacia es que al permitir solo respuestas dicotómicas, sí/no, respecto al consumo de los distintos tipos de medicamentos no contempla el uso de terapias combinadas para una misma enfermedad (considera siempre la monoterapia). Para obtener una estimación más cercana a la realidad se realizó un análisis de sensibilidad en el que se contempló que una proporción de los participantes estaría recibiendo terapia combinada para 2 de los problemas de salud crónicos más frecuentes en que esta situación es común: la hipertensión y la diabetes. Se calculó por tanto el número medio de medicamentos consumidos y la prevalencia de polifarmacia e hiperpolifarmacia, asumiendo que los pacientes que tomaban antihipertensivos consumían 1,8 antihipertensivos por paciente (un solo antihipertensivo en el 38,3% de los casos, 2 antihipertensivos en el 43,5% de los casos, 3 antihipertensivos en el 15% de los casos y 4 antihipertensivos en un 3,2% de los casos, basándonos en la bibliografía previa[21,22]), y que los pacientes que consumían medicamentos para la diabetes tomaban una media de 1,5 antidiabéticos (monoterapia en un 54,2% de los casos y 2 antidiabéticos en un 45,8% de los casos[23]). Se asumió que esta distribución era homogénea para todos los participantes en todas las categorías de polifarmacia.

Para identificar factores asociados a la polifarmacia e hiperpolifarmacia se realizaron análisis por regresión logística multivariante con todas las variables incluidas en la tabla 1.

Se estableció un límite para la significación estadística de alfa < 0,05. Todos los análisis estadísticos se realizaron con el software IBM SPSS Statistics versión 20 (IBM Corp, Armonk, NY, EE. UU.).

Cómo citar este artículo: M. Gutiérrez-Valencia, P. Aldaz Herce, E. Lacalle-Fabo, et al.. Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017. Med Clin (Barc). 2019. https://doi.org/10.1016/j.medcli.2018.12.013

Tabla 1
Características de los participantes del estudio

Característica	Total (n = 7.023) N (%)	Con polifarmacia (n = 1.914) N (%)	Sin polifarmacia (n = 5.109) N (%)	Valor de p*
Sexo				
Hombre	2.850 (40,6)	607 (21,3)	2.243 (78,7)	< 0,001
Mujer	4.173 (59,4)	1.307 (31,3)	2.866 (68,7)	
Edad (años), media (DE)	76,0 (7,6)	77,6 (7,3)	75,4 (7,6)	< 0,001
65-75	3.652 (59,1)	786 (21,6)	2.856 (78,4)	< 0,001
76-85	2.502 (35,6)	838 (33,5)	1.664 (66,5)	
> 85	879 (12,5)	290 (33,0)	589 (67,0)	
Estado civil (n = 7.012)				
Soltero	752 (8,1)	120 (21,0)	452 (79,0)	< 0,001
Casado	3567 (50,8)	865 (24,3)	2.702 (75,7)	
Viudo	2.567 (36,6)	867 (33,8)	1.700 (66,2)	
Divorciado/separado	306 (4,4)	61 (19,9)	245 (80,1)	
Nivel de estudios				
Sin estudios	339 (4,8)	148 (43,7)	191 (56,3)	< 0,001
Educación primaria	4.411 (62,8)	1.301 (29,5)	3.110 (70,5)	
Educación secundaria, bachillerato o enseñanzas profesionales	1.638 (23,3)	348 (21,2)	1.290 (78,8)	
Estudios universitarios o equivalentes	635 (9,0)	117 (18,4)	518 (81,6)	
Nacionalidad				
Española	6.924 (98,6)	1.896 (27,4)	5.028 (72,6)	0,024
Otros	99 (1,4)	18 (18,2)	81 (81,8)	
Índice de Katz, media (DE)	5,5 (1,2)	5,1 (1,5)	5,7 (0,9)	< 0,001
6	5.519 (78,6)	1.155 (20,9)	4.364 (79,1)	< 0,001
4-5	1.057 (15,1)	508 (48,1)	549 (51,9)	
2-3	203 (2,9)	122 (60,1)	81 (39,9)	
0-1	244 (3,5)	129 (52,9)	115 (47,1)	
Número de problemas de salud crónicos, media (DE)	4,3 (2,8)	7,0 (2,7)	3,3 (2,2)	< 0,001
Deterioro cognitivo				
No	6.501 (92,6)	1.677 (25,8)	48,24 (74,2)	< 0,001
Sí	522 (7,4)	237 (45,4)	285 (54,6)	
Déficits sensoriales				
Déficit auditivo				
No	6.708 (95,5)	1.789 (26,7)	4919 (73,3)	< 0,001
Sí	315 (4,5)	125 (39,7)	190 (60,3)	
Déficit visual				
No	6652 (94,7)	1719 (25,8)	4933 (74,2)	< 0,001
Sí	371 (5,3)	195 (52,6)	176 (47,4)	
Incontinencia urinaria				
No	5909 (84,1)	1347 (22,8)	4562 (77,2)	< 0,001
Sí	1114 (15,9)	567 (50,9)	547 (49,1)	
Estado de salud percibido				
Muy bueno	441 (6,3)	18 (4,1)	423 (95,9)	< 0,001
Bueno	2.745 (39,1)	288 (10,5)	2.457 (89,5)	
Regular	2.593 (36,9)	918 (35,4)	1.675 (64,6)	
Malo	997 (13,9)	529 (54,1)	448 (45,9)	
Muy malo	267 (3,8)	161 (60,3)	106 (39,7)	
Modalidad de seguro sanitario				
Sanidad pública	6.222 (88,6)	1.741 (28,0)	4.481 (72,0)	< 0,001
Mutualidades del Estado	283 (4,0)	52 (18,4)	231 (81,6)	
Seguro privado	518 (7,4)	121 (23,4)	397 (76,6)	
Ingreso hospitalario en el último año				
No	5.992 (85,3)	1.460 (24,4)	4.532 (75,6)	< 0,001
Sí	1.031 (14,7)	454 (44,0)	577 (56,0)	
Servicio de urgencias en el último año				
No	4.826 (68,7)	996 (20,6)	3830 (79,4)	< 0,001
Sí	2.197 (31,3)	918 (41,8)	1.279 (58,2)	
Consulta con médico de familia en el último mes				
No	3.971 (56,5)	811 (20,4)	3.160 (79,6)	< 0,001
Sí	3.052 (43,5)	1.103 (36,1)	1.949 (63,9)	
Consulta con especialista en el último mes				
No	5.911 (84,2)	1.472 (24,9)	4.439 (75,1)	< 0,001
Sí	1.112 (15,8)	442 (39,7)	670 (60,3)	
IMC, media (DE)				
Peso insuficiente	72 (1,0)	18 (25,0)	54 (75,0)	< 0,001
Normopeso	1.978 (28,2)	449 (22,7)	1.529 (77,3)	
Sobrepeso	2.841 (40,5)	729 (25,7)	2.112 (74,3)	
Obesidad	1.487 (21,2)	532 (35,8)	955 (64,2)	
No sabe/no contesta	645 (9,2)	186 (28,8)	459 (71,2)	

DE: desviación estándar; IMC: índice de masa corporal.
* Comparación entre grupo con polifarmacia y sin polifarmacia.

Cómo citar este artículo: M. Gutiérrez-Valencia, P. Aldaz Herce, E. Lacalle-Fabo, et al.. Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017. Med Clin (Barc). 2019. https://doi.org/10.1016/j.medcli.2018.12.013

Aspectos éticos

Este estudio respeta los principios fundamentales establecidos en la Declaración de Helsinki y sus actualizaciones, y cumple los requisitos establecidos en la legislación en el ámbito de la investigación biomédica, la protección de datos de carácter personal y la bioética. Según la metodología de la ENSE *los ficheros de microdatos están anonimizados. Los ficheros de microdatos de la ENSE son de uso público, no identificables, y por tanto no requieren acuerdos para su uso. Los ficheros de uso público no se consideran confidenciales, de acuerdo con el Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos. No es necesario aplicar los principios de protección de datos a la información anónima, es decir, información que no guarda relación con una persona física identificada o identificable, ni a los datos convertidos en anónimos de forma que el interesado no sea identificable, o deje de serlo. En consecuencia, el Reglamento no afecta al tratamiento de la información que se publica de la ENSE. Incluso con fines estadísticos o de investigación, su uso no requiere la aprobación de un comité de ética acreditado.*

Resultados

Características principales

La muestra total de la ENSE 2017 comprende 29.195 individuos, de los que se seleccionaron 7.023 con 65 o más años. La edad media fue de 76,0 (7,6) años, y un 59,4% eran mujeres. Las características principales de los individuos participantes se describen en la tabla 1. El 92,5% declararon padecer en el momento de la entrevista un problema de salud crónico o de larga duración (ha durado o se espera que dure al menos 6 meses). Los problemas de salud crónicos más frecuentes fueron hipertensión arterial (56,0%), artrosis (51,8%), hipercolesterolemia (43,3%), diabetes (22,4%), depresión (18,0%), osteoporosis (13,0%), afecciones prostáticas (12,2%), ansiedad crónica (11,3%), EPOC (10,2%) y enfermedades tiroideas (10,2%). La mujeres presentaban de media un mayor número de problemas de salud crónicos que los hombres (4,7; DE 2,9 vs. 3,8; DE 2,6), al igual que las personas de más edad frente a las más jóvenes > 85 años: 5,1 (DE 2,9), 76 a 85 años 4,8 (DE 2,9), 65 a 75 años 3,8 (DE 2,7). Del mismo modo las personas con mayor nivel de estudios padecían menos problemas de salud crónicos que aquellas con menor nivel de estudios: sin estudios 5,6 (DE 3,2), estudios primarios 4,6 (DE 2,8), estudios secundarios 3,8 (DE 2,6) y estudios universitarios 3,5 (DE 2,5). Los hombres valoraron su estado de salud en los últimos 12 meses como bueno o muy bueno en el 52,6% de los casos, frente a un 40,4% en las mujeres, como regular en un 34,2% de los casos frente a un 38,7% en mujeres y como malo o muy malo en un 13,1% de los casos frente a un 20,9% en las mujeres ($p < 0,001$). Los hombres valoraron el dolor padecido en las últimas 4 semanas como ninguno (48,4%), muy leve (10,7%), leve (15,1%), moderado (17,5%), severo (6,7%) y extremo (1,5%), siendo en mujeres un 26,6%, 9,8%, 16,4%, 27,7%, 16,3% y 3,2% respectivamente.

Polifarmacia

Del total de los participantes encuestados el 91,9% refirió haber consumido algún medicamento recetado por un médico en las últimas 2 semanas, y el 11,2% algún medicamento no recetado por un médico. Globalmente, el 91,9% había consumido algún medicamento en las últimas 2 semanas; 1.914 individuos presentaron polifarmacia (27,3%, IC 95%: 26,2-28,3) y 65 presentaron hiperpolifarmacia (0,9%, IC 95%: 0,7-1,1). Las mujeres presentaron polifarmacia e hiperpolifarmacia con más frecuencia que los

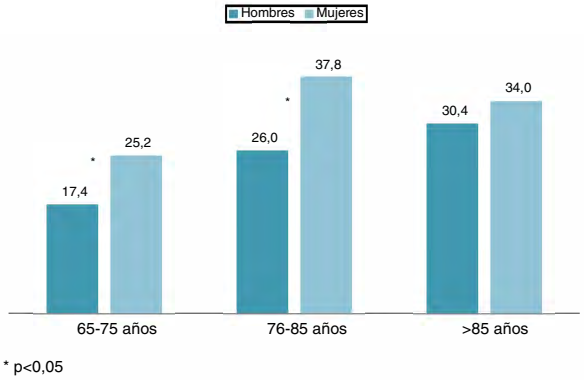


Figura 1. Prevalencia de polifarmacia (%) por grupos de edad y sexo.

hombres (31,3% vs. 21,3%, $p < 0,001$ y 1,3% vs. 0,3%, $p < 0,001$ respectivamente). La polifarmacia fue más frecuente en los individuos entre 76 y 85 años (65-75 años: 21,6%, 76-85: 33,5% y > 85: 33,0%). Las diferencias entre hombres y mujeres se mantuvieron en los distintos grupos de edad, aunque no fueron estadísticamente significativas en mayores de 85 años (fig. 1). Se encontraron diferencias en la prevalencia de polifarmacia entre las distintas comunidades autónomas (fig. 2). Ceuta, Cantabria y La Rioja presentaron las menores tasas de polifarmacia, mientras que Andalucía, Galicia y Navarra presentaron las más altas. Respecto a los fármacos más consumidos los grupos más utilizados fueron los antihipertensivos (56,4%), los analgésicos (47,0%), los agentes modificadores de lípidos (38,2%), los fármacos para el tracto alimentario (32,2%), ansiolíticos, hipnóticos y sedantes (26,8%), los fármacos usados en diabetes (20,2%) y los fármacos para el corazón (19,4%). La figura 3 muestra las diferencias en el consumo de distintos fármacos en función del sexo y del grupo de edad. En la figura 4 se muestra la asociación entre el consumo de los medicamentos más frecuentes y las enfermedades más comunes registradas para las que están indicados.

Los participantes consumían una media de 3,3 (DE 2,2) medicamentos, 2,9 (DE 2,0) en hombres y 3,6 (DE 2,3) en mujeres ($p < 0,001$).

El análisis de sensibilidad considerando la posible politerapia para la hipertensión y la diabetes mostró que la media de medicamentos consumidos ascendía a 3,9 (DE 2,5) medicamentos por persona, y que la prevalencia de polifarmacia e hiperpolifarmacia ascendían a 37,5% y 2,5% respectivamente.

El análisis multivariante mostró que la polifarmacia se asociaba positivamente al número de problemas de salud crónicos, a la dependencia para las ABVD, a un peor estado de salud percibido, al ingreso hospitalario o visita a urgencias en el último año, a la consulta en el último mes con un médico de familia y médico especialista, a la obesidad y a la viudedad, pero no al sexo ni a una mayor edad. También se apreció que se asociaba negativamente con el déficit visual y auditivo y con la incontinencia urinaria. Las *odds ratio* (OR) ajustadas para la presencia de polifarmacia se muestran en la tabla 2.

Discusión

En este estudio que analiza la prevalencia de polifarmacia e hiperpolifarmacia en la población mayor no institucionalizada en España se encontró un consumo frecuente de medicamentos (hasta en un 91,9% de los encuestados), y se estimó que el 27,3% de la población anciana presenta polifarmacia (IC 95%: 26,2-28,3) y solo un 0,9% hiperpolifarmacia (IC 95%: 0,7-1,1). Se encontraron diferencias importantes en la prevalencia de polifarmacia entre las distintas comunidades autónomas, con valores que oscilan entre el

Cómo citar este artículo: M. Gutiérrez-Valencia, P. Aldaz Herce, E. Lacalle-Fabo, et al.. Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017. Med Clin (Barc). 2019. https://doi.org/10.1016/j.medcli.2018.12.013

Tabla 2
Número de medicamentos consumidos y factores asociados a polifarmacia

	N.º medicamentos Media (DE)	Polifarmacia (≥ 5) OR ajustado (IC 95%)
Sexo		
Hombre	2,9 (2,0)	1
Mujer	3,6 (2,3)	1,04 (0,89-1,21)
Edad (años)		
65-75	2,9 (2,1)	1
76-85	3,7 (2,2)	1,12 (0,96-1,31)
> 85	3,8 (2,2)	1,00 (0,79-1,27)
Estado civil (n = 7.012)[a]		
Soltero	2,9 (2,1)	1
Casado	3,1 (2,1)	1,16 (0,88-1,53)
Viudo	3,7 (2,3)	1,46 (1,10-1,93)
Divorciado/separado	2,8 (2,2)	0,92 (0,60-1,43)
Nivel de estudios		
Sin estudios	4,3 (2,4)	1
Educación primaria	3,5 (2,2)	0,82 (0,61-1,10)
Educación secundaria, bachillerato o enseñanzas profesionales	2,9 (2,1)	0,87 (0,63-1,22)
Estudios universitarios o equivalentes	2,6 (2,1)	0,91 (0,61-1,37)
Nacionalidad		
Española	3,3 (2,2)	1
Otros	2,6 (2,4)	0,87 (0,45-1,70)
Índice de Katz		
6	2,9 (2,0)	1
4-5	4,6 (2,3)	1,39 (1,06-1,83)
2-3	5,3 (2,5)	1,78 (1,19-2,65)
0-1	4,6 (2,5)	1,67 (1,09-2,56)
Número de problemas de salud crónicos	-	1,73 (1,67-1,79)
Deterioro cognitivo		
No	3,2 (2,2)	1
Sí	4,5 (2,3)	0,85 (0,66-1,09)
Déficits sensoriales		
Déficit auditivo		
No	3,3 (2,2)	1
Sí	4,2 (2,3)	0,44 (0,32-0,61)
Déficit visual		
No	3,3 (2,2)	1
Sí	4,8 (2,4)	0,73 (0,55-0,97)
Incontinencia urinaria		
No	3,0 (2,1)	1
Sí	4,8 (2,4)	0,51 (0,39-0,68)
Estado de salud percibido		
Muy bueno	1,5 (1,5)	1
Bueno	2,3 (1,7)	1,66 (0,97-2,85)
Regular	3,9 (2,0)	3,28 (1,92-5,59)
Malo	4,9 (2,3)	4,43 (2,55-7,70)
Muy malo	5,4 (2,5)	3,76 (2,01-7,03)
Modalidad de seguro sanitario		
Sanidad pública	3,4 (2,3)	1
Mutualidades del Estado	2,8 (2,0)	0,76 (0,51-1,13)
Seguro privado	3,0 (2,1)	1,22 (0,93-1,62)
Ingreso hospitalario en el último año		
No	3,1 (2,1)	1
Sí	4,4 (2,3)	1,24 (1,03-1,50)
Servicio de urgencias en el último año		
No	2,9 (2,1)	1
Sí	4,2 (2,3)	1,32 (1,14-1,54)
Consulta con médico de familia en el último mes		
No	2,8 (2,1)	1
Sí	3,9 (2,2)	1,37 (1,20-1,57)
Consulta con especialista en el último mes		
No	3,2 (2,2)	1
Sí	4,1 (2,3)	1,20 (1,01-1,43)
IMC		
Normopeso	2,9 (4,6)	1
Peso insuficiente	3,1 (2,1)	0,86 (0,44-1,66)
Sobrepeso	3,2 (2,1)	1,11 (0,94-1,32)
Obesidad	3,9 (2,3)	1,28 (1,06-1,55)
No sabe/no contesta	3,4 (2,3)	1,12 (0,86-1,46)

DE: desviación estándar; IMC: índice de masa corporal; OR: *odds ratio*
[a] Debido a los valores perdidos para el estado civil (n = 11), las *odds ratio* y los intervalos de confianza se calcularon para una muestra de 7.012 individuos (99,8% del total).

Cómo citar este artículo: M. Gutiérrez-Valencia, P. Aldaz Herce, E. Lacalle-Fabo, et al.. Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017. Med Clin (Barc). 2019. https://doi.org/10.1016/j.medcli.2018.12.013

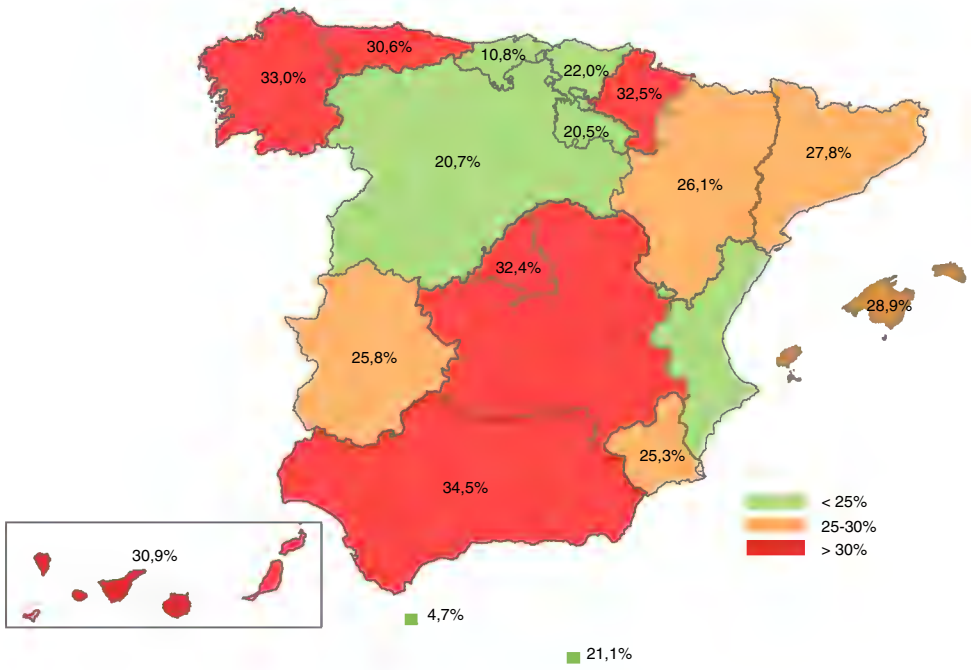


Figura 2. Prevalencia de polifarmacia por comunidades autónomas.

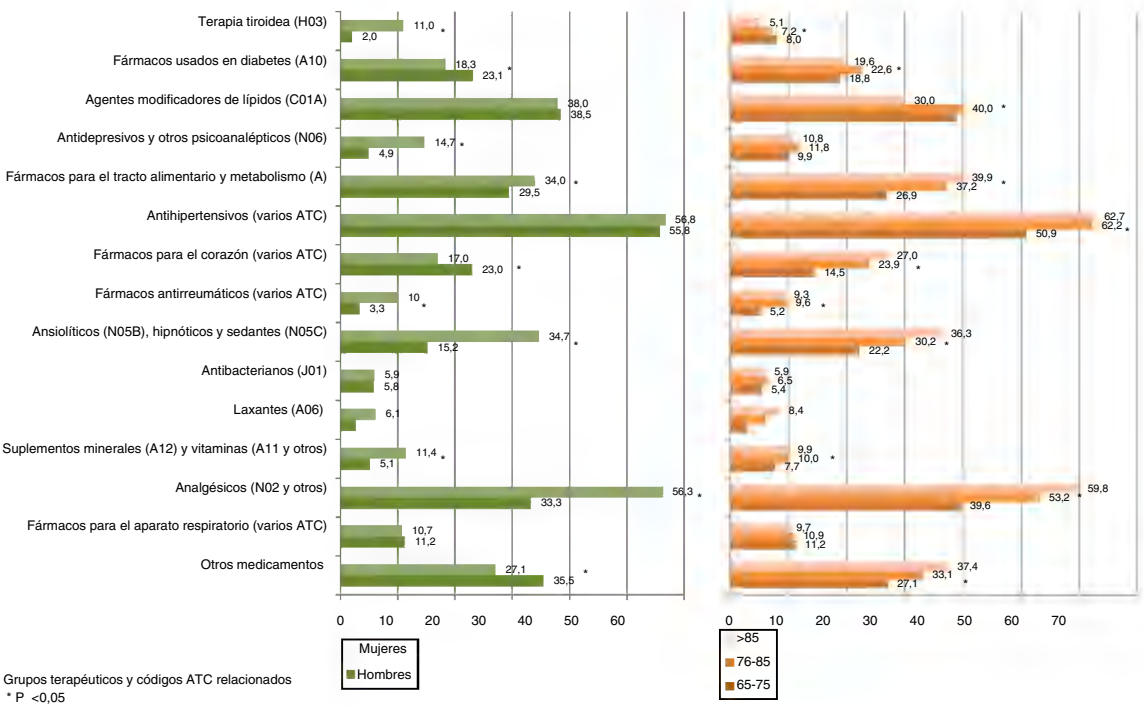
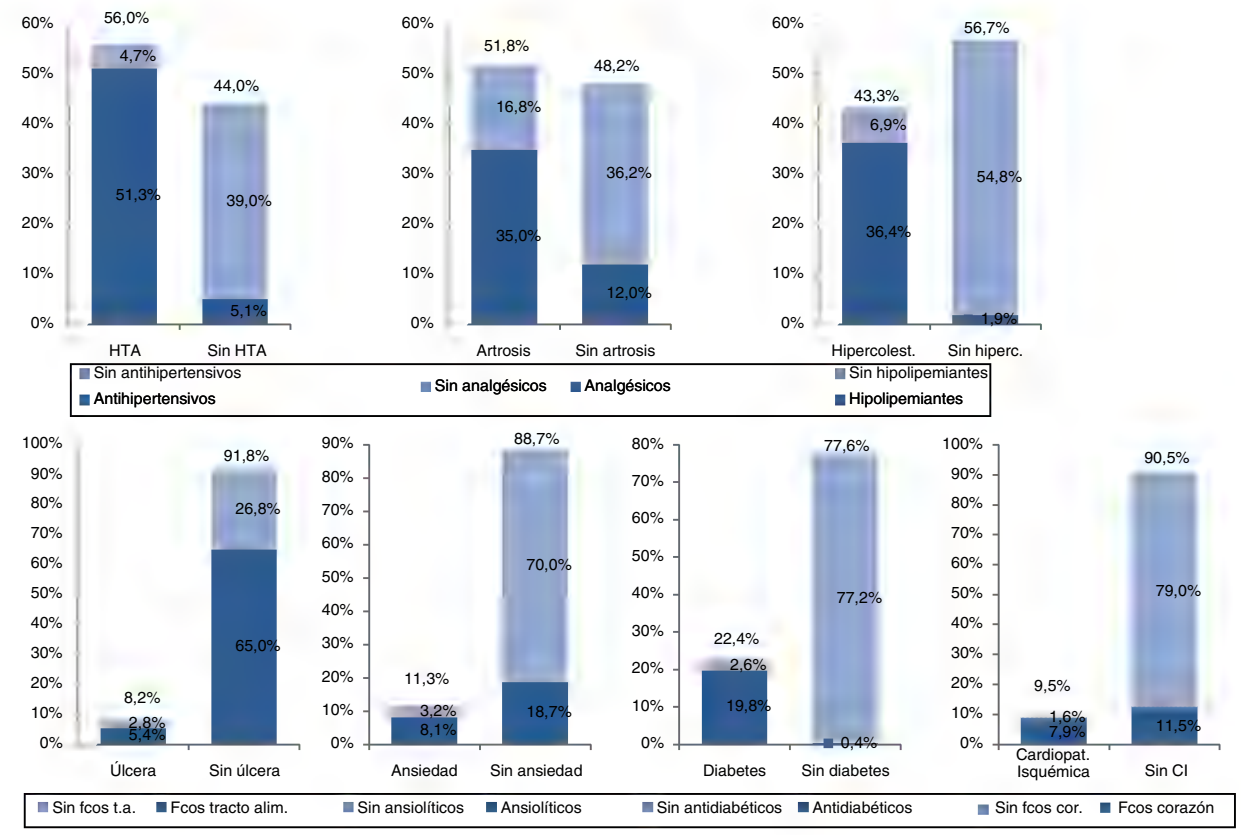


Figura 3. Consumo de distintos fármacos en función del sexo y del grupo de edad.

4,7% y el 32,4%. Estas variaciones podrían ser debidas a las diferencias en determinantes sociodemográficos y en los sistemas sanitarios entre distintas comunidades. Se encontraron también notables diferencias entre sexos en el patrón de consumo de medicamentos. Globalmente, las mujeres consumían más medicamentos que los hombres, y especialmente en analgésicos, ansiolíticos, hipnóticos y sedantes, antidepresivos, laxantes, fármacos para enfermedades tiroideas y antirreumáticos. Los hombres consumían, sin embargo, más fármacos para la diabetes y para el corazón. También se apreció un aumento del consumo de medicamentos en grupos de edad crecientes, salvo para las mujeres mayores de 85 años, que presentaban menor prevalencia de polifarmacia que aquellas que tenían entre 76 y 85 años. Algunos grupos de medicamentos tenían un consumo creciente al aumentar la edad (como analgésicos, laxantes, ansiolíticos, hipnóticos y sedantes, fármacos para el corazón, para el tracto alimentario y otros medicamentos), pero esta tendencia no se repetía para otros grupos farmacológicos como los agentes modificadores de lípidos, fármacos para trastornos tiroideos o para el aparato respiratorio. Pese a las diferencias encontradas en la prevalencia de polifarmacia en distintos sexos y grupos de edad, el

Cómo citar este artículo: M. Gutiérrez-Valencia, P. Aldaz Herce, E. Lacalle-Fabo, et al.. Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017. Med Clin (Barc). 2019. https://doi.org/10.1016/j.medcli.2018.12.013



Porcentajes sobre el total. p<0,001 para todas las pruebas

Figura 4. Prevalencia de fármacos más frecuentes y enfermedades con indicaciones comunes.

análisis multivariante, incluyendo diversos factores, no encontró asociación entre la presencia de polifarmacia y la edad o el sexo. Tampoco se halló una asociación entre la polifarmacia y otras características en cuya presencia se encontró una mayor prevalencia, como un menor nivel de estudios o la existencia de deterioro cognitivo. Sí que se evidenció, sin embargo, una asociación positiva con el número de problemas de salud crónicos, la dependencia para las actividades básicas de la vida diaria, el estado de salud percibido o los contactos con el sistema sanitario; y una asociación negativa con los déficits sensoriales y la incontinencia. Estos datos indican que el aumento de prevalencia de polifarmacia en mujeres, individuos de más edad o con menos nivel de estudios se debe probablemente a la mayor presencia de estos otros factores explicativos en estos grupos poblacionales (por ejemplo, el mayor número de problemas de salud crónicos en mujeres y personas más mayores, un peor estado de salud percibido, o una mayor dependencia para las actividades básicas de la vida diaria). Las diferencias en las características basales de los distintos sectores poblacionales podrían explicar también los distintos patrones en el consumo de determinados grupos de medicamentos. Por ejemplo, el mayor grado de dolor y de dependencia y el peor estado de salud percibido por parte de las mujeres puede tener relación con el mayor consumo de analgésicos, antidepresivos y ansiolíticos, hipnóticos y sedantes en este sector poblacional. Por otra parte, el análisis multivariante también sugiere que ciertas características, como los déficits sensoriales y la incontinencia, podrían conducir a una menor prescripción de medicamentos, independientemente del número de enfermedades, lo que podría entenderse como un signo de infraprescripción en estas personas o como una prescripción adaptada a las características del paciente (en cuanto a pronóstico, objetivo terapéutico, etc.). En cualquier caso, se muestra que la prescripción de medicamentos no depende solo del número de enfermedades, sino también de cómo estas afectan al estado de salud y a la vida diaria de los individuos, y de la interacción con el sistema sanitario.

La prevalencia de polifarmacia encontrada en estudios previos tiene una gran variabilidad en función del lugar y de la metodología de cada estudio. Algunos estudios poblacionales realizados en otros países en mayores de 65 años en atención primaria estimaron que la prevalencia de polifarmacia alcanzaba un 44% en Suecia[24], un 39% en Estados Unidos[25], un 41,2% en Suiza[26] y hasta un 70,3% en Francia[27]. Otros estudios realizados en el ámbito regional en España en mayores en atención primaria, que registran cada fármaco individualmente, muestran prevalencias de entre un 45% y un 83,1%[13–15]. Un reciente estudio de ámbito europeo estima una prevalencia de polifarmacia a partir de encuestas y según la misma definición de entre un 26,3% y un 39,9%, alcanzando en España un 31,6%[28]. Existen también estudios que estimaron la prevalencia de polifarmacia en población mayor española no institucionalizada con encuestas nacionales de salud previas o encuestas europeas de salud en España[2,16]. Martín-Pérez et al.[2] mostraron una prevalencia de polifarmacia de 19,7% y 24,5% en las ENSE de 2006 y 2012 respectivamente utilizando la misma definición de polifarmacia, y la media de medicamentos consumidos estimada en estas encuestas fue de 2,87 y 2,93 medicamentos por individuo respectivamente, frente a los 3,3 estimados en nuestro estudio. Asimismo, Carmona-Torres et al.[16] estimaron que la prevalencia de polifarmacia era del 21,9% y la de hiperpolifarmacia de 0,6% analizando conjuntamente 4 encuestas entre 2006 y 2014. Cabe destacar que en el estudio de Carmona-Torres et al. incluyen para el cómputo del número de medicamentos consumidos productos homeopáticos y naturistas, no incluidos aquí al no poder considerarse medicamentos, lo que pudo haber sobreestimado ligeramente las cifras. De todos estos datos se puede deducir que existe una tendencia al aumento en el consumo de medicamentos, la polifarmacia y la hiperpolifarmacia

Cómo citar este artículo: M. Gutiérrez-Valencia, P. Aldaz Herce, E. Lacalle-Fabo, et al.. Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017. Med Clin (Barc). 2019. https://doi.org/10.1016/j.medcli.2018.12.013

en la población de edad avanzada en España a lo largo de los últimos años. Esto puede deberse a diversos factores, como el aumento de la multimorbilidad, la aparición de nuevos medicamentos en el mercado o la medicalización de la vida[29]. En cuanto al tipo de medicamentos más consumidos encontramos resultados similares a otros estudios, predominando antihipertensivos, analgésicos, agentes modificadores de lípidos y fármacos para el tracto alimentario[16], coincidiendo con problemas de salud crónicos más frecuentes en esta población.

En cuanto a las implicaciones de los resultados de este estudio, hay que destacar las consecuencias que pueden acompañar al aumento de la polimedicación en la población mayor en nuestro país, más allá del aumento directo del gasto. La polifarmacia supone una mayor complejidad terapéutica al asociarse a un aumento de las interacciones medicamento-medicamento y medicamento-enfermedad, reacciones adversas, cascadas terapéuticas o peor adherencia terapéutica[9]. Pero además de ser una cuestión cuantitativa, es un cambio cualitativo, ya que la polifarmacia está estrechamente ligada al uso inadecuado de medicamentos, que hace referencia a los tratamientos en los que el riesgo es superior al beneficio clínico potencial esperado, especialmente cuando existen alternativas terapéuticas más seguras o eficaces[30]. La polifarmacia y el uso inadecuado de medicamentos van a suponer un reto cada vez mayor para el clínico, que encontrará cada vez más pacientes polimedicados y con mayor complejidad, por lo que es fundamental conocer los medicamentos potencialmente inadecuados en ancianos más frecuentes en nuestro medio (como el empleo de benzodiacepinas de vida media larga)[31], así como ciertas herramientas que ayuden a detectar y atajar este problema[32].

El empleo de los datos oficiales de la ENSE tienen la ventaja de ser obtenidos mediante una cuidada metodología, incluyendo el muestreo, el diseño de los formularios, la preparación de los encuestadores, la supervisión en la ejecución, o la depuración de los datos, que garantizan contar con una muestra representativa de la población y con datos altamente fiables. Además, al preguntar específicamente sobre medicamentos consumidos, se evita el problema de sobreestimación que puede darse en estudios basados en registros de prescripción o dispensación de fármacos al desconocer estos el grado de adherencia al tratamiento; y al preguntar sobre las 2 últimas semanas se reduce el riesgo del sesgo de memoria que se produce si se pregunta por periodos de tiempo más largos. Permite también obtener conjuntamente datos de individuos que utilizan distintas modalidades de seguros sanitarios (hasta un 11,4% de los participantes en este estudio podrían utilizar sistemas distintos a la sanidad pública), cuestión que puede sesgar los resultados en estudios basados en registros de medicación en administraciones públicas o aseguradoras. Además de la propia metodología de la ENSE, este estudio cuenta con otras fortalezas, como el evaluar los distintos factores asociados a la polifarmacia mediante un análisis multivariante que incluye variables muy relevantes en personas de edad avanzada, como la dependencia para las ABVD o síndromes geriátricos. Este tipo de variables no habían sido incluidas en estudios previos realizados con encuestas nacionales de salud en España para estudiar el uso de medicamentos, y muestran en este estudio que son factores determinantes que modulan el consumo de fármacos en la población de edad avanzada.

Por otra parte, el empleo de Encuestas de Salud para la estimación de datos farmacoepidemiológicos tiene también ciertas limitaciones. Al tratarse de datos autorreportados hay que tener en cuenta que el grado de conocimiento de la medicación consumida y específicamente de su indicación no siempre es óptimo, especialmente en personas de edad avanzada[33] y con polifarmacia marcada, lo que podría llevar a una infraestimación en la prevalencia. Esto podría explicar la baja prevalencia encontrada de hiperpolifarmacia. Por otra parte, la ENSE no incluye personas institucionalizadas, que son precisamente aquellas que presentan niveles más altos de polifarmacia según han reportado otros estudios[34,35], lo que puede conducir también a una infraestimación de la polifarmacia en mayores a nivel poblacional, teniendo en cuenta que más del 4% de la población española de 65 años o más estaría institucionalizada[36]. Además, la propia metodología de la encuesta no permite conocer exactamente qué grupos terapéuticos son los que se emplean, o si la polifarmacia se asocia a enfermedades concretas y a su gravedad. Por último, dado que la encuesta no se ha diseñado para este fin, solo puede identificar el uso de medicamentos para una indicación, considerando que para todas las indicaciones se emplearía un medicamento en monoterapia. Para algunos de los problemas de salud más frecuentes, como la hipertensión, el dolor o la diabetes, el empleo de varios fármacos para la misma indicación es común, por lo que esta puede ser la causa más importante de infraestimación de polifarmacia, y lo que puede explicar las tasas de prevalencia de polifarmacia notablemente más bajas que en otros países de nuestro entorno cuando registran cada medicamento individualmente, como los citados anteriormente[24–27]. El análisis de sensibilidad propuesto para tratar de corregir este sesgo, aunque solo realiza la corrección para la hipertensión y la diabetes, estima una prevalencia de polifarmacia hasta 10 puntos más alta (de 27,3% a 37,5%), acercándose así a las cifras obtenidas en estudios realizados en otros países. De hecho, los estudios de ámbito regional realizados en España en mayores en atención primaria que registran cada fármaco individualmente hallan prevalencias bastante mayores[13–15], lo que también parece indicar la infraestimación que se puede dar debida a la metodología de la ENSE.

En conclusión, se encuentra un importante consumo de medicamentos en la población mayor no institucionalizada en España, y continúa la tendencia observada en los últimos años a aumentar la prevalencia de polifarmacia en el tiempo. Los factores que más se asocian a la polifarmacia son el número de problemas de salud crónicos, la dependencia para las actividades básicas de la vida diaria, el estado de salud percibido o los contactos con el sistema sanitario; y de forma inversa los déficits sensoriales y la incontinencia. Conocer los patrones de consumo de medicamentos en nuestra población y los factores asociados es fundamental para comprender el fenómeno de la polifarmacia en las personas mayores y el alcance de sus consecuencias para la población, los profesionales y los sistemas sanitarios.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Anexo. Material adicional

Se puede consultar material adicional a este artículo en su versión electrónica disponible en http://dx.doi.org/10.1016/j.medcli.2018.12.013.

Bibliografía

1. Abellán García A, Ayala García A, Pérez Díaz J, Pujol Rodríguez R (2018). Un perfil de las personas mayores en España, 2018. Indicadores estadísticos básicos. Madrid, Informes Envejecimiento en red n.°17. p. 34. Disponible en: http://envejecimiento.csic.es/documentos/documentos/enred-indicadoresbasicos18.pdf.
2. Martin-Perez M, Lopez de Andres A, Hernandez-Barrera V, Jiménez-García R, Jiménez-Trujillo I, Palacios-Ceña D, et al. Prevalencia de polifarmacia en la población mayor de 65 años en España: análisis de las Encuestas Nacionales de Salud 2006 y 2011/12. Rev Esp Geriatr Gerontol. 2017;52:2–8.
3. Cho S, Lau SW, Tandon V, Kumi K, Pfuma E, Abernethy DR. Geriatric drug evaluation: Where are we now and where should we be in the future? Arch Intern Med. 2011;171:937–40.
4. Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasquín B, Sánchez-Castellano C, Sánchez-García E. Exclusion of older adults from ongoing clinical trials about type 2 diabetes mellitus. J Am Geriatr Soc. 2013;61:734–8.

5. Gutierrez-Valencia M, Izquierdo M, Malafarina V, Alonso-Renedo J, Gonzáñez-Glaría B, Larrayoz-Sola B, et al. Impact of hospitalization in an acute geriatric unit on polypharmacy and potentially inappropriate prescriptions: A retrospective study. Geriatr Gerontol Int. 2017;17:2354–60.
6. Chang CB, Chen JH, Wen CJ, Kuo HK, Lu IS, Chiu LS, et al. Potentially inappropriate medications in geriatric outpatients with polypharmacy: Application of six sets of published explicit criteria. Br J Clin Pharmacol. 2011;72:482–9.
7. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt PMLA, Janssen MJA, Karapinar-Çarkit F. Prevalence and preventability of drug-related hospital readmissions: A systematic review. J Am Geriatr Soc. 2018;66:602–8.
8. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: A systematic review. J Am Geriatr Soc. 2014;62:2261–72.
9. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13:57–65.
10. Cabre M, Elias L, Garcia M, Palomera E, Serra-Prat M. Avoidable hospitalizations due to adverse drug reactions in an acute geriatric unit. Analysis of 3,292 patients. Med Clin (Barc). 2018;150:209–14.
11. Gutierrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero A, Inzitari M, Martinez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. Br J Clin Pharmacol. 2018;84:1432–44.
12. Dobler CC, Harb N, Maguire CA, Armour CL, Coleman C, Murad MH. Treatment burden should be included in clinical practice guidelines. BMJ. 2018;363, k4065.
13. Blanco-Reina E, Ariza-Zafra G, Ocana-Riola R, Leon-Ortiz M, Bellido-Estevez I. Optimizing elderly pharmacotherapy: polypharmacy vs. undertreatment. Are these two concepts related? Eur J Clin Pharmacol. 2015;71:199–207.
14. Blanco-Reina E, Garcia-Merino MR, Ocana-Riola R, Aguilar-Cano L, Valdellós J, Bellido-Estévez I, et al. Assessing potentially inappropriate prescribing in community-dwelling older patients using the updated version of STOPP-START criteria: A comparison of profiles and prevalences with respect to the original version. PloS One. 2016;11, e0167586.
15. Cruz-Esteve I, Marsal-Mora JR, Galindo-Ortego G, Galván-Santiago L, Serrano-Godoy M, Ribes-Murillo E, et al. Análisis poblacional de la prescripción potencialmente inadecuada en ancianos según criterios STOPP/START (estudio STARTREC). Aten Primaria. 2017;49:166–76.
16. Carmona-Torres JM, Cobo-Cuenca AI, Recio-Andrade B, Laredo-Aguilera JA, Martins MM, Rodriguez-Borrego MA. Prevalence and factors associated with polypharmacy in the older people: 2006-2014. J Clin Nurs. 2018;27:2942–52.
17. Encuesta Nacional de Salud de España 2017 (ENSE 2017). Ministerio de Sanidad, Consumo y Bienestar Social e Instituto Nacional de Estadística, 2018. Disponible en: https://www.msssi.gob.es/estadEstudios/estadisticas/encuestaNacional/encuesta2017.htm.
18. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17:230.
19. Calderon-Larranaga A, Vetrano DL, Onder G, Gimeno-Feliu LA, Coscollar-Santaliestra C, Carfí A, et al. Assessing and measuring chronic multimorbidity in the older population: A proposal for its operationalization. J Gerontol A Biol Sci Med Sci. 2017;72:1417–23.
20. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of Adl: A standardized measure of biological and psychosocial function. JAMA. 1963;185:914–9.
21. Rodríguez-Roca GC, Valls-Roca F, Pallarés-Carratalá V, Llisterri JL, Barrios V, Alonso-Moreno FJ, et al. Control de la presión arterial en una población hipertensa española ≥ 65 años asistida en Atención Primaria. Datos del estudio PRESCAP 2006. SEMERGEN. 2009;35:426–34.
22. Barrios V, Escobar C, Alonso-Moreno FJ, Prieto MA, Pallares V, Rodríguez-Roca G, et al. Evolution of clinical profile, treatment and blood pressure control in treated hypertensive patients according to the sex from 2002 to 2010 in Spain. J Hypertens. 2015;33:1098–107.
23. Orlando V, Guerriero F, Putignano D, Monetti VM, Tari DU, Farina G, et al. Prescription patterns of antidiabetic treatment in the elderly. Results from Southern Italy. Curr Diabetes Rev. 2015;12:100–6.
24. Morin L, Johnell K, Laroche ML, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: Register-based prospective cohort study. Clin Epidemiol. 2018;10:289–98.
25. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. JAMA. 2015;314:1818–31.
26. Blozik E, Rapold R, Von Overbeck J, Reich O. Polypharmacy and potentially inappropriate medication in the adult, community-dwelling population in Switzerland. Drugs Aging. 2013;30:561–8.
27. Herr M, Sirven N, Grondin H, Pichetti S, Sermet C. Frailty, polypharmacy, and potentially inappropriate medications in old people: Findings in a representative sample of the French population. Eur J Clin Pharmacol. 2017;73:1165–72.
28. Midao L, Giardini A, Menditto E, Kardas P, Costa E. Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. Arch Gerontol Geriatr. 2018;78:213–20.
29. Cerecedo Pérez MJ, Tovar Bobo M, Rozadilla Arias A. Medicalización de la vida. «Etiquetas de enfermedad: todo un negocio». Aten Primaria. 2013;45:434–8.
30. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther. 2007;32:113–21.
31. Salgueiro E, Elizarde BC, Elola AI, Garcia-Pulido B, Nicieza-Garcia ML, Manso G. Los criterios STOPP/START más frecuentes en España. Una revisión de la literatura. Rev Esp Geriatr Gerontol. 2018;53:274–8.
32. Delgado Silveira E, Montero Errasquin B, Munoz Garcia M, Vélez-Díaz-Pallarés M, Lozano-Montoya I, Sánchez-Castellano C, et al. Mejorando la prescripción de medicamentos en las personas mayores: una nueva edición de los criterios STOPP-START. Rev Esp Geriatr Gerontol. 2015;50:89–96.
33. Modig S, Kristensson J, Ekwall AK, Hallberg IR, Midlov P. Frail elderly patients in primary care–their medication knowledge and beliefs about prescribed medicines. Eur J Clin Pharmacol. 2009;65:151–5.
34. Onder G, Liperoti R, Fialova D, Topinkova E, Tosato M, Danese P, et al. Polypharmacy in nursing home in Europe: Results from the SHELTER study. J Gerontol A Biol Sci Med Sci. 2012;67:698–704.
35. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: A systematic review. J Am Med Dir Assoc. 2015;16:e1–12.
36. Envejecimiento en Red (2014). Estadísticas sobre residencias: distribución de centros y plazas residenciales por provincia. Datos de Dic de 2013. Madrid, Informes en Red, n.° 7. Disponible en: http://envejecimiento.csic.es/documentos/documentos/enred-estadis.

Cómo citar este artículo: M. Gutiérrez-Valencia, P. Aldaz Herce, E. Lacalle-Fabo, et al.. Prevalencia de polifarmacia y factores asociados en adultos mayores en España: datos de la Encuesta Nacional de Salud 2017. Med Clin (Barc). 2019. https://doi.org/10.1016/j.medcli.2018.12.013

Publicado en:
Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. *Br J Clin Pharmacol.* 2018;84(7):1432–1444. doi:10.1111/bcp.13590

Publicado en:
Gutiérrez-Valencia M, Izquierdo M, Lacalle-Fabo E, et al. Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes. *Eur J Clin Pharmacol.* 2018;74(7):961-970. doi:10.1007/s00228-018-2452-2.

Artículo eliminado por restricciones de derechos de autor

Publicado en:
Gutiérrez-Valencia, M. , Izquierdo, M. , Malafarina, V. , Alonso-Renedo, J. , González-Glaría, B. , Larrayoz-Sola, B. , Monforte-Gasque, M. P., Latasa-Zamalloa, P. and Martínez-Velilla, N. (2017), Impact of hospitalization in an acute geriatric unit on polypharmacy and potentially inappropriate prescriptions: A retrospective study. *Geriatr Gerontol Int*, 17: 2354-2360. doi:10.1111/ggi.13073

Rev Clin Esp. 2016;**216(4)**:205–221

Revista Clínica Española

www.elsevier.es/rce

REVIEW

Interventions to optimize pharmacologic treatment in hospitalized older adults: A systematic review☆

M. Gutiérrez Valencia[a,b,*], N. Martínez Velilla[a,b,c], E. Lacalle Fabo[d], I. Beobide Telleria[e], B. Larrayoz Sola[d], M. Tosato[f]

[a] *Servicio de Geriatría, Complejo Hospitalario de Navarra, Pamplona, Spain*
[b] *IdiSNa, Navarra Institute for Health Research, Pamplona, Spain*
[c] *Red de Investigación en Servicios Sanitarios en Enfermedades Crónicas (REDISSEC), Pamplona, Spain*
[d] *Servicio de Farmacia, Complejo Hospitalario de Navarra, Pamplona, Spain*
[e] *Servicio de Farmacia, Fundación Matia, San Sebastián, Spain*
[f] *Centro Medicina Dell'Invecchiamento, Università Cattolica Sacro Cuore, Policlinico A. Gemelli, Roma, Italy*

KEYWORDS
Elderly;
Hospitalized;
Polypharmacy;
Inappropriate prescribing;
Treatment review

Abstract
Objective: To summarise the evidence on interventions aimed at optimising the drug treatment of hospitalised elderly patients.
Material and methods: We conducted a search in the main medical literature databases, selecting prospective studies of hospitalised patients older than 65 years who underwent interventions aimed at optimising drug treatment, decreasing polypharmacy and improving the medication appropriateness, health outcomes and exploitation of the healthcare system.
Results: We selected 18 studies whose interventions consisted of medication reviews, detection of predefined drugs as potentially inappropriate for the elderly, counselling from a specialised geriatric team, the use of a computer support system for prescriptions and specific training for the nursing team. Up to 14 studies assessed the medication appropriateness, 13 of which showed an improvement in one or more of the parameters. Seven studies measured the impact of the intervention on polypharmacy, but only one improved the outcomes compared with the control. Seven other studies analysed mortality, but none of them showed a reduction in that rate. Only 1 of 6 studies showed a reduction in the number of hospital readmissions, and 1 of 4 studies showed a reduction in the number of emergency department visits.
Conclusions: Despite the heterogeneity of the analysed interventions and variables, we obtained better results in the process variables (especially in medication appropriateness) than in those that measured health outcomes, which had greater variability.

☆ Please cite this article as: Gutiérrez Valencia M, Martínez Velilla N, Lacalle Fabo E, Beobide Telleria I, Larrayoz Sola B, Tosato M. Intervenciones para optimizar el tratamiento farmacológico en ancianos hospitalizados: una revisión sistemática. Rev Clin Esp. 2016;216:205–221.

* Corresponding author.
E-mail address: marta.guva@gmail.com (M. Gutiérrez Valencia).

PALABRAS CLAVE
Anciano;
Hospitalizados;
Polifarmacia;
Prescripción inadecuada;
Revisión de tratamientos

Intervenciones para optimizar el tratamiento farmacológico en ancianos hospitalizados: una revisión sistemática

Resumen
Objetivo: Resumir la evidencia sobre las intervenciones orientadas a optimizar el tratamiento farmacológico en ancianos hospitalizados.
Material y métodos: Se realizó una búsqueda en las principales bases de datos bibliográficas, seleccionando estudios prospectivos en pacientes mayores de 65 años hospitalizados que realizaran intervenciones dirigidas a optimizar el tratamiento farmacológico, disminuir la polifarmacia y mejorar la adecuación terapéutica, los resultados en salud o el aprovechamiento del sistema sanitario.
Resultados: Se seleccionaron 18 estudios. Las intervenciones consistieron en revisiones de medicación, detección de medicamentos predefinidos como potencialmente inadecuados en ancianos, asesoramiento de un equipo especializado en geriatría, uso de un sistema informático de apoyo a la prescripción o formación específica al equipo de enfermería. Hasta 14 estudios evaluaron la adecuación terapéutica, demostrando 13 de ellos una mejoría en alguno de los parámetros. Siete estudios midieron el impacto de la intervención sobre la polifarmacia, pero solo uno mejoró los resultados respecto al control. Otros siete estudios analizaron la mortalidad, no demostrándose una disminución de la misma en ninguno. Solo uno de seis estudios mostró una reducción de reingresos hospitalarios y uno de cuatro estudios una disminución de las visitas a urgencias.
Conclusiones: Pese a la heterogeneidad de las intervenciones y de las variables analizadas, se obtuvieron mejores resultados en las variables de proceso, especialmente en la adecuación terapéutica, que en aquellas que midieron resultados en salud, donde hubo una mayor variabilidad.

Background

Drug therapy is one of the most important tools available for preserving and improving health; however, the use of medications is not without risk. The high prevalence of adverse events due to medication[1] is a significant public health problem, due to the significant morbidity and mortality they cause,[2,3] which entail a significant consumption of resources and high healthcare costs.[4,5] This problem is especially relevant for the elderly, who have numerous factors that contribute to a greater risk of drug iatrogenesis. These factors include age-related changes in pharmacokinetics and pharmacodynamics[6,7] and the combination of chronic diseases that inevitably lead to polypharmacy.

A number of studies in Spain have shown that the prevalence of polypharmacy (defined as the consumption of more than 5 drugs a day) in patients older than 65 years is approximately 50%[8,9] and that polymedicated patients consume a mean of almost 9 medications a day.[8] Polypharmacy is strongly linked to drug-related adverse events, interactions and interferences between the drugs and the disease itself,[10,11] to lack of treatment adherence[12] and, ultimately, to mortality.[13] Other patient-related factors, such as frailty, geriatric syndromes, dependence and cognitive impairment, frequently overlap, increasing the complexity of medication use, which ultimately leads to poorer health outcomes. For example, it is estimated that between 10% and 20% of hospital admissions for elderly patients in Spain are associated with medication-related adverse events,[14,15] which quadruple the risk when compared with younger patients.[16]

All of these problems gain special relevance in elderly hospitalized patients. Hospitalization is an especially delicate situation for the elderly and is associated with higher morbidity, mortality and cognitive and functional impairment.[17,18] The incorporation of new prescribers and the increase in the number of drugs during hospitalization contribute to the risk of iatrogenesis and the complexity of administering drugs.[19,20]

The progressive aging of the population predicts that medication-related problems in the elderly will be increasingly common. Fortunately, most medication-related adverse events are considered preventable.[21] Improving therapeutic appropriateness could therefore help minimize the problem. The issue of prescription quality in the elderly has generated significant interest in the scientific community, which, in an attempt to define it, has coined terms such as ''therapeutic appropriateness'' and has led to the development of numerous tools to quantify it (Appendix A).

Considering the complexity of administering drugs to elderly hospitalized patients and the high prevalence of inappropriate prescriptions,[19,22] it seems that we need to incorporate strategies aimed at optimizing drug treatment. Although it has been previously mentioned that hospitalization is an especially appropriate period for implementing strategies for improving the quality of the use of

medications,[23] most studies have been implemented in other healthcare settings.

The aim of this review is to summarize the evidence on interventions aimed at optimizing the drug treatment of hospitalized elderly patients.

Materials and methods

Search strategy

In August 2015, we conducted a search in the following scientific literature databases to locate primary studies, without setting any date restrictions: MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and the Cochrane Library. The search was designed with MeSH terms (Medical Subject Headings) for MEDLINE and was adapted to the other databases according to its descriptors or through keywords. We combined the following search terms: ''Aged'' and (''Hospitalization'', ''Inpatients'' or ''Hospitals''); and (''Drug utilization review'', ''Polypharmacy'', ''Inappropriate prescribing'' or ''Medication therapy management''). A manual search was also conducted, reviewing the references cited in the selected studies and in relevant systematic reviews.

Study selection

We included studies that met the following criteria: (a) prospective studies (not necessarily controlled or randomized), (b) inclusion of interventions aimed at optimizing the drug treatment in terms of the prescription, (c) inclusion of at least 80% of the sample composed of hospitalized patients 65 years of age or older, and (d) measurement of quantifiable process variables (change in therapeutic appropriateness measured by validated tools or polypharmacy) or endpoints (clinical, use of healthcare resources, financial, humanistic, etc.).

We excluded studies with the following criteria: (a) systematic reviews and meta-analyses, presentations at congresses or scientific meetings and study protocols; (b) published in languages other than English and Spanish; (c) focus on a single disease or medical condition or regarding a certain medication or therapeutic group; and (d) inclusion of interventions directed exclusively to improving treatment adherence or decreasing reconciliation errors.

Data collection and analysis

To select the studies, 2 reviewers examined the titles and abstracts of those studies identified in the search and then examined the full text of those studies that were not excluded, ultimately evaluating the ones that met the inclusion criteria. The relevant data were extracted from the selected articles, including the study design, number of participants, demographic characteristics, type of intervention and practitioner who performed it, follow-up time, degree of therapeutic appropriateness, polypharmacy, mortality, adverse reactions to medications, falls, changes in Barthel index, hospital readmissions, emergency department visits, time of admission, financial savings per patient and health-related quality of life. The main characteristics of the measurement methods for therapeutic appropriateness employed in the studies are shown in Table 1.

The quality of the prescription can be assessed using process variables (see whether the prescription coincides with the accepted standards) or results (consequences for the patient, the healthcare system and society).[24]

Ultimately, 2 reviewers separately assessed the included studies according to the risk of bias criteria developed by the Cochrane Effective Practice and Organization of Care group[25] for the main variables.

Results

Search results

A total of 794 references were identified, among which were 41 duplicates. After reviewing the titles and abstracts of 753 publications, 677 were excluded for not meeting the inclusion criteria or meeting exclusion criteria. The remaining 76 publications were assessed. Ultimately, 19 publications were selected for this review. These publications referred to 18 studies[26–44] that met all the defined criteria (2 studies referred to the same publication) (Fig. 1).[37,38]

Study characteristics

The number of participants in the studies varied from 43 to 3974, with a mean of 518 patients and a median of 316. Fifteen studies were conducted in Europe and the remaining 3 in the United States. Most studies had a control group, except for 2,[46,47] and 12 were also randomized. The follow-up time varied between the hospitalization period itself [40,42–44] and 12 months.[29,32,41]

Participant characteristics

The mean age of the participants ranged from 74.5[35] to 86.6 years[32]; 2 of the studies did not provide this datum.[27,28] The proportion of women ranged from 3%[28] to 71%[26]; 1 study did not provide this information.[42] The age inclusion criteria in the studies were an age greater than 65 years in 9 studies,[27,28,30,31,35,36,40,43,44] greater than 70 in 4,[29,33,37,42] greater than 75 in 2[26,41] and greater than 80 in another.[32] Two studies did not have age criteria for inclusion,[34,39] but more than 80% of the participants were older than 65 years. A number of studies also required other inclusion criteria, such as multiple diseases,[44] frailty[28,41] and the consumption of more than 3 medications.[27,41]

Intervention characteristics

The intervention was performed by pharmacists in 9 studies, by a multidisciplinary team in 3,[28,36,41] by pharmacists and clinical pharmacologists in 1,[33] by geriatricians in 1,[37] by nurses in 1,[31] and by physicians other than the prescriber (without specifying specialty) in 2.[35,43] One intervention consisted of a software application used by the prescribing physician.[40]

Table 1 Methods for assessing medication appropriateness.

Criterion (year of publication)	Years of updates	Country	Study population	Main characteristics
Explicit criteria				
Beers criteria (1991)	1997, 2003, 2007, 2012, 2015	USA	>65 years	• List of medicinal products to avoid • List of medicinal product or therapeutic groups to avoid in certain diseases (since 1997) • List of medicinal products to use with caution (since 2012) • Inappropriate prescription due to drug interactions and renal function (since 2015)
STOPP–START criteria (2008)	2014	Ireland	>65 years	• STOPP: list of potentially inappropriate medications, organized by physiological system • START: underprescription criteria (health condition – indicated drug)
PRISCUS list (2010)		Germany	>65 years	• List of potentially inappropriate medications. Classified by therapeutic group. • Proposes therapeutic alternatives and precautions if used
National quality indicators in the use of drug therapy for the elderly (2004)	2010	Sweden	>75 years	• Specific medicinal product indicators: selection, indication, dosage, polypharmacy, drug interactions, use of medicinal products with altered renal function and in the presence of certain symptoms • Specific indicators of diagnosis: rational, irrational and dangerous use
ACOVE (1999)	2001, 2007	USA	>65 years frail	• Quality indicators for improving the quality of care in various chronic conditions. Not focused exclusively on drug treatment. 35% of indicators for treatment
Criterios implícitos				
MAI (1992)		USA	All	• Ten questions are assigned to each medicinal product regarding the indication, effectiveness, dosage, instructions, regimen, drug–drug interactions, drug–disease interactions, duplication, duration and cost • Responses based on a 3-point Likert scale (A: appropriate, C: inappropriate). Each inappropriate item scores between 1 and 3 points based on its importance. The sum of all items creates a weighted score for each drug between 0 and 18. By adding up the scores for the drugs, we can obtain an overall index • Higher scores mean lower therapeutic suitability
FORTA (2008)	2014	Germany	>65 years	• Records inappropriate prescriptions and omissions for indicated medicinal products • Drugs are classified into 4 categories: A (Indispensable), B (Beneficial), C (Questionable), D (To be avoided). Based on the evidence of safety, efficacy and suitability for the age
AOU (1999)		USA	All	• Measures underprescription. Requires the clinical discretion of a healthcare practitioner who compares the medical history and the list of medicinal products to establish treatment omissions

Abbreviations: ACOVE, Assessing Care of Vulnerable Elders; AOU, Assessment of Underutilization of Medication tool; FORTA, Fit for the Aged; MAI, Medication Appropriateness Index; START, Screening Tool to Alert Doctors to Right Treatment; STOPP, Screening Tool of Older Persons' Potentially Inappropriate Prescriptions.

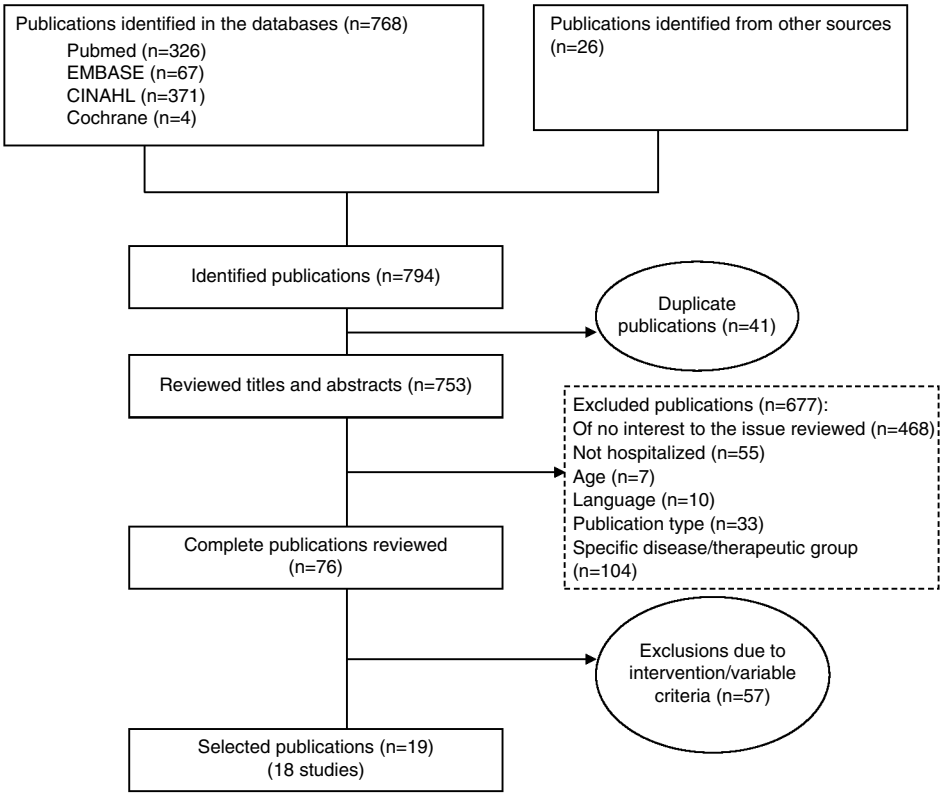


Figure 1 Database search.

In terms of type of intervention, most of the studies (13, 72%) conducted medication reviews with subsequent recommendations by or discussions with the prescribing physician. The intervention in 2 studies was based on detecting explicit criteria such as the Screening Tool of Older Person's Potentially Inappropriate Prescriptions (STOPP)[35,41] and the Screening Tool to Alert Doctors to Right Treatment (START).[35] In another study, the intervention consisted of advising a team of geriatric medicine specialists.[28] We also included a study with an educational approach, based on training nurses on clinical pharmacology and tools for detecting medication-related problems.[31] A number of studies performed other types of intervention, such as patient information, counseling and education[27,29,32–34,37] and medication reconciliation,[36,37,39] which are beyond the scope of this review.

Variables analyzed

Process variables

Among the 14 studies that measured therapeutic appropriateness, 13 achieved an improvement in at least one of the parameters due to the intervention.

The most widely used measurement tool was the Medication Appropriateness Index (MAI),[45,46] which was employed in 6 studies.[28–30,35,36,43] All 6 studies showed significant improvements in this scale after the intervention. The study by Michelek et al.[42] used the Fit for the Aged (FORTA) system,[47] achieving an increase in the prescription of category A drugs (indispensable) compared with the control group, but without reaching statistical significance. Two studies[28,35] measured medication underutilization through the Assessment of Underutilization of Medication index,[48] both of which achieved improvements in this criterion compared with the control group.

In terms of the explicit methods (see Appendix A in the supplementary material), the Beers criteria were employed in 4 studies,[28,29,40,43] in its updated versions of 1997[49] and 2003,[50] but only 2 of them[28,40] achieved improvements after the intervention. The STOPP and START criteria[51] were employed to quantify therapeutic appropriateness after the intervention in 2 studies. A statistically significant improvement was observed with the STOPP criteria[41,43] but not in the study that applied the START criteria.[43] Only one study measured appropriateness using the Priscus criteria[43] but could not demonstrate clear improvement attributable to the intervention (42.4–40.6%) ($p = .421$). Two interventions reported in Swedish studies attempted to decrease the prevalence of inappropriate medications based on quality indicators described in Sweden,[52] one successfully,[34] the other without achieving significant differences compared with the control group.[31] Two studies included the Assessing Care Of Vulnerable Elders (ACOVE) criteria[53] to measure underprescription. While Spinewine et al.[29] showed a marked improvement with the intervention (OR, 6.1; 95% CI 2.2–17), the improvement did not achieve statistical significance ($p = .739$) in the study by O'Sullivan et al.[43] The studies by Delgado-Silveira et al.[44] and Lipton et al.[27] reported a reduction in medication-related problems due to the intervention.

Among the 8 studies that measured the effect of the intervention on polypharmacy,[26,31,36–38,40,42,43] only 1 showed better results than those of the control group.[26]

Outcome variables

Seven of the studies analyzed the effect of the interventions on mortality after a follow-up period of 3[31,33] 6[35,38,39] or 12 months,[29,32] without conclusive results. The study by Michalek et al.[42] achieved a significant reduction in the number of falls in the intervention group (3.4% vs. 21.4%, $p < .001$) and an improved Barthel index, although that did not achieve statistical significance. In the study by Gallagher et al.,[35] the reduction in the prevalence of falls 6 months after the intervention did not reach statistical significance ($p = .332$).

Among the 6 studies that analyzed the influence on hospital readmissions at 3,[31,33,37] 6[35] or 12 months of admission,[29,32] only the study by Legrain et al.[37] achieved a statistically significant reduction (20.2% vs. 28.4%, $p = .01$). Among the 4 studies that quantified emergency department visits,[29,32,33,39] only the study by Gillespie et al.[32] achieved a 47% reduction at 1 year compared with the control group. None of the interventions achieved a significant reduction in hospital stays.[33,35,36,40]

In terms of the analysis of secondary costs, Gillespie et al.[32] showed a reduction of $400 (USD) per patient when compared with the control group. This savings was due to the reduction in expenses associated with readmissions and emergency department visits ($230 less per patient when taking into account the intervention costs). Legrain et al.[37] showed a reduction of €797; €519 per patient if the intervention cost was discounted.

Two studies measured the health-related quality of life using the EuroQol-5D questionnaire at 3[33] and 6 months.[34] Although the first study achieved no significant differences, the second showed an improvement in overall health, although not in the other parameters.

The main characteristics and results of the studies are listed in Table 2, which also shows the potential sources of bias.

Discussion

This review provides a summary of the evidence on various strategies for optimizing treatments for elderly hospitalized patients, aimed at reducing polypharmacy and improving therapeutic appropriateness, health results and the use of the healthcare system.

Among the analyzed variables, it is worth noting the good results regarding the improvement in therapeutic appropriateness, which appears to be independent of the personnel who perform the intervention and the type of intervention (except in the Bergqvist et al. study,[31] which used an educational approach).

Although the majority of studies managed to improve therapeutic appropriateness in one or more of the parameters, the results differed depending on the measurement method. While all of the studies that used the MAI scale or STOPP criteria achieved an improvement, the same was not true for studies using Beers, Priscus or ACOVE criteria. These results provide an introduction to the debate on the applicability and validity of measurement tools for appropriateness. The difficulty in applying these tools in settings other than those from where the tools originate (healthcare levels, countries) has been widely commented in the literature.[54–56] An example of this challenge is the use of the Beers criteria in the studies by Spinewine et al.[29] (Belgium) and O'Sullivan et al. (Ireland),[43] which were not able to detect positive results in terms of therapeutic appropriateness. The usefulness of the Beers criteria in the European setting is questionable[57]; however, the criteria are still widely used for being one of the first tools developed. The validity of the measurement methods for appropriateness has also been the subject of controversy, given that the process variables should be related to relevant health outcomes (mortality, morbidity, medication-related adverse events and quality of life) to be valid.[58] Although there are studies that show a significant association between the use of inappropriate medications (according to the Beers criteria) and the health outcomes in certain healthcare settings (residence and outpatient),[59–61] the use of inappropriate medications for hospitalized patients is not associated with a significant increase in the risk of adverse events,[62] the hospital stay or mortality.[63,64] The degree of therapeutic appropriateness measured with the MAI scale has been shown to be related to health outcomes in the primary care setting.[65,66] The use of inappropriate medications, according to the STOPP criteria, has been associated with the onset of adverse events in elderly hospitalized patients.[67] However, a study[68] showed that most medication-related problems in elderly patients who live in the community are not detected using STOPP or START criteria. A number of studies that compared the Beers and STOPP criteria seem to show a lower sensitivity for the former in detecting potentially inappropriate medications[69,70] or for preventing hospitalizations due to medication-related adverse events.[67]

In light of the fact that the available evidence on the predictive validity of explicit criteria is not definitive or the fact that the results can differ depending on the method of analysis employed, it is worth questioning the suitability of the measurement systems for therapeutic appropriateness being used and thus their published results. Given that the tools are employed both to measure results and to perform interventions, we should consider that the health endpoints can also be affected by this validity, especially if the intervention is based exclusively on detecting explicit criteria, as in the study by Gallagher et al.[35]

The use of explicit methods has numerous practical advantages (Appendix A), but interventions based on implicit methods (standardized or not) provide a broader vision on the patient's situation, their preferences, life expectancy and the fixed therapeutic objectives. A recent study[71] showed that a number of more significant causes for prescribers not modifying the treatment (according to the recommendations included in the STOPP/START criteria) are patient disability, dependence and risk of adverse events, variables that, in the elderly, can be much more important than survival itself. Regardless of the method employed, this type of information is important for adapting the intervention to each patient's needs. However, only 6[26,29,37,40–42] studies conducted a comprehensive geriatric assessment, and 8 studies did not record any information on the functional, cognitive and nutritional condition or on the presence

Table 2 Main characteristics and results of the studies.

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Owens 1990[26] USA	Controlled randomized	>75 years *n* = 436 (221/215) Women: 71% Mean age: 83.5/83	Medication review and recommendation to responsible team	3 months	Drug	No. of medications at day 3: 5.3 (I) vs. 5.9 (C) ($p < .05$). No differences at 6 weeks and 3 months Increase in the number of medications at day 3: 18% (I) vs. 40% (C) ($p < .005$) Medications with no apparent indication: 11% (I) vs. 19% (C) ($p < .025$) Inappropriate medications (potential adverse effects and availability of an alternative): 20% (I) vs. 37% (C) ($p < .005$)	
Owens 1992[27] USA	Controlled randomized	>65 years, 3 or more medications *n* = 236 (123/113) Women: 51%	Medication review and pharmacist counseling at discharge and for 3 months	3 months	Clinical pharmacists	Patients with MRP: 82% (I) vs. 93% (C) ($p = .05$) Patients with suboptimal or nonindicated medication: 51 (I) vs. 68 (C) ($p = .01$). Other categories (dosage or regimen problems, M–M interactions, duplication, allergies): ns Mean score differences for: prescription appropriateness: 0.59 (I) vs. 0.76 (C) ($p = .01$). Dosage: 0.09 (I) vs. 0.13 (C) ($p = .02$). Suboptimal or nonindicated: 0.17 (I) vs. 0.24 (C) ($p = .03$). Other categories: ns	
Schmader 2004[28] USA	Controlled randomized	>65 years and frailty criteria *n* = 834 Women: 3/2%	Geriatric assessment and intervention	12 months	Multidisciplinary team: geriatrician, social worker, nurse, pharmacist	(P) ADRs (events per 1000 days): 206 (I) vs. 64 (C). RR = 1.85 ($p = .0001$) Severe ADRs (events per 1000 days): 27 (I) vs. 15 (C) ($p = .93$) (S) Difference in change of: Unnecessary medications: −0.5 ($p < .0001$) MAI score: −5.4 ($p < .0001$) IM (Beers): −0.1 ($p = .03$) Medication underutilization (AOU): −0.3 ($p < .0001$)	

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Spinewine 2007[29] Belgium	Controlled randomized	>70 years *n* = 203(103/100) Women: 71.9/66.7% Mean age: 82.4/81.9	Medication review and recommendation to attending physician Patient interview and information	12 months	Clinical pharmacist	(P) Prescription appropriateness (at admission, at discharge and at 3 months): Change in mean MAI score per patient: decreases more in intervention group: 24.1−7.1 ($p < .001$), OR = 9.1 (95% CI 4.2−21.6) IM reduction (Beers): similar I−C, OR = 0.6 (95% CI 0.3−1.1) Mean change ACOVE criteria underutilization per patient: I decreases more; OR = 6.1 (95% CI 2.2−17) (S) Prevalence of unnecessary medications (MAI): decreases from 87.4% to 37.5% (I) and 77.8% (C) Mortality at 1 year: 22.5% (I) vs. 30.1% (C) ($p < .30$) Readmissions at 1 year: 32.6% (I) vs. 33.7% (C) ($p = 1.0$) Emergency department visits at 1 year: 7.9% (I) vs. 12% (C) ($p = .45$) Satisfied with information on medications received at 1 month: 80% vs. 60.9% ($p = .1$)	Blinding of evaluators to the results: unblinded evaluator Contamination: physicians who treated patients in the 2 groups
Bergkvist 2009[30] Sweden	Controlled nonrandom-ized	>65 years *n* = 43 (28/25) Women: 61/64% Mean age: 82/84	Medication review and discussion with multidisciplinary team	2 weeks after dis-charge	Drug	Change in MAI score (admission−discharge-after 2 weeks): ns Reduction in the no. of medications with inappropriate characteristics according to MAI: less in the intervention group ($p = .049$)	Random sequence generation: nonrandomized Hiding of the assignment: historical control Initial imbalance: control group was older and had more inappropriate drugs at the start

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Bergqvist 2009[31] Sweden	Controlled nonrandomized	>65 years *n* = 460(250/210) Women: 56/53% Mean age: 80.3	Nurse training in clinical pharmacology for MRP detection. Tools: SYM (Symptoms Assessment Form) and JWA (Janus Web Application)	3 months	Nurses	(P) Readmissions at 3 months: 38% (I) vs. 36% (C) (p = .86) (S) Proportion of inappropriate medications at discharge: ns Medication-related readmissions: ns Deaths: 24% (I) vs. 23.3% (C) (p = .91)	Random sequence generation: nonrandomized Hiding of the assignment: historical control Blinding of evaluators to the results: unblinded evaluator
Gillespie 2009[32] Sweden	Controlled randomized	>80 years *n* = 400 (199/201) Women: 58.7% Mean age: 86.6	Medication review and recommendation to responsible physician Patient counseling	12 months	Drug	Readmissions: 217 (I) vs. 223 (C) (Estimate = 0.97) Medication-related readmissions: 9 (I) vs. 45 (C) (estimate = 0.2) Reduction in emergency department visits: 47%; 49 (I) vs. 93 (C) (Estimate = 0.53) Difference readmissions + emergency department visits: 16%; 266 (I) vs. 316 (C) (Estimate = 0.84) Mortality at 1 year: 57 (I) vs. 61 (C) (p = .82) Overall cost reduction: $400/patient (I−C) Cost reduction by emergency department visits: $100/patient (I−C) Cost reduction by readmissions: $300/patient (I−C) Savings counting the cost of the intervention: $230/patient (I−C)	Contamination: I and C same ward

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Lisby 2010[33] Denmark	Controlled randomized	>70 years *n* = 99 (50/49) Women: 60/61% Mean age: 80.2/78.2	Systematic review of medication, with recommendations to the responsible physician and patient counseling	3 months	Pharmacist and clinical pharmacologist	(P) Hospital stay: 239.9 (I) vs. 238.6 (C) h ($p > .05$) (S) Time to readmission, no. of readmissions, emergency department and PC visits, death, health-related quality of life (EQ-5D): ns	Contamination: I and C same ward
Bladh 2011[34] Sweden	Controlled randomized	>80% participants > 65 years *n* = 345 Women: 61% Mean age: 82	Medication review (with MiniQ tool) and feedback with physicians Information at discharge	6 months	Clinical pharmacist	Change in health-related quality of life (EQ-5D) at 6 months: greater in overall health 3.14 (I) vs. 2.77 (C); $p = .02$, but not in other parameters PIP: decreases in intervention group 0.39 (admission) vs. 0.26 (discharge) ($p = .039$)	Blinding of evaluators to the results: unblinded evaluator Contamination: I and C same ward
Gallagher 2011[35] Ireland	Controlled randomized	>65 years *n* = 382: 190/192 Women: 53.2/53.1% Mean age: 74.5/77	STOPP/START detection and recommendation to attending physician	6 months	Medical researcher	(P) Patients with reduction in MAI admission–discharge score: 71.1% (I) vs. 35.4% (C) (ARR = 35.7%) Rate of unnecessary polypharmacy at discharge: 5.4% (I) vs. 19.8% (C) ($p < .001$) All MAI criteria differ significantly between I–C at discharge and at 6 months Mean MAI score decreases from 10 to 3 (I) ($p < .001$) and remains after 6 months ($p < .001$) Patients with AOU admission–discharge reduction: 31.6% (I) vs. 10.4% (C) (ARR = 21.2%) (S) Prevalence decreases after 6 months: 5.8% (I) vs. 8.4% (C) ($p = .332$) Mortality after 6 months: 5.3% (I) vs. 7.3% (C) ($p = .414$) Hospital stay: 8 (I) vs. 8.5 days (C) ($p = .471$) Readmission rate: 67 (I) vs. 64 (C) ($p = .691$) Fewer visits to PC physician ($p = .063$)	Blinding of evaluators to the results: unblinded evaluator

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Hellstrom 2011[36] Sweden	Controlled nonrandomized	>65 years (*n* = 210) Women: 60/51% Mean age: 83/81.8	Reconciliation, medication review and monitoring	3 months	Multidisciplinary team (includes clinical pharmacist)	Reduction in medicines with inappropriate characteristics (MAI): 51% vs. 39% ($p = .0446$) ITT; 60% vs. 44% ($p = .01$) PP Differences in mean MAI score per patient or drug at discharge: ns Medication-related readmissions or emergency department visits: 6 (I) vs. 12 (C) ($p = .0469$) Hospital stay: 16 vs. 13 days ($p = .09$)	Random sequence generation: nonrandomized Hiding of the assignment: historical control
Legrain 2011[37] France	Controlled randomized	>70 years *n* = 665 (317/348) Women: 69.7/62.6% Mean age: 86.1	Review of long-term therapy, patient education, reconciliation at discharge	6 months	Geriatrician researcher (different from regular medical team)	(P) Readmissions or emergency department visits at 3 months: 23% (I) vs. 30.5% (C) ($p = .03$) and 6 months: 35.3% (I) vs. 40.8% (C) ($p = .15$) Event-free survival at 3 months: longer in intervention group HR = 0.72 ($p = .03$); and at 6 months: HR = 0.81 ($p = .10$) (S) Readmissions at 3 months: 20.2% (I) vs. 28.4% (C) ($p = .01$); and at 6 months: 32.5 (I) vs. 38.2 (C) ($p = .12$). Mortality at 3 months: 12% (I) vs. 13.2% (C) ($p = .63$); and at 6 months: 17.7% (I) vs. 18.7% (C) ($p = .74$) Difference in cost at 6 months (I−C): €797/patient Savings including intervention cost: €519/patient	Incomplete data from results: 380 excluded after randomization
Bonnet-Zamponi 2012[38]						Medication-related readmissions: 34.7% vs. 40.4% ($p = .54$). No. of medications, polypharmacy, mean daily dose: ns Difference in cost due to medication-related readmissions: €392 vs. €953.5 per patient ($p = .13$)	Incomplete data from results: 380 excluded after randomization

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Hellstrom 2012[39] Sweden	Controlled nonrandomized	85% > 65 years *n* = 3974 (1216/2758) Women: 54.2/55.5% Mean age: 78.3/79.5	Reconciliation, medication review and monitoring	6 months	Clinical pharmacist	(P) Duration of emergency department visits/readmission: HR 0.95 ($p = .266$) (S) Event-free survival: HR = 0.96 ($p = .305$) Mean number of emergency department visits at 6 months: 1.02 (I) vs. 1.03 (C) ($p = .89$) Mortality at 6 months: 18.2% (I) vs. 17.3% (C) ($p = .55$) Mean number of PC visits: 1.58 (I) vs. 1.71 (C) ($p = .057$) Patients who visited PC: 68.5% (I) vs. 70.3% (C) ($p = .34$)	Random sequence generation: nonrandomized Hiding of the assignment: historical control Initial imbalance: intervention group younger than control group
Ghibelli 2013[40] Italy	Controlled nonrandomized	>65 years *n* = 134 (60/74) Women: 58.3/64.8% Mean age: 81.1/81.3	Intercheck® (computer support system for prescriptions)	Admission	Computer system	Reduction in number of patients with PIM (Beers) admission–discharge: 41.7–11.6% ($p < .001$) Mean reduction in PIM by patient admission–discharge: 0.5–0.1 ($p < .001$) Reduction in number of patients with potentially severe M–M interaction admission–discharge: 45–33.3% ($p = .703$) Reduction in new potentially severe M–M interactions: 59–33% ($p < .001$) Hospital stay: 10.4 (I) vs. 10.1 (C) days ($p = .84$)	Random sequence generation: nonrandomized Hiding of the assignment: historical control
Dalleur 2014[41] Belgium	Controlled randomized	>75 years Frail patients according to the ISAR scale and more than 3 medicines *n* = 146 (74/72) Women: 63% Mean age: 85	STOPP recommendations to responsible physician	12 months	Multidisciplinary team specialized in geriatric medicine	Reduction in PIM by STOPP criteria at discharge: 39.7% (I) vs. 19.3% (C) ($p = .013$)	

Table 2 (*Continued*)

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (*n*) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Michalek 2014[42] Germany	Controlled randomized	>70 years *n* = 114: 58/56 Mean age: 84/83	FORTA instrument and recommendations to attending physician	Admission	Physicians other than the one responsible	Patients with polypharmacy (>5 medications) at discharge: 84% (I) vs. 84% (C) ($p = .935$) Increases in control and intervention Category A FORTA medications at discharge: 4 vs. 3 ($p = .051$). Increases in both Over and underprescription: less in intervention group ($p = .03$ and $p = .025$) Patients with an increased Barthel index at discharge: 76% (I) vs. 71% (C) ($p < .226$) Patients with falls: 3.4% (I) vs. 21.4% (C) ($p < .001$) Proportion of falls/1000 patients/year: 1.5 (I) vs. 10.6 (C) days ($p = .004$)	
O'Sullivan 2014[43] Ireland	Uncontrolled	>65 years (*n* = 361) Women: 50.1% Median age: 77 years	Structured review of medication and computer support system for decision making	Admission	Drug	Reduction in MAI score from admission to discharge: 15–12 ($p < .001$). 59.3% patients with lower scores Change in underprescription by ACOVE criteria admission–discharge: 28.3–26.9% ($p = .739$) Median no. of medications: 9 at admission 12 at discharge Patients with 5 or more medications: 84.5% at admission and 95.8% at discharge 10 or more medications: 43.5% at admission and 66.8% at discharge Change in STOPP criteria admission–discharge: 62.4–55.5% patients ($p < .001$) Change in Beers CD criteria admission–discharge: 31.8–31.6% patients ($p = .282$) Change in Priscus criteria admission–discharge: 42.4–40.6% patients ($p = .421$) Change in START criteria admission–discharge: 31–31.5% patients ($p = .512$) Potential M–M interactions: 57.7% patients at admission and 63.9% at discharge ($p = .50$) Incorrect dosage in RF: 9.7% patients at admission and 7.2% at discharge ($p < .05$)	Blinding of evaluators from results: the evaluator is the same individual who performs the intervention

Table 2 *(Continued)*

Author Year Location	Study design	Population (I/C) Inclusion criteria Sample (n) % Women Age	Intervention	Follow-up time	Staff who performed the intervention	Results (P, primary variables; S, secondary variables)	High risk of bias (type: reason)
Delgado-Silveira 2015[44] Spain	Uncontrolled	>65 years, multiple diseases [85% hospitalized] n = 287 53.3% women (hospitalized) Mean age (hospitalized): 85	Pharmaceutical intervention (clinical judgment and Checkthemeds®) and attending physician's recommendation	Admission	Drug	MRP: 96.4% patients PI resolved 58.9% of the MRP (association PI-resolution; $p < .001$) PIP for START/STOPP: 65%	Blinding of evaluators from results: the individual who assesses the resolution of MRP is the one who performed the intervention

Abbreviations: AOU, assessment of underutilization of medication index; Beers CD, Beers criteria considering diagnosis; C, control group; HR, hazard ratio; I, intervention group; CI, confidence interval; PI, pharmaceutical intervention; M–M interactions, medication–medication interactions; RF, renal failure; ITT, intent-to-treat analysis; MAI, medical appropriateness index; IM, inappropriate medication; PC, primary care; PIM, potentially inappropriate medication; ns, not statistically significant; PP, per protocol analysis; PIP, potentially inappropriate prescriptions; MRP, medication-related problems; ADR, adverse drug reactions; RR, relative risk.

of geriatric syndromes.[27,30,31,33,34,36,39,44] Only the study by Legrain et al.[37] recorded the patients' preferences regarding their health. If the practitioners who conduct the intervention do not know these data, the recommendations for modifying the treatment will not correctly fit the patient's characteristics and will probably not be accepted by the prescriber.

Acceptance of these recommendations is essential to interpreting the endpoints, because the interventions need to result in treatment changes in order to affect the patient's health. Consequently, a low degree of acceptance of the recommendations can lead to a lack of improvement in the endpoints. The study by Lisby et al.,[33] for example, had a degree of acceptance of the recommendations of 39% and achieved no benefits in any of the study variables (hospital stay, readmissions, emergency department visits, mortality and quality of life). In contrast, those studies with a higher proportion of accepted recommendations achieved more noticeable improvements. The study by Gillespie et al.,[32] in which 77% of the recommendations were accepted, showed a reduction in emergency department visits. The study by Legrain et al.,[37] with an acceptance of 70.9%, hospital readmissions decreased significantly.

Other factors that could have affected the health outcomes are methodological, such as the low number of participants in a number of the studies and the studies' low power for detecting significant differences. The studies that had no statistically significant results in terms of mortality, readmissions or emergency department visits had not defined these variables as primary objectives.[29,33,35,39] Age is another factor worth considering. The studies with better health outcomes were those whose participants had a higher mean age,[32,37] which suggests that patients with greatest risk and frailty are the ones most likely to benefit from strategies that optimize the drug therapy.

In terms of the impact of interventions on other significant variables such as quality of life and financial savings, it is difficult to make relevant conclusions, given the little evidence provided by the analyzed studies.

The results of this review are similar to those of other published studies. Various reviews have been conducted on the drug treatment optimization in elderly patients, not focused on the hospital setting. Two of these studies concluded that some interventions with different approaches (educational, treatment reviews, geriatric services, multidisciplinary teams, computer support systems, etc.) can improve the degree of therapeutic appropriateness.[72,73] In the review by Patterson et al.[74], the impact of these interventions on clinical outcomes was uncertain, although benefits were demonstrated in terms of reducing inappropriate prescriptions. In the study by Holland et al.,[75] which examined the impact of treatment reviews performed by pharmacists on hospitalizations and mortality, also found no positive effect on these parameters. On the other hand, we found reviews on hospitalized patients, although not specifically elderly, such as the study by Christensen et al.[76] focusing on medical reviews, which show a reduction in emergency department visits, with no influence on mortality or hospital readmissions. Similarly, Graabaek et al.,[77] in a recent systematic review of medication reviews performed by clinical pharmacists, indicated a positive effect in the use and cost of medications and a number of improvements in

the use of healthcare resources, which was not statistically significant.

In terms of the bias of the included studies, the fact that the evaluator of the results knew which group each patient belonged to was a high risk of bias. Given the presence of several nonrandomized studies, the risks of associated bias were also frequent.

Future research should be aimed at checking the validity of the tools for measuring and improving therapeutic appropriateness, which confer a greater reliability to the studies and a greater impact of interventions for optimizing therapeutic appropriateness on health outcomes. Moreover, quality controlled clinical trials need to be developed, with sufficient sample sizes and with the necessary methodological quality to detect the expected impact on clinical variables such as hospital readmissions, emergency department visits and quality of life.

Conclusions

The analyzed studies show that the therapeutic appropriateness of elderly hospitalized patients can be improved by interventions with various approaches (systematic treatment reviews, support software for decision making and detection of explicit criteria of inappropriate prescription), implemented by various practitioners (clinical pharmacists, geriatricians, multidisciplinary teams, etc.). However, there is significant variability in the endpoints. The role of these interventions in health outcomes (the consequences for patients, healthcare system and society) is uncertain.

We need to address the applicability and validity of the tools that assess therapeutic appropriateness to obtain more reliable results with greater impact on health. Explicit criteria for optimizing treatments should not be considered the gold standard, and their implementation should preferably be combined with implicit methods so as to address especially important issues for elderly patients, such as the sociofamiliar context, functional and cognitive conditions and life expectancy.

The clinical variables for elderly patients should be properly selected, given that the therapeutic objectives are often different, and the functional aspects or those related to quality of life can be more important in this population than others, such as mortality. The selection of objectives can benefit from consensus in multidisciplinary teams that include a comprehensive geriatric assessment.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

The authors would like to thank the Hospital Complex of Navarra and the Miguel Servet Foundation for the assistance provided and the grant of the Specialized Healthcare Post-training Program.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rceng.2016.01.004.

References

1. Thomsen LA, Winterstein AG, Sondergaard B, Haugbolle LS, Melander A. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. Ann Pharmacother. 2007;41:1411–26.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200–5.
3. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1997;277:301–6.
4. Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. J Am Pharm Assoc (Wash). 2001;41:192–9.
5. Field TS, Gilman BH, Subramanian S, Fuller JC, Bates DW, Gurwitz JH. The costs associated with adverse drug events among older adults in the ambulatory setting. Med Care. 2005;43:1171–6.
6. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57:6–14.
7. ElDesoky ES. Pharmacokinetic–pharmacodynamic crisis in the elderly. Am J Ther. 2007;14:488–98.
8. Molina Lopez T, Caraballo Camacho ML, Palma Morgado D, Lopez Rubio S, Dominguez Camacho JC, Morales Serna JC. Prevalencia de polimedicación y riesgo vascular en la población mayor de 65 años. Aten Primaria. 2012;44:216–22.
9. Proupín Vázquez N, Aparicio Ruiz M, Garea Sarandeses P, Segade Buceta X, Arceo Túñez A, López Rodríguez L. Resumen de polimedicación en pacientes adultos con dolencias crónicas en un centro de salud. Cad Aten Primaria. 2008;15:275–9.
10. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother. 2007;5:345–51.
11. Goldberg RM, Mabee J, Chan L, Wong S. Drug–drug and drug–disease interactions in the ED: analysis of a high-risk population. Am J Emerg Med. 1996;14:447–50.
12. Leal Hernandez M, Abellan Aleman J, Casa Pina MT, Martinez Crespo J. Paciente polimedicado: ¿conoce la posología de la medicación?, ¿afirma tomarla correctamente? Aten Primaria. 2004;33:451–6.
13. Gomez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-Leon J. Polypharmacy in the elderly: a marker of increased risk of mortality in a population-based prospective study (NEDICES). Gerontology. 2015;61:301–9.
14. Perez Menendez-Conde C, Bermejo Vicedo T, Delgado Silveira E, Carretero Accame E. Resultados negativos asociados al uso de medicamentos que motivan ingreso hospitalario. Farm Hosp. 2011;35:236–43.
15. Ministerio de Sanidad y Consumo. Estudio Nacional de Efectos Adversos ligados a la hospitalización ENEAS 2005.
16. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci. 2002;24:46–54.
17. Krumholz HM. Post-hospital syndrome – an acquired, transient condition of generalized risk. N Engl J Med. 2013;368:100–2.
18. Lafont C, Gerard S, Voisin T, Pahor M, Vellas B. Reducing «iatrogenic disability» in the hospitalized frail elderly. J Nutr Health Aging. 2011;15:645–60.

19. Tosato M, Landi F, Martone AM, Cherubini A, Corsonello A, Volpato S, et al. Potentially inappropriate drug use among hospitalised older adults: results from the CRIME study. Age Ageing. 2014;43:767–73.
20. Sganga F, Landi F, Vetrano DL, Corsonello A, Lattanzio F, Bernabei R, et al. Impact of hospitalization on modification of drug regimens: results of the criteria to assess appropriate medication use among elderly complex patients study. Geriatr Gerontol Int. 2015, doi:10.1111/ggi.12517 [in press].
21. Martin MT, Codina C, Tuset M, Carne X, Nogue S, Ribas J. Problemas relacionados con la medicación como causa de ingreso hospitalario. Med Clin (Barc). 2002;118:205–10.
22. Gallagher P, Lang PO, Cherubini A, Topinková E, Cruz-Jentoft A, Montero Errasquín B, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. Eur J Clin Pharmacol. 2011;67:1175–88.
23. Hortal Carmona J, Aguilar Cruz I, Parrilla Ruiz F. Un modelo de deprescripción prudente. Med Clin (Barc). 2015;144:362–9.
24. Brook RH. Quality – can we measure it. N Engl J Med. 1977;296:170–2.
25. EPOC. Cochrane effective practice and organisation of care review group. Oslo: Norwegian Knowledge Centre for the Health Services; 2015.
26. Owens NJ, Sherburne NJ, Silliman RA, Fretwell MD, The Senior Care Study. The optimal use of medications in acutely ill older patients. J Am Geriatr Soc. 1990;38:1082–7.
27. Lipton HL, Bero LA, Bird JA, McPhee SJ. The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing. A randomized controlled trial. Med Care. 1992;30:646–58.
28. Schmader KE, Hanlon JT, Pieper CF, Sloane R, Ruby CM, Twersky J, et al. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. Am J Med. 2004;116:394–401.
29. Spinewine A, Swine C, Dhillon S, Lambert P, Nachega JB, Wilmotte L, et al. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. J Am Geriatr Soc. 2007;55:658–65.
30. Bergkvist A, Midlöv P, Höglund P, Larsson L, Eriksson T. A multi-intervention approach on drug therapy can lead to a more appropriate drug use in the elderly. LIMM-Landskrona Integrated Medicines Management. J Eval Clin Pract. 2009;15:660–7.
31. Bergqvist M, Ulfvarson J, Karlsson EA. Nurse-led medication reviews and the quality of drug treatment of elderly hospitalized patients. Eur J Clin Pharmacol. 2009;65:1089–96.
32. Gillespie U, Alassaad A, Henrohn D, Garmo H, Hammarlund-Udenaes M, Toss H, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. Arch Intern Med. 2009;169:894–900.
33. Lisby M, Thomsen A, Nielsen LP, Lyhne NM, Breum-Leer C, Fredberg U, et al. The effect of systematic medication review in elderly patients admitted to an acute ward of internal medicine. Basic Clin Pharmacol Toxicol. 2010;106:422–7.
34. Bladh L, Ottosson E, Karlsson J, Klintberg L, Wallerstedt SM. Effects of a clinical pharmacist service on health-related quality of life and prescribing of drugs: a randomised controlled trial. BMJ Qual Saf. 2011;20:738–46.
35. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clin Pharmacol Ther. 2011;89:845–54.
36. Hellström LM, Bondesson A, Höglund P, Midlöv P, Holmdahl L, Rickhag E, et al. Impact of the Lund Integrated Medicines Management (LIMM) model on medication appropriateness and drug-related hospital revisits. Eur J Clin Pharmacol. 2011;67:741–52.
37. Legrain S, Tubach F, Bonnet-Zamponi D, Lemaire A, Aquino JP, Paillaud E, et al. A new multimodal geriatric discharge-planning intervention to prevent emergency visits and rehospitalizations of older adults: the optimization of medication in AGEd multicenter randomized controlled trial. J Am Geriatr Soc. 2011;59:2017–28.
38. Bonnet-Zamponi D, d'Arailh L, Konrat C, Delpierre S, Lieberherr D, Lemaire A, et al. Drug-related readmissions to medical units of older adults discharged from acute geriatric units: results of the optimization of medication in AGEd multicenter randomized controlled trial. J Am Geriatr Soc. 2013;61:113–21.
39. Hellstrom LM, Hoglund P, Bondesson A, Petersson G, Eriksson T. Clinical implementation of systematic medication reconciliation and review as part of the Lund Integrated Medicines Management model – impact on all-cause emergency department revisits. J Clin Pharm Ther. 2012;37:686–92.
40. Ghibelli S, Marengoni A, Djade CD, Nobili A, Tettamanti M, Franchi C, et al. Prevention of inappropriate prescribing in hospitalized older patients using a computerized prescription support system (INTERcheck (R)). Drugs Aging. 2013;30:821–8.
41. Dalleur O, Boland B, Losseau C, Henrard S, Wouters D, Speybroeck N, et al. Reduction of potentially inappropriate medications using the STOPP criteria in frail older inpatients: a randomised controlled study. Drugs Aging. 2014;31:291–8.
42. Michalek C, Wehling M, Schlitzer J, Frohnhofen H. Effects of «Fit fOR The Aged» (FORTA) on pharmacotherapy and clinical endpoints – a pilot randomized controlled study. Eur J Clin Pharmacol. 2014;70:1261–7.
43. O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, Cullinan S, O'Sullivan R, et al. The impact of a structured pharmacist intervention on the appropriateness of prescribing in older hospitalized patients. Drugs Aging. 2014;31:471–81.
44. Delgado Silveira E, Fernandez-Villalba EM, García-Mina Freire M, Albiñana Pérez MS, Casajús Lagranja MP, Peris Martí JF. Impacto de la intervención farmacéutica en el tratamiento del paciente mayor pluripatológico. Farm Hosp. 2015;39:192–202.
45. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992;45:1045–51.
46. Samsa GP, Hanlon JT, Schmader KE, Weinberger M, Clipp EC, Uttech KM, et al. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. J Clin Epidemiol. 1994;47:891–6.
47. Kuhn-Thiel AM, Weiss C, Wehling M. Consensus validation of the FORTA (Fit fOR The Aged) List: a clinical tool for increasing the appropriateness of pharmacotherapy in the elderly. Drugs Aging. 2014;31:131–40.
48. Jeffery S, Ruby C, Twersky J, Hanlon J. Effect of an interdisciplinary team on suboptimal prescribing in a long-term care facility. Consult Pharm. 1999;14:1386–91.
49. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. Arch Intern Med. 1997;157:1531–6.
50. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163:2716–24.
51. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46:72–83.
52. Swedish National Board of Health and Welfare (Socialstyrelsen). Indikatorer för utvärdering av kvaliteten i äldres läkemedelsterapi [*Indicators for evaluation of the quality of drug yse in the elderly*]; 2003.
53. Wenger NS, Shekelle PG. Assessing care of vulnerable elders: ACOVE project overview. Ann Intern Med. 2001;135:642–6.

54. Budnitz DS. Inappropriate medication use in hospitalized older adults – is it time for interventions? J Hosp Med. 2008;3: 87–90.
55. Page RL, Linnebur SA, Bryant LL, Ruscin JM. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. Clin Interv Aging. 2010;5:75–87.
56. Lam MP, Cheung BM. The use of STOPP/START criteria as a screening tool for assessing the appropriateness of medications in the elderly population. Expert Rev Clin Pharmacol. 2012;5:187–97.
57. O'Connor MN, Gallagher P, O'Mahony D. Inappropriate prescribing: criteria, detection and prevention. Drugs Aging. 2012;29:437–52.
58. Pronovost PJ, Nolan T, Zeger S, Miller M, Rubin H. How can clinicians measure safety and quality in acute care? Lancet. 2004;363:1061–7.
59. Perri M, Menon AM, Deshpande AD, Shinde SB, Jiang R, Cooper JW, et al. Adverse outcomes associated with inappropriate drug use in nursing homes. Ann Pharmacother. 2005;39:405–11.
60. Chang CM, Liu PY, Yang YH, Yang YC, Wu CF, Lu FH. Use of the Beers criteria to predict adverse drug reactions among first-visit elderly outpatients. Pharmacotherapy. 2005;25:831–8.
61. Lau DT, Kasper JD, Potter DE, Lyles A, Bennett RG. Hospitalization and death associated with potentially inappropriate medication prescriptions among elderly nursing home residents. Arch Intern Med. 2005;165:68–74.
62. Laroche ML, Charmes JP, Nouaille Y, Fourrier A, Merle L. Impact of hospitalisation in an acute medical geriatric unit on potentially inappropriate medication use. Drugs Aging. 2006;23:49–59.
63. Onder G, Landi F, Liperoti R, Fialova D, Gambassi G, Bernabei R. Impact of inappropriate drug use among hospitalized older adults. Eur J Clin Pharmacol. 2005;61:453–9.
64. Page RL, Ruscin JM. The risk of adverse drug events and hospital-related morbidity and mortality among older adults with potentially inappropriate medication use. Am J Geriatr Pharmacother. 2006;4:297–305.
65. Lund BC, Carnahan RM, Egge JA, Chrischilles EA, Kaboli PJ. Inappropriate prescribing predicts adverse drug events in older adults. Ann Pharmacother. 2010;44:957–63.
66. Schmader KE, Hanlon JT, Landsman PB, Samsa GP, Lewis IK, Weinberger M. Inappropriate prescribing and health outcomes in elderly veteran outpatients. Ann Pharmacother. 1997;31:529–33.
67. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med. 2011;171:1013–9.
68. Verdoorn S, Kwint HF, Faber A, Gussekloo J, Bouvy ML. Majority of drug-related problems identified during medication review are not associated with STOPP/START criteria. Eur J Clin Pharmacol. 2015;71:1255–62.
69. Ryan C, O'Mahony D, Kennedy J, Weedle P, Byrne S. Potentially inappropriate prescribing in an Irish elderly population in primary care. Br J Clin Pharmacol. 2009;68:936–47.
70. Conejos Miquel MD, Sánchez Cuervo M, Delgado Silveira E, Sevilla Machuca I, González-Blazquez S, Montero Errasquin B, et al. Potentially inappropriate drug prescription in older subjects across health care settings. Eur Geriatr Med. 2010;1:9–14.
71. Lozano-Montoya I, Velez-Diaz-Pallares M, Delgado-Silveira E, Montero-Errasquin B, Cruz Jentoft AJ. Potentially inappropriate prescribing detected by STOPP–START criteria: are they really inappropriate? Age Ageing. 2015;44:861–6.
72. Kaur S, Mitchell G, Vitetta L, Roberts MS. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. Drugs Aging. 2009;26:1013–28.
73. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;370:173–84.
74. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2014;10:CD008165.
75. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. Br J Clin Pharmacol. 2008;65:303–16.
76. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev. 2013;2:Cd008986.
77. Graabaek T, Kjeldsen LJ. Medication reviews by clinical pharmacists at hospitals lead to improved patient outcomes: a systematic review. Basic Clin Pharmacol Toxicol. 2013;112: 359–73.

Gutiérrez-Valencia, M, Izquierdo, M, Beobide-Telleria, I, et al. Medicine optimization strategy in an acute geriatric unit: The pharmacist in the geriatric team. Geriatr. Gerontol. Int. 2019; 19: 530– 536. https://doi.org/10.1111/ggi.13659