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**VNiVERSiDAD
D SALAMANCA**

**Educational Intervention and Development of a Tool to
Improve the Use of Potentially Inappropriate
Medication in Older Adults**

TESIS DOCTORAL

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**VNiVERSiDAD
D SALAMANCA**

**Educational Intervention and Development of a Tool to
Improve the Use of Potentially Inappropriate
Medication in Older Adults**

Trabajo presentado para optar al Grado de Doctor en Farmacia por la Universidad de Salamanca por:

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CERTIFICAN:

Que Dña. **Daniela Almeida Rodrigues** ha realizado bajo su dirección el trabajo titulado **“Educational Intervention and Development of a Tool to Improve the Use of Potentially Inappropriate Medication in Older Adults”**, y que autorizan su presentación en el formato de **Compendio de artículos**, para optar al Grado de Doctor por la Universidad de Salamanca, al considerar que se han alcanzado los objetivos inicialmente previstos.

Y para que conste, firman el presente certificado en Salamanca, a veintiocho de Julio de dos mil veinticinco.

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Dedicación

A mis queridos padres y abuelos, por su amor incondicional, apoyo inagotable y por creer siempre en mí. A mis amigos, por su compañía y aliento en los momentos difíciles y en los de alegría. A mis profesores y mentores, por su guía, sabiduría y paciencia. Esta tesis es tanto mía como vuestra.

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PRÓLOGO

El trabajo de doctorado desarrollado y presentado en esta tesis constituye una parte del plan de trabajo de una beca de investigación financiada por la Fundação para a Ciência e a Tecnologia (FCT) titulada “Educational intervention to reduce potentially inappropriate medications prescription in older adults” (2022.10605.BD).

La tesis aquí presentada refleja el trabajo de doctorado desarrollado y se estructura de manera que permita comprender el contexto, el enfoque metodológico adoptado, así como los principales resultados obtenidos.

En la **introducción** se contextualiza el problema de Salud Pública que representan actualmente los medicamentos potencialmente inapropiados (PIM) en la población mayor, destacando su prevalencia, consecuencias clínicas y la necesidad urgente de estrategias de intervención eficaces para optimizar la prescripción en este grupo etario.

A continuación, se presenta el **objetivo principal** y **objetivos específicos** del estudio, que guiaron el desarrollo del proyecto.

Los **7 capítulos** siguientes incluyen los distintos trabajos llevados a cabo, de los cuales se derivan 4 artículos ya publicados, 1 capítulo de libro aceptado para publicación, y 1 artículo actualmente en proceso de sumisión a una revista científica indexada.

Por último, se presenta una **discusión** crítica de los hallazgos obtenidos, las principales **conclusiones** del proyecto y las posibles líneas de investigación futura en el ámbito de la mejora de la adecuación terapéutica en adultos mayores.

Índex

RESUMEN GENERAL	12
INTRODUCCIÓN	12
JUSTIFICACIÓN Y ESQUEMA DE LA TESIS	19
RESULTADOS.....	21
DISCUSIÓN	24
CONCLUSIONES	28
BIBLIOGRAFÍA	29
ABSTRACT.....	35
I. INTRODUCTION	38
1. Polypharmacy	40
2. Potentially Inappropriate Medication	43
2.1. Criteria for Potentially Inappropriate Medication Identification	44
3. Challenges in Managing Appropriate Medication Use in Older Adults	47
3.1. Limitations in Clinical Guidelines and Prescribing Practices	47
3.2. Barriers to Effective Communication and Care Coordination	48
3.3. Health Literacy and Medication Adherence	49
3.4. Sociodemographic and Sociocultural Factors	49
4. Primary Healthcare for Older Adults: Current Challenges and Emerging Opportunities	50
5. Digital Technologies for Medication Management of Older Adults in Primary Care.....	51
II. OBJECTIVES.....	68
III. Effectiveness of Interventions to Reduce Potentially Inappropriate Medication in Older Patients: A Systematic Review	70
IV: Barriers and facilitators of health professionals in adopting digital health-related tools for medication appropriateness: A systematic review.....	102
V. Comparing AGS Beers 2019, STOPP version 2, and EU(7)-PIM list in Portuguese older adults in primary health care.....	140

<i>VI. Usability of APIMedOlder: A Web Application to Manage Potentially Inappropriate Medication in Older Adults</i>	170
<i>VII. Exploring the impact of APIMedOlder web-based application: a retrospective analysis of searches made by healthcare professionals</i>	180
<i>VIII. Understanding potentially inappropriate medication: A focus group study with general practitioners</i>	194
<i>IX. Reducing Potentially Inappropriate Prescriptions Through a Multifaceted Intervention: a Nonrandomized Cluster-Control Based Intervention</i>	210
X. DISCUSSION	231
REFERENCES	239
XI. CONCLUSIONS AND FUTURE DIRECTIONS	242
APPENDIX	244
A. Presented communications related to the PhD project	245
B. Event organization related to the PhD project	249
C. Additional Thesis-Related Publications	251
D. Authorization from the Health Ethics Committee of the Regional Health Administration (ARS) of the Centre for the Implementation of the Educational Interventions (Proc. 37/2022)	253
E. Authorization from the Ethics Committee of the Polytechnic Institute of Guarda (IPG) for the Implementation of the Usability Study of the APIMedOlder Web Application (No. 3/2022)	255
F. Authorization from the Ethics Committee of the Regional Health Administration (ARS) of the North for the Implementation of the Focus Group Study (Ref: CE/2023/70)	257
G. Email Confirming Acceptance for Publication – Book Chapter “Exploring the Impact of APIMedOlder Web-Based Application: A Retrospective Analysis of Searches Made by Healthcare Professionals”	260
H. Poster for the Dissemination of the Educational Intervention	262
I. Flyer for the Dissemination of the Educational Intervention	264
J. Educational Material for the Intervention	266

Tables

Table 1: Ageing Index by Place of Residence in Portugal [6].....38

List of Acronyms

Adverse Drug Reactions (ADRs)

American Geriatrics Society (AGS)

Regional Health Administration of the Centre (Administração Regional de Saúde do Centro – ARSC)

Clinical Decision Support Systems (CDSS)

Confidence Interval (CI)

Defined Daily Dose (DDD)

Drug-Drug Interactions (DDIs)

Defined Daily Doses per 1000 inhabitants per day (DID)

Deoxyribonucleic acid (DNA)

Electronic Health Records (EHRs)

General Practitioners (GPs)

International Normalized Ratio (INR)

Medication Appropriateness Index (MAI)

National Health Service (NHS)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Nomenclature of Territorial Units for Statistical Purposes (Nomenclatura das Unidades Territoriais para Fins Estatísticos – NUTS)

Potentially Inappropriate Medication (PIM)

Proton Pump Inhibitors (PPIs)

Screening Tool of the Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START)

System Usability Scale (SUS)

Local Health Units (Unidades Locais de Saúde – ULS)

United States of America (USA)

World Health Organization (WHO)

RESUMEN GENERAL

INTRODUCCIÓN

El envejecimiento se refiere al declive gradual de las funciones fisiológicas y cognitivas a lo largo del tiempo, esenciales para la supervivencia y reproducción [1]. La mejora de las condiciones de vida, el estatus socioeconómico y la atención médica han aumentado la esperanza de vida humana, lo que ha llevado a un cambio demográfico global hacia una población envejecida [2]. Se espera que la población mundial de adultos mayores de 65 años aumente más del doble, pasando de 761 millones en 2021 a 1.6 mil millones en 2050 [3]. Portugal es uno de los diez países con mayor proporción de personas mayores, con un porcentaje de adultos mayores que se incrementará del 22.6% en 2021 al 34.5% en 2050 [3].

El envejecimiento conlleva un deterioro progresivo de las funciones fisiológicas y cognitivas, lo que altera, significativamente, la farmacocinética y farmacodinámica de los medicamentos. Se incluyen el deterioro de la función renal y hepática, alteraciones en la composición corporal y una mayor sensibilidad a los medicamentos, lo que aumenta el riesgo de efectos adversos [4–7]. A pesar de ser los principales usuarios de medicamentos, los adultos mayores siguen estando poco representados en los ensayos clínicos, lo que limita la evidencia disponible sobre la seguridad y eficacia de muchos tratamientos en esta población [8]. El envejecimiento también conlleva un aumento de la multimorbilidad lo que conduce al uso de múltiples medicamentos, dando lugar a la polifarmacia definida, comúnmente, como el uso simultáneo de cinco o más medicamentos [9,10]. Aunque la polifarmacia puede ser necesaria, también aumenta el riesgo de resultados negativos para la salud, como reacciones adversas a los medicamentos, interacciones medicamentosas, disminución de la adherencia, mayor riesgo de caídas y hospitalizaciones relacionadas con medicamentos, deterioro cognitivo y mayor mortalidad. [11,12].

La polifarmacia es un problema común entre los adultos mayores. Su prevalencia ha aumentado considerablemente en las últimas décadas debido al envejecimiento de la población y los avances en la atención médica [13]. La prevalencia global de polifarmacia y hiperpolifarmacia (uso de 10 o más medicamentos) en la población mayor es del 39.1% y 13.3%, respectivamente, con Europa registrando una de las tasas más altas [14]. En Portugal, la prevalencia alcanza el 51,3% [15].

Los factores de riesgo incluyen la edad avanzada, comorbilidades, y un estado de salud autopercibido pobre, entre otros [16]. El aumento de la polifarmacia eleva la frecuencia y variedad de reacciones adversas y de interacciones medicamentosas [17]. A medida que aumenta el número de medicamentos prescritos, también lo hace el riesgo de sufrir efectos adversos [18]. La polifarmacia puede también afectar los perfiles farmacocinéticos de los medicamentos, como ocurre cuando múltiples fármacos compiten por los mismos sitios de unión a proteínas plasmáticas [19]. La polifarmacia está asociada con un mayor riesgo de hospitalizaciones, ya que las reacciones adversas a los medicamentos son una causa importante de visitas a urgencias y admisiones hospitalarias en esta población [12,20]. También está vinculada a un aumento en la tasa de caídas, que a su vez puede llevar a fracturas, pérdida de movilidad y discapacidad [21]. Además, se asocia con deterioro cognitivo, con un riesgo más alto en aquellos que toman cinco o más medicamentos [22]. La no adherencia al tratamiento es otro desafío, especialmente cuando los adultos mayores tienen limitaciones cognitivas o físicas [23,24].

La prevalencia del uso de Medicamentos Potencialmente Inapropiados (PIM) en los adultos mayores es una preocupación significativa en los sistemas de salud a nivel mundial. El uso de PIM afecta entre el 9.4% y el 81.0% de los adultos mayores, dependiendo del entorno y los criterios utilizados, siendo la prevalencia media de PIM en adultos de 65 años o más del 27.8% [25]. En los servicios ambulatorios, la prevalencia de PIM es del 36.7%, siendo más alta en África (47.0%) y América del Sur (46.9%) [26]. En los hogares de ancianos, la prevalencia de PIM es del 43.2%, con tasas más altas en los países europeos [27]. Los PIM pueden afectar negativamente la salud funcional de los adultos mayores, con un número acumulado de PIM correlacionado con una mayor dependencia para realizar actividades diarias tras el alta hospitalaria [28]. Además, su uso está vinculado a un mayor riesgo de caídas y fracturas, y algunas clases de PIM, como los antipsicóticos y los sedantes, se asocian con un mayor riesgo de deterioro cognitivo [29]. El uso de PIM está influenciado por factores como el nivel educativo bajo, vivir en circunstancias socioeconómicas desfavorecidas, la presencia de polifarmacia, múltiples problemas de salud, y el estilo de vida poco saludable [30,31].

La identificación de PIM en adultos mayores es crucial para mejorar las prácticas de prescripción. Existen varias herramientas desarrolladas para ayudar a los clínicos a evaluar la idoneidad de los medicamentos, que se clasifican en criterios explícitos, implícitos y mixtos [32]. Los criterios explícitos se basan en reglas y listas de medicamentos o grupos de

medicamentos que, generalmente, deben evitarse en adultos mayores, como los Beers Criteria, la EU(7)-PIM list y el Screening Tool of the Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) [32–35]. Los criterios implícitos requieren juicio clínico y la opinión de expertos para evaluar las condiciones y medicamentos específicos de cada paciente, como el Medication Appropriateness Index (MAI) [32,36,37]. Los criterios mixtos combinan elementos de ambos enfoques, ofreciendo una evaluación más completa [38]. Un ejemplo de esta combinación son los Australian Prescribing Appropriateness Criteria [39].

Entre las herramientas más conocidas se encuentran los Criterios de Beers, que fueron introducidos en 1991 para ayudar a los profesionales de la salud a evaluar las prescripciones en pacientes mayores [40]. Estos criterios se actualizan periódicamente, y son ampliamente utilizados, aunque se desarrollaron en Estados Unidos. En Europa, en 2008, se desarrollaron los criterios STOPP/START, que incluyen listas de medicamentos inapropiados y subprescritos para adultos mayores [41]. En 2015 se introdujo la lista EU(7)-PIM, elaborada por expertos de siete países europeos, que aborda los medicamentos inapropiados basándose en la evidencia clínica de los riesgos y alternativas más seguras para los adultos mayores [35]. Esta lista tiene en cuenta los sistemas de salud y las prácticas de prescripción de los países participantes.

Entre las ventajas de la lista EU(7)-PIM destaca su utilidad para identificar PIM en personas mayores, facilitando comparaciones internacionales y estudios multicéntricos [35,42]. Su estructura permite su uso en bases de datos clínicas y administrativas, apoyando el análisis automatizado y la evaluación de intervenciones [35]. En 2020, fue adaptada al contexto portugués mediante la revisión de medicamentos autorizados y la inclusión de sustancias adicionales, resultando en una versión final con 184 PIM, lo que refuerza su relevancia [43].

Los desafíos en la gestión de la polifarmacia y la prescripción de medicamentos inapropiados se deben a varios factores, como las limitaciones en la formación específica de los clínicos, la falta de directrices específicas para adultos mayores, y la complejidad de evaluar los beneficios frente a los riesgos de tratamiento [44,45]. Además, la falta de revisiones regulares de medicamentos y la tendencia a continuar con tratamientos tolerables sin considerar la interrupción de los mismos, pueden aumentar el riesgo de exposición a medicamentos inapropiados [45,46]. También la falta de comunicación entre diferentes proveedores de

atención médica y la dificultad de acceso a servicios de salud contribuyen a estos problemas [44,47].

Los Centros de salud de Atención Primaria son el primer punto de contacto, especialmente para los adultos mayores, con médicos de familia asignados a cada ciudadano, quienes ofrecen atención personalizada y continua [48]. Juegan un papel clave en la gestión de la multimorbilidad y la polifarmacia, ayudando a abordar los PIM y garantizando el uso seguro de las terapias [48]. Además, los médicos de atención primaria (GP) a menudo trabajan en equipo con otros profesionales de la salud, como farmacéuticos y enfermeros, para proporcionar una atención integral [49].

La integración de tecnologías innovadoras, como los registros de salud electrónicos (EHRs), la prescripción electrónica (e-prescribing) y los sistemas de apoyo a la decisión clínica (CDSS), está transformando la gestión de medicamentos [50,51]. Estas herramientas ayudan a los GP a identificar medicamentos inapropiados, prevenir interacciones y ajustar dosis de manera personalizada [52,53]. También permiten optimizar los recursos y mejorar la eficiencia en la atención, además de ayudar en la identificación de oportunidades para la desprescripción de medicamentos innecesarios [54].

Para que estas herramientas digitales tengan un impacto real en la mejora del uso de medicamentos y en los resultados de salud de las personas mayores, es fundamental asegurar su integración exitosa en la atención primaria mediante la participación de los actores implicados, el fortalecimiento de la infraestructura, el apoyo y la formación profesional, el desarrollo de regulaciones claras y estándares de buenas prácticas, así como una atención prioritaria a la seguridad del paciente, la privacidad y la equidad [55]. La investigación aplicada es clave para entender cómo implementar estas herramientas de forma eficaz en la práctica clínica.

Esta tesis de doctorado se centra en el desarrollo, implementación y evaluación de una intervención dirigida a médicos de atención primaria en Portugal, con el objetivo de mejorar la adecuación de la prescripción en adultos mayores mediante el uso de una herramienta digital: APIMedOlder.

OBJETIVOS

Considerando el alto consumo de medicamentos por parte de los pacientes mayores en Portugal, el objetivo principal es reducir la prescripción de PIM en esta población (≥ 65 años) mediante una intervención dirigida a médicos de atención primaria de las Unidades Locales de Salud (Unidades Locais de Saúde - ULS), bajo la Administración Regional de Salud del Centro (Administração Regional de Saúde do Centro - ARSC).

Los objetivos específicos son:

- i. revisar sistemáticamente la literatura para analizar y sintetizar la evidencia sobre intervenciones diseñadas para reducir la prescripción y el uso de PIM en adultos mayores;
- ii. revisar y analizar sistemáticamente los estudios publicados para identificar las barreras y facilitadores que influyen en los profesionales de la salud en la adopción de herramientas digitales para mejorar la adecuación de la medicación;
- iii. determinar la prevalencia del uso de PIM en personas mayores según los criterios Beers 2019, STOPP v2 y la lista portuguesa EU(7)-PIM, y analizar el nivel de concordancia entre estas herramientas;
- iv. desarrollar una aplicación web para la identificación de PIM (APIMedOlder) y llevar a cabo un estudio de usabilidad para evaluar su aceptación y utilidad entre los profesionales de la salud, así como evaluar su nivel de acceso y utilización;
- v. explorar las percepciones, conocimientos y conciencia de los GP sobre los PIM, las barreras para la prescripción y desprescripción de medicamentos en adultos mayores, así como los desafíos y facilitadores en la adopción de herramientas digitales para optimizar el uso de los medicamentos, a través de un estudio con grupos focales;
- vi. realizar una intervención multifacética que incluya un componente educativo para los médicos de atención primaria sobre el contenido y la aplicabilidad de la aplicación web APIMedOlder, reforzando su papel en el apoyo a la toma de decisiones clínicas;
- vii. evaluar el impacto de la intervención en la reducción de la prescripción de PIM en adultos mayores.

METODOLOGÍA

Esta tesis sigue un enfoque metodológico mixto, combinando métodos cualitativos y cuantitativos en diferentes fases del estudio:

Fase 1: Revisión sistemática de la literatura

Se realizaron dos revisiones sistemáticas con el objetivo de analizar las intervenciones previas implementadas para reducir la prescripción de PIM en adultos mayores e identificar los factores que afectan a la adopción de herramientas digitales para mejorar la adecuación de las prescripciones.

Fase 2: Estudio transversal sobre la prevalencia de PIM

Se realizó un estudio observacional transversal con el objetivo de determinar la prevalencia del uso de PIM en personas mayores, utilizando tres herramientas de evaluación: los criterios Beers 2019, STOPP v2 y la lista portuguesa EU(7)-PIM. Además, se analizó el nivel de concordancia entre estas herramientas para identificar similitudes y discrepancias en la detección de PIM.

Fase 3: Desarrollo y evaluación de la herramienta APIMedOlder

Se diseñó y desarrolló una aplicación web para la identificación de PIM. Posteriormente, se realizó un estudio de evaluación de usabilidad con profesionales de la salud con el fin de obtener retroalimentación sobre su funcionalidad y facilidad de uso. Además, se analizó el nivel de acceso y uso de la herramienta.

Fase 4: Estudio cualitativo con médicos de atención primaria

Se llevaron a cabo grupos focales con médicos para explorar sus percepciones sobre la polimedicación, el uso de PIM y la adopción de herramientas digitales para optimizar la prescripción en personas mayores

Fase 5: Intervención y análisis de impacto

Se implementó una intervención en unidades de salud de atención primaria seleccionadas de la ARSC, utilizando un diseño por conglomerados no aleatorizado (nonradnomized controlled cluster design) que asignó cuatro de las ocho unidades al grupo de intervención. Los médicos recibieron formación sobre el uso de APIMedOlder. Se comparó la prescripción de PIM antes, durante y después de la intervención para evaluar su impacto.

JUSTIFICACIÓN Y ESQUEMA DE LA TESIS

La justificación de este estudio radica en la creciente preocupación por la seguridad y eficacia de la farmacoterapia en la población adulta mayor en Portugal. Este grupo etario presenta un riesgo elevado de sufrir efectos adversos derivados de la polifarmacia, lo que se traduce en un aumento en la frecuencia de interacciones medicamentosas y reacciones adversas [17]. A pesar de los avances en la medicina y la farmacología, la prescripción inadecuada sigue siendo un desafío significativo para los profesionales de la salud, afectando la calidad de vida de los pacientes y aumentando la carga sobre los sistemas de salud [25].

El uso irracional de medicamentos, en especial aquellos que son potencialmente inapropiados, contribuye a la disminución de la calidad de vida de los pacientes mayores, además de aumentar la frecuencia de hospitalizaciones y el riesgo de complicaciones graves [28,56,57]. Este fenómeno también implica una mayor presión sobre los recursos del sistema de salud, lo que subraya la necesidad urgente de encontrar soluciones que optimicen la prescripción y uso de medicamentos [56-58].

En este contexto, la utilización de herramientas de apoyo a la decisión clínica se presenta como una solución viable para reducir el riesgo de prescripción de PIM [59]. Estas herramientas pueden proporcionar a los médicos las evidencias necesarias para tomar decisiones más informadas y adecuadas en cuanto a la medicación de los adultos mayores. Además, el uso de estas herramientas puede facilitar la integración de los profesionales de la salud, promoviendo una atención más centrada en el paciente y mejorando los resultados terapéuticos [53]. De esta forma, se puede lograr una mejora significativa en la calidad de la atención, minimizando los riesgos y maximizando los beneficios para los pacientes.

Además, el contexto actual en el que los avances tecnológicos y el uso de herramientas digitales se están consolidando como una parte esencial de la medicina moderna hace que la implementación de estas tecnologías sea aún más relevante. Las aplicaciones web y las herramientas digitales no solo mejoran la precisión y eficiencia en la prescripción, sino que también permiten a los médicos actualizarse de forma continua sobre los mejores tratamientos para sus pacientes [53,54].

La estructura de la tesis se organiza en un compendio de 4 artículos ya publicados, 1 capítulo de libro aceptado para publicación, y 1 artículo actualmente en proceso de sumisión a una

revista indexada, cada uno abordando una fase específica del estudio. Los trabajos se centrarán en temas clave relacionados con la intervención para reducir la prescripción de PIM y promover la adopción de herramientas digitales en la práctica clínica. Cada uno de estos artículos contribuyó al objetivo general de mejorar la seguridad y eficacia de la farmacoterapia en la población adulta mayor en Portugal, abordando diferentes aspectos relacionados con la prescripción de medicamentos y el uso de herramientas digitales en la toma de decisiones clínicas.

La combinación de enfoques cualitativos y cuantitativos en el desarrollo de estas herramientas, así como en el análisis de su impacto, permite una evaluación exhaustiva de las mejores prácticas para optimizar la atención farmacéutica en pacientes mayores. Además, la evidencia generada por este estudio contribuirá a establecer directrices que ayuden a los profesionales de salud en la toma de decisiones clínicas más adecuadas, alineadas con las necesidades y la seguridad de los pacientes mayores.

RESULTADOS

A continuación se presenta un resumen los resultados de los estudios realizados, organizados según los capítulos de la tesis:

Capítulo 3 – “Effectiveness of Interventions to Reduce Potentially Inappropriate Medication in Older Patients: A Systematic Review”

Se identificaron 47 estudios que evaluaron diversas intervenciones para reducir los PIM en adultos mayores, abarcando entre 52 y 124802 pacientes. Las intervenciones fueron la revisión de medicamentos, estrategias educativas, sistemas de apoyo a la toma de decisiones clínicas y enfoques organizacionales y multifacéticos. En el entorno hospitalario, la revisión de medicamentos fue la intervención más eficaz (75%), mientras que en atención primaria, las estrategias educativas demostraron ser las más efectivas. A pesar de los hallazgos positivos, se observó la necesidad de más estudios para confirmar la efectividad de estas intervenciones.

Capítulo 4 – “Barriers and facilitators of health professionals in adopting digital health-related tools for medication appropriateness: A systematic review”

Se revisaron 15 estudios que identificaron 125 barreras y 108 facilitadores para la adopción de herramientas digitales de salud. Las barreras más comunes incluyeron la necesidad de formación adicional y el tiempo requerido para su uso. Los facilitadores se centraron en la facilidad de uso y la integración en el trabajo diario de los profesionales. El estudio destacó la importancia de estos factores para el diseño de herramientas digitales eficaces.

Capítulo 5 – “Comparing AGS Beers 2019, STOPP version 2, and EU(7)-PIM list in Portuguese older adults in primary health care”

En un estudio retrospectivo de 1200 adultos mayores portugueses, se compararon los tres criterios de identificación de PIM. La prevalencia de PIM fue del 63,8% según la lista EU(7)-PIM, 66,8% según los criterios de Beers 2019, y 50,1% según los criterios STOPP v2, lo que resalta la necesidad de intervenciones específicas para mejorar la adecuación de las prescripciones en adultos mayores. Se observó una baja concordancia entre los criterios ($< 0,834$). La lista EU(7)-PIM mostró una buena capacidad para identificar un número elevado

de PIM relevantes en la población estudiada, sugiriendo que puede ser una herramienta útil y adaptada para la evaluación de la adecuación de la medicación en adultos mayores en el contexto portugués.

Capítulo 6 – “Usability of APIMedOlder: A Web Application to Manage Potentially Inappropriate Medication in Older Adults”

La evaluación de la usabilidad de la aplicación web APIMedOlder realizada por 15 profesionales de la salud (farmacéuticos, médicos, enfermeros, y técnicos de farmacia) reveló una calificación general de “Mejor imaginable” (puntuación media de 87,17 puntos), con puntuaciones individuales entre 75 y 100 puntos. Los resultados mostraron una alta consistencia interna ($\alpha = 0,881$), destacando la facilidad de uso y la eficiencia en el aprendizaje como puntos fuertes de la herramienta.

Capítulo 7 – “Exploring the impact of APIMedOlder web-based application: a retrospective analysis of searches made by healthcare professionals”

Durante un año (16 de noviembre de 2022 a 16 de noviembre de 2023), se registraron 400 búsquedas en la aplicación, con un 42,8% de ellas relacionadas con PIM. Los farmacéuticos fueron los usuarios más frecuentes, seguidos de médicos y estudiantes. Los medicamentos más buscados fueron omeprazol, quetiapina, furosemida, alprazolam y paracetamol. Aunque la difusión de la aplicación aún es limitada, los datos sugieren su potencial para reducir la prescripción de PIM en adultos mayores.

Capítulo 8 – “Understanding potentially inappropriate medication: A focus group study with general practitioners”

Se realizaron cinco grupos focales con 37 médicos de atención primaria del norte de Portugal. El análisis temático identificó cinco temas principales: factores asociados a la polifarmacia, desafíos en la desprescripción, problemas relacionados con los PIM, estrategias para el manejo de la polifarmacia y barreras y facilitadores en la adopción de herramientas digitales. Se destacaron ocho barreras (como la falta de tiempo y formación) y nueve facilitadores (como la facilidad de uso y el apoyo institucional). Los resultados evidencian la complejidad del manejo farmacológico en adultos mayores y el potencial de las herramientas digitales para optimizar la prescripción.

Capítulo 9 – “Reducing Potentially Inappropriate Prescriptions Through a Multifaceted Intervention: a Nonrandomized Cluster-Control Based Intervention”

La intervención educativa multifacética, que incorporó la herramienta digital APIMedOlder, sugirió un beneficio moderado y a corto plazo en la contención del aumento de la prescripción de PIM en adultos mayores en atención primaria. No obstante, los efectos sostenidos a largo plazo parecen limitados, lo que pone de manifiesto la necesidad de estrategias continuas de apoyo y refuerzo para mantener las mejoras en las prácticas de prescripción.

DISCUSIÓN

La integración de los resultados sugiere que las intervenciones educativas combinadas con herramientas digitales tienen el potencial de mejorar la prescripción de medicamentos, especialmente a corto plazo; sin embargo, mantener estas mejoras a lo largo del tiempo sigue siendo un desafío y depende del apoyo continuo, la implicación y las condiciones estructurales en la atención primaria.

De acuerdo con la revisión sistemática, las intervenciones educativas para reducir la prescripción de PIM en adultos mayores demostraron ser efectivas en el 75% de los casos analizados. Sin embargo, al considerar solo estudios controlados, no se encontró una superioridad clara frente a otras estrategias. Las intervenciones multifacéticas que incluyen componentes educativos resultan ser soluciones prometedoras, destacando la educación como un elemento central para mejorar la prescripción en atención primaria. Por otro lado, el uso de herramientas digitales para apoyar la prescripción enfrenta barreras como la falta de tiempo, resistencia al cambio y dificultades de uso. Sin embargo, facilitadores como la facilidad de uso, la retroalimentación en tiempo real y la integración en la rutina clínica son clave para su adopción. La combinación de intervenciones educativas con herramientas digitales, como APIMedOlder, ofrece un enfoque potente para reducir PIM, ya que refuerza el conocimiento y mejora la toma de decisiones clínicas. Para su implementación exitosa en atención primaria, es fundamental una formación práctica continua que prepare a los profesionales para integrar estas tecnologías, superando las barreras y mejorando la seguridad y calidad del cuidado al paciente mayor.

El estudio sobre la prevalencia del uso de PIM reveló tasas elevadas de prescripción de estos fármacos entre los adultos mayores. Además, se observó una baja concordancia entre los distintos criterios, lo que refleja la complejidad inherente a la evaluación de la adecuación de la medicación en esta población. La elevada frecuencia de PIM confirma estas dificultades y refuerza la utilidad de una herramienta como APIMedOlder, que reúne y adapta criterios validados en una plataforma amigable y de fácil acceso.

La herramienta APIMedOlder fue evaluada mediante un estudio de usabilidad, cuyos resultados mostraron una alta aceptación por parte de los profesionales de salud. Se destacó su carácter intuitivo y su facilidad de integración en el flujo de trabajo clínico. Estos resultados coinciden con los facilitadores identificados en la revisión anterior sobre herramientas digitales, donde la facilidad de uso, la integración en el flujo clínico y el soporte

en tiempo real son clave para su adopción. Los datos de uso registrados en la plataforma, en los que el 42,8% de las búsquedas estuvieron relacionadas con PIM, reflejan una utilización relevante y creciente concienciación sobre la importancia de este problema clínico. En conjunto, estos hallazgos sugieren que APIMedOlder tiene un gran potencial para apoyar la toma de decisiones clínicas y promover una prescripción más segura en el cuidado de adultos mayores.

Los grupos focales realizados con médicos de atención primaria permitieron identificar desafíos importantes en la desprescripción, tales como la resistencia de los pacientes, el tiempo limitado de consulta y la escasa infraestructura digital. A pesar del conocimiento general de los criterios para identificar PIM, su aplicación sistemática en la práctica diaria resultó ser limitada. Las barreras identificadas en el estudio cualitativo, como el tiempo limitado, el desconocimiento de criterios explícitos y la dificultad para incorporarlos en la rutina clínica, ayudan a explicar los resultados observados en el estudio transversal, en los que se evidenció la persistencia de PIM. La brecha entre el conocimiento y la práctica clínica subraya la necesidad de herramientas accesibles y fáciles de usar, como APIMedOlder, que faciliten la incorporación de criterios en la toma de decisiones y mejoren la seguridad del medicamento. Estos hallazgos coinciden con la revisión sistemática previa, que subrayaba la importancia de la facilidad de uso, la integración en el flujo clínico y el soporte en tiempo real para la adopción de herramientas digitales. En conjunto, los resultados muestran que, aunque estas soluciones tienen gran potencial para apoyar una prescripción más segura, su efectividad depende de abordar los múltiples retos que enfrentan los médicos en la práctica diaria. La combinación de intervenciones educativas personalizadas y herramientas digitales intuitivas y bien integradas parece esencial para superar barreras y optimizar la gestión de medicamentos en adultos mayores.

El análisis de la intervención mostró diferencias entre el grupo intervenido y el control, evidenciando la complejidad de modificar conductas de prescripción. Se observaron indicios de un posible impacto favorable a corto plazo, que parece disminuir tras seis meses, lo que sugiere la necesidad de intervenciones continuas para mantener cambios sostenibles. Estos resultados, integrados con la evidencia de revisiones sistemáticas, refuerzan que no existe una estrategia única para abordar la prescripción inapropiada en adultos mayores, sino que se requieren intervenciones multifacéticas, contextualizadas y sostenidas. Las sesiones educativas parecen aumentar el compromiso y la conciencia de los médicos, pero barreras como la falta de tiempo, la carga laboral y limitaciones tecnológicas pueden limitar la

traducción de estas intervenciones en cambios duraderos. Además, persiste la brecha entre el conocimiento y su aplicación práctica: aunque los médicos conocen y valoran los criterios para evitar PIM y tienen acceso a herramientas como APIMedOlder, enfrentan obstáculos para la desprescripción. Esto subraya la necesidad de crear entornos facilitadores con tiempo, capacitación, infraestructura y colaboración interdisciplinaria.

A nivel práctico y de política sanitaria, APIMedOlder puede desempeñar un papel clave en la mejora de la seguridad del paciente y la calidad de la atención médica. Su integración en los sistemas de prescripción electrónica y en programas de formación médica continua podría potenciar su impacto. A su vez, su inclusión en las estrategias nacionales de salud permitiría alinear los objetivos clínicos con las prioridades del sistema sanitario, promoviendo decisiones más seguras, personalizadas y basadas en evidencia. También cabe destacar su potencial como modelo adaptable a otros contextos internacionales con desafíos similares en la gestión de la polifarmacia y los PIM.

Entre las principales fortalezas del estudio se encuentra el enfoque integral, que combinó intervenciones educativas, el desarrollo de una herramienta digital basada en criterios clínicos validados, y la inclusión de la perspectiva de los usuarios finales. La herramienta fue desarrollada teniendo en cuenta las necesidades de los médicos de atención primaria, lo que favoreció su aceptabilidad y relevancia clínica. Asimismo, el estudio aportó evidencia desde una perspectiva de ciencia de implementación, analizando tanto los resultados como los factores que influyen en la adopción de la intervención.

No obstante, también se identificaron limitaciones relevantes. La herramienta no fue integrada con sistemas electrónicos existentes, lo cual podría haber mejorado su adopción y uso en tiempo real. Además, los datos disponibles para evaluar el impacto de la intervención no incluían información clínica detallada, como dosis o duración del tratamiento, lo que impidió valorar adecuadamente ciertos PIM dependientes de estos parámetros. Finalmente, aunque los resultados son prometedores, la generalización de los mismos a otras regiones o sistemas de salud debe realizarse con cautela.

La integración de estrategias educativas con herramientas digitales como APIMedOlder representa una solución factible, en aumento y con gran potencial para mejorar la adecuación de la medicación en adultos mayores en atención primaria. Esta tesis ofrece un modelo

reproducible que puede ser adaptado a otros contextos, contribuyendo a la mejora de la calidad de la atención y a la promoción de un envejecimiento más saludable y seguro.

CONCLUSIONES

Las conclusiones de este proyecto destacan la importancia de combinar intervenciones educativas con herramientas digitales para reducir los PIM en adultos mayores. Este enfoque integrado mejora el conocimiento de los profesionales y apoya la toma de decisiones clínicas mediante asistencia en tiempo real basada en evidencia. Sin embargo, su implementación requiere abordar barreras sistémicas, las necesidades prácticas de los médicos de familia y la complejidad del cuidado en atención primaria.

Mantener una interfaz simple e intuitiva en APIMedOlder es clave para facilitar su integración en el trabajo diario. La aceptación positiva observada puede potenciarse con formación continua y un ciclo constante de evaluación y retroalimentación para mejorar la usabilidad.

Es fundamental actualizar periódicamente la herramienta para reflejar cambios en el mercado farmacéutico y en las guías clínicas, asegurando así su relevancia y confiabilidad. Futuras investigaciones deben explorar la integración de APIMedOlder en sistemas de salud existentes para optimizar su uso, evaluar su impacto a largo plazo en la toma de decisiones y en resultados clínicos, y analizar su implementación en distintas regiones y contextos.

También se recomienda investigar la percepción de los pacientes sobre estas tecnologías, para mejorar su aceptación en procesos de desprescripción. Asimismo, la incorporación de tecnologías emergentes podría potenciar recomendaciones personalizadas y mejorar la gestión de medicamentos. Futuros estudios también podrían centrarse en la adaptación de los criterios internacionales más utilizados al contexto portugués, con base en los perfiles locales de prescripción y las características del sistema de salud.

En conjunto, este proyecto aporta una contribución innovadora y, basada en la evidencia, al campo de la farmacoterapia geriátrica, avanzando hacia prácticas de prescripción más seguras y estructuradas para adultos mayores.

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ABSTRACT

Potentially inappropriate medication (PIM) use among older adults is a widespread challenge associated with increased adverse drug events, hospitalizations, and healthcare costs. This thesis addresses the development, implementation, and evaluation of a multifaceted intervention combining educational strategies with a digital tool, APIMedOlder, aimed at reducing PIM prescription in older patients within primary care settings in Portugal.

Initially, a systematic review of 47 studies identified effective interventions to reduce PIM, highlighting that medication review was most effective in hospital settings, whereas educational strategies yielded better results in primary care. A complementary review on barriers and facilitators to digital health tool adoption identified key factors affecting healthcare professionals' engagement, including training needs, time constraints, ease of use, and workflow integration.

A retrospective study comparing established PIM criteria in 1200 Portuguese older adults revealed high PIM prevalence and poor concordance between criteria, emphasizing the complexity of medication management in this population.

The APIMedOlder web application was developed based on the EU(7)-PIM list and assessed for usability by a multidisciplinary group of healthcare professionals, achieving high satisfaction scores and positive feedback regarding its ease of use. Over one year, usage data recorded 400 searches predominantly by pharmacists and physicians, with a significant proportion related to PIM, indicating growing awareness and engagement.

Focus groups with 37 general practitioners revealed five main themes: factors associated with polypharmacy, challenges in deprescribing, problems related to PIM, strategies to manage polypharmacy, and barriers and facilitators to adopting digital tools for medication optimization. Participants highlighted time constraints, limited integration of tools, and inconsistent application of PIM criteria as key challenges, reinforcing the need for accessible and integrated solutions like APIMedOlder to support clinical decision-making.

Finally, a nonrandomized cluster-controlled intervention involving educational sessions and APIMedOlder use suggested a modest short-term reduction in PIM prescribing to older adults by general practitioners, though long-term sustainability appeared limited. These findings

underscore the necessity of continuous educational support, system integration, and addressing practical barriers to achieve lasting improvements.

Overall, this research demonstrates that combining targeted educational interventions with user-friendly digital tools offers a promising and scalable approach to enhancing prescribing safety in older adults. Recommendations include integrating APIMedOlder into electronic health record systems, providing ongoing training, and evaluating clinical outcomes over longer periods. Future studies should also explore patient perspectives and leverage emerging technologies to further personalize and optimize medication management in geriatric care.

Keywords: Potentially Inappropriate Medication (PIM); Digital Health Tools; Primary Care; Older Adults.

CHAPTER 1

Introduction

I. INTRODUCTION

Improved living conditions, socioeconomic status, and healthcare resources have led to a substantial increase in human life expectancy, alongside with a significant decline in mortality rates over the past several decades [1,2]. Therefore, the global demographic shift toward an aging population has been one of the most significant public health trends of the 21st century [3,4]. The global population of older adults aged 65 years and older is expected to more than double, from 761 million in 2021 to 1.6 billion by 2050 [5]. Portugal is one of the top ten countries in the world with the largest shares of people aged 65 years or over, with the percentage of older adults increasing from 22.6% in 2021 to 34.5% in 2050 [5]. Furthermore, Portugal has a high aging index of 192.4, with the Centre region of the country showing the highest value at 246.3 [6] (Table 1).

Table 1: Ageing Index by Place of Residence in Portugal [6].

Place of Residence (NUTS - 2024)	Ageing Index
Portugal	192.4
Mailand	194.4
North	205.0
Centre	246.3
West and Tagus Valley	207.3
Greater Lisbon	152.9
Setúbal Peninsula	160.6
Alentejo	226.9
Algarve	178.1
Autonomous Region of the Azores	128.0
Autonomous Region of Madeira	178.7

NUTS: Nomenclature of Territorial Units for Statistical Purposes (Nomenclatura das Unidades Territoriais para Fins Estatísticos).

With increasing age, physiological and cognitive functions – which are essential for survival and reproduction – gradually decline [7,8]. Aging is increasingly understood as a complex biological process driven by multiple interacting mechanisms [8]. These occur at the molecular level (such as deoxyribonucleic acid – DNA, damage and mitochondrial dysfunction), the cellular level (including senescence and altered intercellular communication), and the systemic level (like dysregulation in nutrient sensing pathways) [8]. These age-related changes significantly affect both pharmacokinetics and pharmacodynamics, including: (a) a decline in renal and hepatic function, impairing the

kidneys' and liver's ability to metabolize and excrete drugs, potentially leading to drug accumulation and an elevated risk of adverse effects [9,10]; (b) alterations in body composition, with an increase in fat mass relative to lean mass [11], which may impact the distribution of lipophilic drugs, while reduced total body water can influence the pharmacokinetics of hydrophilic medication [9]; and (c) heightened drug sensitivity, particularly due to changes in receptor response, increasing the likelihood of adverse reactions [12]. All these changes contribute to an increased vulnerability in older adults to side effects and drug interactions, requiring careful dose adjustment [12]. Although older adults are the primary users of medication, they remain significantly underrepresented in clinical trials due to factors such as complex pathophysiology, altered organ function, or simply due to their age [13,14]. While some clinical trials including older adults have emerged in recent years, the overall evidence base for most medication in this age group remains limited [13]. This lack of representation is particularly concerning, as age-related physiological changes can significantly impact the pharmacokinetics and pharmacodynamics of many drugs, increasing the risk of adverse outcomes in this population [13]. Consequently, emerging pharmacovigilance methods, such as leveraging digital health technologies, electronic health records, and real-world data, are helping to generate more age-relevant evidence on the safety and effectiveness of treatments in this population [15].

As people grow older and experience such physiological changes and complex health needs, there is a significant rise in multimorbidity - the presence of two or more chronic conditions [16]. Consequently, this often leads to the use of multiple medication, given rise to the concept of polypharmacy, which, although there are several definitions, the most widely used is the concomitant use of five or more drugs [17]. While polypharmacy can be necessary to manage complex health issues, it also increases the risk of negative health outcomes [18]. Moreover, this increases the likelihood of prescribing Potentially Inappropriate Medication (PIM) to older adults, which are defined as medicines that carry more risks than benefits, particularly when safer or more effective alternatives are available [19]. The relevance of polypharmacy and PIM to the health of older adults lies in their strong association with adverse outcomes, such as adverse drug reactions (ADRs), drug interactions, decreased medication adherence, increased risk of falls, hospital admissions, cognitive impairment, and higher mortality rates [18,20–23].

1. Polypharmacy

Polypharmacy is a widespread issue affecting older adults across the globe. Its prevalence has increased substantially over the past few decades, driven by the aging population, advances in medical care, and improved access to healthcare services [23]. The overall prevalence of polypharmacy and hyper polypharmacy (defined as multiple drugs ≥ 10) in the global older population was 39.1% (95% confidence interval, CI, 35.5%-42.7%) and 13.3% (95% CI, 10.4%-16.5%), respectively [24]. The prevalence of polypharmacy across different regions was as follows: 45.8% (95% CI 41.5%-50.2%) in Europe, 45.5% (95% CI 26.7%-64.3%) in Oceania, 40.8% (95% CI 29.8%-51.6%) in North America, 29.0% (95% CI 20.0%-38.0%) in Asia, and 28.4% (95% CI 24.0%-32.8%) in South America [24]. In a recent study assessing the prevalence of polypharmacy in older adults in 27 European countries, and Israel, an overall prevalence of polypharmacy of 36.2% (95% CI 35.6%–36.8%), ranging from 25.0% (95% CI 24.5%–25.5%) to 51.8% (95% CI 51.1%–52.5%) was found [25]. Portugal stood out with one of the highest rates (51.3%, 95% CI 50.6%–52.0%) [25].

Risk factors associated with polypharmacy include older age, comorbidities, poor self-perceived health status, limitations in physical activity, a history of falls, depression, and pain [26]. Lower socioeconomic status has also been associated to higher polypharmacy use, with older adults of lower educational backgrounds having 21% higher chances of experiencing polypharmacy compared to those with higher education levels [27]. These results extended to other measures of socioeconomic disadvantage, such as occupation, income, and social class [27].

Polypharmacy is a complex, multifactorial process that elevates both the frequency and variety of ADRs and drug-drug interactions (DDIs) [28]. The risk of suffering from drug reactions and interactions rises as the number of prescribed drugs increases [29]. Older adults were estimated to be twice as likely to experience ADRs compared to younger patients [30]. In a prospective cohort study of hospitalized older adults taking five or more drugs, those taking five to nine had a 50% likelihood of having a DDI, while the risk increased to 100% for those taking twenty or more [31].

The concomitant use of several drugs, especially in the context of polypharmacy, has the potential to affect the pharmacokinetic profiles of the drugs involved [9]. Some medication that changes gastric pH, like proton pump inhibitors (PPIs) can impair the absorption of drugs

that require an acidic environment, such as certain antifungals (ketoconazole or itraconazole) [32]. Once absorbed, drugs are distributed throughout the body, often binding to plasma proteins like albumin [33]. When multiple drugs compete for these binding sites, it can increase the free concentration of unbound drugs [34], potentially enhancing their effects or toxicity. For example, co-administration of warfarin with other highly protein-bound drugs, such as diclofenac, can increase the risk of gastrointestinal bleeding [32]. When two or more drugs are metabolized by the same enzyme, enzyme inhibition or induction can also occur [32]. For example, warfarin is primarily metabolized by the cytochrome P450 enzymes 2C9, 2C19, 1A2, and 3A4 [35,36]. Medication that inhibits these enzymes, such as clopidogrel or omeprazole, can raise the International Normalized Ratio (INR), potentially increasing the risk of bleeding, while drugs that induce these enzymes, like carbamazepine, may lower the INR, reducing warfarin's effectiveness [35]. Some drugs can impair renal function or compete for excretion pathways, leading to accumulation of other drugs in the body. Non-steroidal anti-inflammatory drugs (NSAIDs) can reduce kidney function, affecting the elimination of drugs like lithium, potentially leading to toxicity [37]. Given the age-related decline in liver and kidney function, older adults are particularly vulnerable to DDIs [38]. Reduced drug clearance associated with aging, when combined with polypharmacy, amplifies the risk of drug toxicity, ADRs, and reduced therapeutic efficacy [39].

There is an association between polypharmacy and increased hospitalizations, as ADRs are a leading cause of emergency department visits and hospital admissions in this age group [20]. ADRs are estimated to account for 8.7% (95% CI 7.6%–9.8%) of hospital admissions among older adults, with NSAIDs being among the most frequently implicated drug classes [40]. A recent systematic review and meta-analysis estimated the overall incidence of ADRs in the older population to be 12.94% (95% CI 12.29%-13.60%), with even higher rates observed in inpatient (17.53%, 95% CI 16.31%-18.74%) and outpatient (19.54%, 95% CI 14.31%-24.78%) settings [41]. When polypharmacy is present, older adults have a 50% higher rate of hospitalization compared to those not experiencing it [21]. Moreover, a significant increase in mortality in older adults associated with polypharmacy or excessive polypharmacy is well-documented [21]. Among the serious cases of ADRs in older patients reported to the Portuguese Pharmacovigilance System from 2013 to 2017, 34% led to hospitalization and in 5.8% of them a fatal outcome occurred [42].

Furthermore, polypharmacy is associated with a higher incidence of falls, leading to a 1.5 to 2 times greater possibility of recurrent falls in older adults [43]. These falls are a significant

source of morbidity and mortality in this population, often resulting in fractures, reduced mobility, disability, or loss of independence [44]. Cognitive impairment is another major concern, as studies indicate that the risk of cognitive impairment is greater in older adults taking five or more drugs and becomes even higher in those taking ten or more [45]. The use of medication with anticholinergic effects can also increase dementia incidence and cognitive decline in this population [46].

Polypharmacy also contributes to medication non-adherence, as managing multiple prescriptions can be challenging, especially for older adults with cognitive impairment, complex regimens and multiple prescribing physicians, and problems such as dissatisfaction with the drug formulation or difficulties with medication storage [47,48]. Poor adherence resulting from complex medication regimens can compromise the management of chronic conditions, increasing the risk of treatment failure, adverse health outcomes, and reduced quality of life in older adults [39]. Additionally, polypharmacy increases the complexity of treatment regimens, heightening the risk of prescribing cascade where a side effect or ADR from a drug is mistakenly identified as a new medical condition, leading to the prescription of an additional medication to treat the misinterpreted symptoms [39,49]. For instance, an older adult using a NSAID for arthritis pain might develop high blood pressure, leading to the prescription of an antihypertensive medication [49]. This antihypertensive medication could then cause dizziness, prompt the prescription of an antiemetic, and further complicate the medication regimen and increasing the risk of DDIs and ADRs [49].

There is also a socioeconomic dimension to the impact of polypharmacy, as it increases healthcare costs due to more frequent healthcare visits and hospitalizations [50,51]. According to the World Health Organization (WHO), approximately 4% of the world's avoidable healthcare costs are attributed to mismanaged or suboptimal prescribing practices [52]. The financial burden of purchasing multiple medication can also be especially challenging for older adults with limited financial resources [51]. In addition, the time and resources required for healthcare professionals to manage polypharmacy, including conducting regular medication reviews, monitoring for potential interactions and ADRs, can be time-consuming, demand specific skills, and necessitate coordination between different healthcare professionals, creating pressure on healthcare systems, especially in countries with aging populations [53].

2. Potentially Inappropriate Medication

The prevalence of PIM among older adults is a significant concern in healthcare systems worldwide, with studies reporting wide-ranging rates from 9.4% to 81.0%, depending on the setting, population, and criteria used to identify PIM [54]. An extensive review of 48 studies using health database research from 2010–2023 found that the average PIM prevalence across adults aged ≥ 65 years was 27.8% (95% CI 25.7%-29.9%), noting considerable variability depending on databases and detection method [54]. In a recent systematic review, among nearly 371.2 million older participants from 17 countries in outpatient services, the overall pooled prevalence of PIM use was 36.7% (95% CI 33.4%-40.0%) [55]. The highest prevalence was observed in Africa at 47.0% (95% CI 34.7%-59.4%), followed by South America at 46.9% (95% CI 35.1%-58.9%), Asia at 37.2% (95% CI 32.4%-42.2%), Europe at 35.0% (95% CI 28.5%-41.8%), North America at 29.0% (95% CI 22.1%-36.3%), and Oceania at 23.6% (95% CI 18.8%-28.8%) [55]. In nursing homes, the overall PIM prevalence was found to be 43.2% (95% CI 37.3%-49.1%), with higher values reported in European countries (49.0% 95% CI, 42.5%–55.5%) [56]. In mainland Portugal, the overall PIM Defined Daily Dose (DDD) frequency was 9.20%, with relatively higher rates observed in the Alentejo and Centre regions and lower rates in the North [57]. Among hospitalized older patients, the prevalence of PIM was found to be notably high, with the usage of at least one PIM ranging between 76.5% and 92.0% depending on the criteria applied [58,59]. Additionally, the number of institutionalized older adults in Portugal taking PIM varies between 79.3% and 86.5% [60–62].

The prevalence of PIM in older adults is influenced by their health status and underlying conditions. For instance, in older patients with dementia the pooled estimate of PIM use was 43% (95% CI 38%-48%) [63]. A study conducted in older adults with diabetes showed that comorbid conditions such as gastrointestinal diseases, osteoarthritis and rheumatoid arthritis, chronic pulmonary disease, chronic kidney disease, tumor, chronic liver disease, hypertension, cardiovascular disease, cerebrovascular disease, hyperlipemia and dementia are associated with an increased likelihood of PIM use [64]. Additionally, the prevalence of older adults using PIM was found to be highest in those with comorbid mental disorders, followed by neurological system disorders [65]. In older adult inpatients with cognitive impairment, the prevalence of PIM varies significantly, ranging from 20.6% to 89.8%, depending on the identification criteria [66].

Several risk factors are associated with PIM use in older adults, significantly impacting their health outcomes and overall quality of care, including lower education, living in socioeconomically deprived circumstances, the presence of polypharmacy, multiple health conditions, unhealthy lifestyle habits, and higher outpatient and emergency department utilization [67–69]. The use of two or more PIM, especially those related to the nervous system and anticholinergic agents, is linked with frailty in older adults, with a bidirectional association [70]. Furthermore, psychotropic medication has been associated to an increased risk of initiating PIM in older adults [71].

PIM can have a significant impact on the functional health of older adults. The cumulative number of PIM is a more critical factor than their presence, as higher PIM counts correlate with increased dependency of older adults in performing daily activities after hospital discharge [72]. Functional decline, lower health-related quality of life, and poorer physical performance have also been associated to PIM use in older adults [73,74]. Certain PIM classes, including antipsychotics, sedatives, anxiolytics, anticholinergics, antidiabetics, opioids, and antihypertensives, have been associated to an increased risk of falls and fractures in older adults [74]. Furthermore, the use of PIM is closely associated with the prevalence of mental health issues among older adults. This is evidenced by findings that older patients prescribed a PIM were more than three times as likely to have a mental disorder as those with other chronic diseases [65].

PIM use among older adults can result in increased utilization of healthcare services, especially on hospitalization, health care expenses, and emergency department visits, leading to higher healthcare costs [75,76]. PIM can also lead to an annual cost of \$419 million for the older population, meaning they can raise the healthcare cost per patient by \$2,000 [77]. Additionally, higher potentially inappropriate prescribing was associated to an increased risk of mortality in this population [72].

2.1. Criteria for Potentially Inappropriate Medication Identification

The identification of PIM in older adults is crucial for improving prescribing practices. Therefore, several tools have been developed over time to assist clinicians in assessing medication appropriateness, categorized into explicit, implicit, and mixed criteria [78]. These tools differ in their approach to identifying PIM, reflecting diverse healthcare settings and populations. Explicit criteria are rule-based and list specific drugs or drug classes that should

generally be avoided in older adults, usually developed from published reviews, expert opinions, and consensus techniques [78,79]. These criteria are often simpler to apply in clinical practice, as they provide straightforward guidance with little or no clinical judgement required [78,80]. Additionally, explicit tools do not account for individual patient differences or the complexity and appropriateness of complete medication regimens [78,79]. Examples include the Beers Criteria [81] and the Screening Tool of the Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) [82]. Implicit criteria, on the other hand, involve a more individualized approach, requiring clinical judgment and expert opinion to evaluate each patient's specific conditions and medication [78,79]. This approach requires clinicians to customize their prescribing choices according to the patient's specific conditions often relying on their understanding of existing literature and clinical experience, leading to variability in clinical decisions [80]. The Medication Appropriateness Index (MAI) is an example of implicit criteria [83,84]. These criteria provide a more tailored approach but are often more time-consuming and complex to apply in routine clinical practice [78,80]. Mixed criteria combine elements of both explicit and implicit tools to provide a more comprehensive assessment of medication appropriateness [80]. An example is the Australian Prescribing Appropriateness Criteria [85].

Among the earliest and most well-known tools is the Beers Criteria, first introduced in 1991 [86]. Originally designed for psychiatric patients, these criteria were developed to assist healthcare professionals in evaluating the quality of prescriptions for older patients. In 2011, the American Geriatrics Society (AGS) took over the responsibility for these criteria and committed to regularly updating them [87]. Since then, it has undergone several revisions, with the latest in 2023 [81]. The Beers Criteria provide an extensive list of medication that should be avoided in older adults due to the high risk of adverse effects, particularly in those with certain medical conditions, and it has become one of the most widely used tools globally, although it is specifically designed for use in the United States of America (USA) [81,88].

In 2008, the STOPP/START Criteria were developed in Europe to address gaps left by the Beers Criteria [89]. The STOPP list identifies inappropriate medication that should generally be avoided, while the START list highlights under prescribed medication that should be considered for older adults. These criteria have been revised with the most recent version being published in 2023 [82]. They are widely used across Europe due to their applicability in various healthcare settings [90]. Although the STOPP/START criteria are considered explicit tools for identifying PIM, only a portion of the criteria can be applied based solely

on the information available in the patient's medication profile [91]. Many of the criteria require additional information, such as the duration of therapy, previous medication, current and past medical conditions, and laboratory data [91].

Similarly, the EU(7)-PIM list, introduced in 2015, is a critical tool designed to address the challenge of PIMs based on clinical evidence of their risks and the better alternatives available in the older population, particularly in Europe [92]. This list was created by experts from seven European countries: Estonia, Finland, France, Germany, the Netherlands, Spain and Sweden [92]. One of the unique aspects of the EU(7)-PIM list is its focus on European healthcare practices. Unlike the Beers Criteria, which originated in the United States, the EU(7)-PIM list considers the prescribing patterns and healthcare systems of the seven participating European countries [92]. This makes the EU(7)-PIM list more relevant and practical for healthcare providers working within European countries. In addition to identifying PIM, the EU(7)-PIM list also emphasizes the need for alternative treatment options, encouraging healthcare providers to choose safer medication whenever possible [92].

While these tools are broadly applicable, some countries have developed more region-specific tools to address local healthcare needs. For instance, Norway has the NORGE Criteria, which are adapted to local prescribing patterns [93]. In France, a PIM list was developed according to the prescribing habits and clinical guidelines pertinent to the French population, thereby enhancing medication safety among older adults [94]. The Austrian consensus panel list has also established a consensus-based list of PIM for geriatric patients in Austria [95]. Moreover, the Canada national consensus panel list aims to identify inappropriate prescribing practices for older people, reflecting the Canadian healthcare system [96]. Germany's PIM list, the PRISCUS list, identifies drugs that are potentially inappropriate for older patients, considering the local healthcare challenges [97]. To our best knowledge, although more specific criteria have not been published for Portugal, some of the most well-known PIM criteria have been adapted to the Portuguese context. This includes the Beers criteria in 2008 [98], the EU(7)-PIM list in 2020 [99], the STOPP criteria version 2 in 2022 [100], and the version 3 of the STOPP criteria is also being translated and adapted into Portuguese, and the corresponding protocol has already been published [101]. Such adaptations are essential to ensure the applicability of tools in national clinical context, considering the specificities of the healthcare system and prescribing patterns in Portugal.

Among the available tools, the EU(7)-PIM list offers advantages for research purposes. It is a comprehensive European list, developed through expert consensus across several countries, aiming to provide a standardized tool to identify PIM in older adults [92]. This standardization enhances the comparability of research findings across countries and supports multicenter studies [92,102]. Its structure, which includes both general rules and substance-specific criteria [92], facilitates its use in large datasets, such as Electronic Health Records (EHRs) and administrative databases, supporting retrospective analysis and automated screening. The Portuguese adaptation of the EU(7)-PIM list, completed in 2020, further strengthens its relevance and applicability in the national context [99]. To ensure its applicability in the Portuguese context, a structured process of operationalization was conducted, which involved several key steps [99]. First, all medications included in the original EU(7)-PIM list were cross-checked against the Infomed database from INFARMED, identifying those with marketing authorisation in Portugal, and allowing for the selection of active substances and drug classes effectively available in the national market [99]. Next, a search for possible PIM not originally included in the EU(7)-PIM list but available in Portugal was carried out [99]. These included substances with similar mechanisms of action to those listed, and their marketing authorization status in the seven countries that contributed to the original list [99]. As a result of this process, five additional active substances were included [99]. The final Portuguese-adapted version of the list included 184 PIM, composed of 178 active substances, 5 drug classes, and 1 therapeutic scheme (sliding scale insulin therapy) [99].

3. Challenges in Managing Appropriate Medication Use in Older Adults

Multiple issues in how pharmacotherapeutic decisions are made and applied contribute to the challenges of polypharmacy and the prescription of inappropriate medication. Assessing the expected benefits versus risks of treatment in older patients presents a significant difficulty due to their reduced life expectancy and lower stress tolerance, making it crucial to carefully weigh therapeutic goals to avoid unnecessary harm and ensure optimal patient outcomes [103].

3.1. Limitations in Clinical Guidelines and Prescribing Practices

The widespread gaps of knowledge and understanding among clinicians, exacerbated by insufficient education and a lack of targeted guidelines results in minimal evidence to support

clinical practice [104]. If there is low awareness of the problem, clinicians may inadvertently contribute to poor health outcomes in older adults, missing opportunities for deprescribing. Additionally, prescribing guidelines often target individual conditions, however, older adults frequently have several chronic conditions, leading to the use of multiple medication and heightening the risk for drug interactions and adverse events when following these guidelines independently [105]. Regular medication review is essential not only to identify PIM, but also to assess the ongoing need for their use and to weigh their associated risks [39]. However, such reviews they may not occur frequently enough as clinic visits are generally short, typically lasting only 15–20 minutes, leading to a tendency to continue medicines rather than discontinue them [106]. Consequently, older adults may be exposed to avoidable risks. Therefore, in several countries, a regular medication review is conducted by pharmacists. In Portugal, the Order of Pharmacists has issued specific guidelines for medication reviews, emphasizing their importance in managing patients on multiple medication [107]. In other countries, including Canada, the United Kingdom, Australia, and New Zealand, pharmacists collaborate with physicians to renew prescriptions, ensuring continuity of care and reducing physicians' workload [108].

3.2. Barriers to Effective Communication and Care Coordination

Multiple providers may lead to inconsistent communication regarding a patient's medication [104], especially for older adults whose drugs may have started years ago, increasing the risk of polypharmacy and PIM. A lack of coordination in medical records across different healthcare settings further complicates this process [106]. This diffusion of responsibility disrupts continuity of care and complicates medication management, leading to inconsistent prescribing practices.

Difficulties in accessibility to primary health care can also contribute to the challenges of managing medication in older adults [109]. On the other side, the easy accessibility of herbal products such as ginseng, ginkgo biloba, turmeric, or St. John's can increase the risk of interactions with commonly prescribed drugs like anticoagulants and antihypertensives, potentially leading to adverse events or reduced treatment efficacy [39].

3.3. Health Literacy and Medication Adherence

Low health literacy and communication difficulties contribute to inadequate patient knowledge and education, as older adults may not receive sufficient information about their medication [104]. Besides, the occurrence of side effects, forgetfulness, challenges in managing medication, and health conditions could also influence adherence by older adults [109]. Managing multiple medications can lead to non-adherence, which in turn reduces treatment effectiveness, raises the risk of adverse health outcomes, and complicates medication management, often resulting in additional prescriptions [39]. This cycle can further exacerbate polypharmacy and PIM, and consequently, the older patient's safety.

3.4. Sociodemographic and Sociocultural Factors

Drug prescribing often fails to account for sex and gender differences, which is especially important since older women are more prone to drug-related harm than men [105]. This happens because sex-based pharmacokinetic differences lead to higher drug concentrations in women, especially in older age [105]. For example, the clearance of drugs like zolpidem is significantly slower in women, leading to higher concentrations and increased risk of adverse effects - further amplified in older women due to age-related decline in drug clearance [105]. Gender-related sociocultural factors also affect medication management, as older women are often less financially secure, more likely to be caregivers, and may receive different drug therapies compared to men [105].

Cultural and social factors, such as beliefs about medication and health can also influence medication management. Patients often feel satisfied with their current polypharmacy and perceive their medication as essential, and they may also believe that deprescribing could worsen their medical conditions or lead to adverse effects [104]. Drug dependence, misunderstanding the effects of aging and medication safety, and receiving mixed messages from healthcare providers can also be factors for older adults not wanting to stop taking medication [104]. Furthermore, the cultural belief that taking drugs is a solution for various health problems [110] can contribute to polypharmacy and PIM in older adults, as this mindset may lead to an over-reliance on pharmacological treatments rather than considering non-pharmacological interventions or lifestyle changes.

4. Primary Healthcare for Older Adults: Current Challenges and Emerging Opportunities

Portugal's National Health Service (NHS) provides universal healthcare to all residents, managed centrally by the Ministry of Health and locally by five regional health administrations [110]. It is primarily tax-funded, with additional contributions from out-of-pocket expenses and private insurance [110]. The NHS delivers primary care and hospital services, organized within Local Health Units (Unidades Locais de Saúde, ULS) that integrate primary healthcare centres and hospitals aiming to enhance the coordination and continuity of care [110]. While the private sector handles dental care, diagnostics, and rehabilitation, often under NHS contracts [119]. Family Health Units and Primary Healthcare Centre Groups were established to enhance primary care integration, while hospitals provide secondary and tertiary care through regional Hospital Centres [110].

Primary healthcare centres are at the forefront of healthcare delivery in Portugal, serving as the first point of contact for most patients, including older adults [111]. Within these centres, each citizen is typically assigned a GP, who provides continuous and personalized care. They are pivotal to primary care systems, providing accessible, patient-centered, and holistic care that improves health outcomes and strengthens healthcare systems [111]. By maintaining long-term relationships with patients, addressing diverse health needs, coordinating care, and integrating innovative practices [111], given that in Portugal the prescription of medicines is exclusively a medical act, general practitioners (GPs) are uniquely positioned to play a central role in managing the complexity of multimorbidity and polypharmacy, addressing PIM and promoting the safe and effective use of therapies. Recently, a study on healthcare access in Portugal found that most individuals relied on a GP in the public sector as their primary point of contact with the healthcare system, with 71% of participants reporting that they usually see the same doctor when they have a health problem and 85% of those doctors being their GPs [112]. Factors such as the GP's familiarity with their health history, trust in the GP, lower costs, and convenient location were appointed as reasons for this preference [112].

GPs often work as part of a multidisciplinary team, including pharmacists, nurses, and social workers, to address the complex needs of older patients. Such collaboration contributes to address both medical and social aspects of their health [113], which is especially important in managing chronic conditions and polypharmacy. GPs play a critical role in identifying

these factors during consultations and connecting patients with appropriate community resources and support services [111].

However, population aging and the rising prevalence of chronic conditions provides significant challenges to the structure of healthcare services and place increasing pressure on GPs, necessitating more effective strategies to manage the complexity of healthcare needs in this population [114]. Many models of general practice continue to prioritize single-disease management, shaped by traditional approaches common in secondary care, medical education, and research that influence clinical practice [115]. Moreover, the prescribing landscape is continuously evolving, driven by the emergence of novel pharmacological therapies, updated clinical guidelines, and rapidly advancing scientific evidence [116].

To remain effective in their role, GPs must engage in continuous professional development and education [117]. Training programs and access to up-to-date resources enable GPs to stay informed and apply evidence-based practices in their clinical decision-making [117]. Tools such as the operationalized EU(7)-PIM list can easily assist Portuguese GPs in evaluating prescriptions and determining whether medication are appropriate for older adults. Moreover, digital health technologies hold immense potential to revolutionize healthcare by enhancing integrated care and enabling seamless data sharing while addressing privacy and security challenges [118].

5. Digital Technologies for Medication Management of Older Adults in Primary Care

Available evidence suggests that the integration of innovative digital technologies in multicomponent interventions to enhance primary care hold promise in improving continuity and comprehensiveness of care, including prescribing practices [119]. Digital tools ranging from EHRs, electronic prescribing (e-prescribing) systems to Clinical Decision Support Systems (CDSS) and mobile health applications have become important tools to improve patient's safety by reducing medication errors and ADRs, and promoting adherence to clinical guidelines [120]. These technologies leverage algorithms and patient-specific data to assist physicians in clinical-decision making and DDIs checking [121].

In primary care settings, digital tools have proven to be highly effective in enhancing the screening process for common chronic diseases, improving early detection and timely interventions [122]. Moreover, they allow to enhance healthcare efficiency by reducing costs,

avoiding unnecessary tests, preventing adverse events, and optimizing resources through automation and simplified workflows, allowing healthcare professionals to allocate their time and resources more effectively [123]. By offering real-time alerts, evidence-based recommendations and up-to-date knowledge, they enhance prescribing accuracy, reduce ADRs, and support adherence to clinical guidelines and regulations [123,124].

Multidisciplinary teams play a crucial role in optimizing medication management. Pharmacists play an important role in improve pharmacotherapy and medication management in older patients [125]. Nurses also play a key role in patient education and adherence monitoring, ensuring that patients understand their medication regimens and follow them correctly [126,127]. Information technology tools also facilitate communication among healthcare providers, enhancing coordinated care and enabling more efficient health monitoring and medical management [123,124]. These platforms allow for the sharing of patient-centered information, reducing the risk of errors and duplications [123,124]. For older adults transitioning between care settings, such tools can ensure continuity of care by maintaining accurate and accessible records.

Despite their potential, digital innovation tools still face significant implementation challenges [123,124]. Interoperability issues remain a challenge, as different systems often lack seamless integration, leading to fragmented medication histories and increasing the risk of prescribing errors [121]. Excessive system notifications can overwhelm healthcare providers, causing them to overlook important warnings and potentially compromising patient safety [121,128]. Usability concerns also limit technology adoption, as some digital tools have complex interfaces that require extensive training, posing a barrier to efficient workflow integration [121,123,124]. The successful integration of digital technologies in primary care requires stakeholder engagement, improved infrastructure, support and training, the development of clear regulations and best practice standards, and a strong focus on patient safety, privacy, and equity [129]. To maximize the benefits of information technology in medication management, it is crucial to invest in user-friendly interfaces and provide training for GPs, advancing the goals of primary care, ultimately addressing the unique challenges of managing the health of an aging population. Ensuring high usability and integrating educational components to raise awareness about PIM are key factors that can enhance the effectiveness of CDSS and promote safer prescribing practices. By integrating real-world data into clinical decision-making processes and fostering a culture of continuous learning, these tools can support healthcare professionals in identifying and managing PIM in a

practical and sustainable way. These considerations highlight the need for applied research that explores how digital tools can be meaningfully implemented in clinical practice to improve medication safety and patient outcomes in older adults.

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CHAPTER 2

Objectives

II. OBJECTIVES

Considering the high consumption of medication by older patients in Portugal, the primary goal of this project is to reduce the prescription of Potentially Inappropriate Medication (PIM) in this population (≥ 65 years old) through a intervention targeted at general practitioners (GPs) working in Local Health Units (Unidades Locais de Saúde - ULS), under the Regional Health Administration of the Centre (Administração Regional de Saúde do Centro - ARSC) in Portugal.

To achieve this, the following specific aims were proposed:

- (i) to systematically review the literature to analyze and synthesize evidence on interventions designed to reduce the prescription and use of PIM in older patients;
- (ii) to systematically review and analyze published studies to identify barriers and facilitators influencing health professionals in adopting digital tools for improving medication appropriateness;
- (iii) to determine the prevalence of PIM use in older adults according to the 2019 Beers criteria, Screening Tool of the Older Persons' Prescriptions (STOPP) v2, and the Portuguese EU(7)-PIM list, and to analyze the level of concordance between these tools;
- (iv) to develop a web application for PIM identification (APIMedOlder) and perform a usability study to assess its acceptability and practicality among healthcare professionals, and evaluate its level of access and use;
- (v) to explore the perceptions, knowledge, and awareness of GPs about PIM, the barriers to prescribing and deprescribing medications for older adults, and the challenges and facilitators in adopting digital tools to optimize medication use, through a focus group study;
- (vi) to realize a multifaceted intervention that includes an educational component for GPs about the content and applicability of the APIMedOlder web application, enhancing its role in supporting clinical decision-making;
- (vii) to assess the impact of the intervention concerning the web application in reducing PIM prescriptions among older adults.

CHAPTER 3

Effectiveness of Interventions to Reduce Potentially Inappropriate Medication in Older Patients: A Systematic Review

III. Effectiveness of Interventions to Reduce Potentially Inappropriate Medication in Older Patients: A Systematic Review

RESUMEN

Las múltiples comorbilidades relacionadas con la edad hacen que los adultos mayores sean propensos al uso de medicamentos potencialmente inapropiados (PIM), lo que resulta en un mayor riesgo de eventos adversos. Han surgido varias estrategias para apoyar la prescripción de PIM, y se han propuesto numerosas intervenciones para reducir los PIM. Este trabajo tiene como objetivo analizar la efectividad de las intervenciones de PIM dirigidas a adultos mayores. Se realizó una revisión sistemática buscando en la literatura en las bases de datos científicas MEDLINE PubMed, EMBASE y Cochrane para estudios de intervención que evaluaron las intervenciones de PIM en adultos mayores (≥ 65 años). Se incluyeron cuarenta y siete artículos, que involucraron de 52 a 124802 pacientes. Se analizaron varios tipos de intervenciones, como la revisión de medicamentos, estrategias educativas, sistemas de apoyo a la toma de decisiones clínicas y enfoques organizacionales y multifacéticos. En el hospital, la intervención más exitosa fue la revisión de medicamentos (75.0%), mientras que en la atención primaria, el análisis de todos los estudios incluidos reveló que las estrategias educativas fueron las más efectivas. Sin embargo, el análisis de intervenciones que tienen mayor evidencia por su diseño fue inconcluso. Los resultados obtenidos en este trabajo sugirieron que las intervenciones dirigidas al entorno de PIM deberían desarrollarse para promover el bienestar de los pacientes mediante la reducción de PIM. Aunque los datos obtenidos sugirieron que la revisión de medicamentos fue la estrategia más asertiva para disminuir el número de PIM en el entorno hospitalario, se necesitan más estudios.

Palabras clave: revisión; medicamentos potencialmente inapropiados; intervenciones; efectividad; adultos mayores.



Effectiveness of Interventions to Reduce Potentially Inappropriate Medication in Older Patients: A Systematic Review

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Background: Age-related multiple comorbidities cause older adults to be prone to the use of potentially inappropriate medicines (PIM) resulting in an increased risk of adverse events. Several strategies have emerged to support PIM prescription, and a huge number of interventions to reduce PIM have been proposed. This work aims to analyze the effectiveness of PIM interventions directed to older adults.

Methods: A systematic review was performed searching the literature in the MEDLINE PubMed, EMBASE, and Cochrane scientific databases for interventional studies that assessed the PIM interventions in older adults (≥ 65 years).

Results: Forty-seven articles were included, involving 52 to 124,802 patients. Various types of interventions were analyzed such as medication review, educational strategies, clinical decision support system, and organizational and multifaceted approaches. In the hospital, the most successful intervention was medication review (75.0%), while in primary care, the analysis of all included studies revealed that educational strategies were the most effective. However, the analysis of interventions that have greater evidence by its design was inconclusive.

Conclusion: The results obtained in this work suggested that PIM-setting-directed interventions should be developed to promote the wellbeing of the patients through PIM reduction. Although the data obtained suggested that medication review was the most assertive strategy to decrease the number of PIM in the hospital setting, more studies are necessary.

Systematic Review Registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021233484], identifier [PROSPERO 2021 CRD42021233484].

Keywords: review, potentially inappropriate medication, interventions, effectiveness, older adults

1 INTRODUCTION

The increase in life expectancy associated with a declined birth rate contributed to rapid population aging (United Nations, 2019). Even though the world population is getting older, aging populations differ by region and level of development (Beard et al., 2016). Globally, it is estimated that in 2050 the number of older adults will reach 1.5 billion and will outnumber adolescents and youth aged 15–24 years (1.3 billion) (United Nations, 2019).

Considering that more than half of older adults have at least two chronic diseases (Barnett et al., 2012), these societal transformations pose a significant challenge in health systems and increase the consumption of health resources, including medicines. In addition, the treatment of chronic diseases is based on single disease-centered guidelines that can lead to an overwhelming of medication, and polypharmacy can easily occur (Barnett et al., 2012). Age-related pharmacokinetic and pharmacodynamic alterations associated with the use of multiple medicines can potentiate the consumption of potentially inappropriate medications (PIM) and facilitate the occurrence of adverse drug reactions (ADR) in frail older adults (Motter et al., 2018; Hefner et al., 2021).

PIM is defined as medicines that should not be prescribed because the risk of adverse events outweighs the clinical benefit, especially when more effective alternatives are available (Renom-Guiteras et al., 2015). The prescription of PIM has received special attention from the health community, and interventions aim to optimize medication prescribing and increase the benefit/risk ratio associated with the patients (Anderson et al., 1997; Simonson and Feinberg, 2005). In the last decades, several studies have been done to evaluate the effectiveness of PIM interventions in primary care, such as in hospitals and nursing homes. Nevertheless, the studies display widely differing methodology and inconsistent results, and to our knowledge, there are no systematic reviews comparing the effectiveness of different kinds of interventions.

Thus, this study aims to critically review the effectiveness of interventions to reduce PIM prescriptions in older adults.

2 METHODS

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines (Page et al., 2021) (Supplementary Table S1). The research protocol is registered on PROSPERO (CRD42021233484).

2.1 Search Strategy

A literature search was conducted in January 2021 and updated in February 2021 on the MEDLINE PubMed, EMBASE. A search was also conducted in the Cochrane database in October 2021. The search strategy was designed to identify relevant studies addressing interventions on PIM prescriptions in older adults, using the following broad-based search terms strategy: “(elderly OR “elderly patient” OR “older patient” OR “older adult” OR

“geriatric patient”) AND (PIM OR PIP OR “potentially inappropriate medicine” OR “potentially inappropriate medication” OR “potentially inappropriate prescribing” OR “prescribing patterns” OR “Prescription Drug Misuse” OR “Prescription Drug Overuse” OR “deprescri” OR “potentially inappropriate prescription”) AND (prevention OR reduction OR decrease OR impact) AND (intervention OR trial).”

2.2 Selection Criteria

This systematic review included the following: 1) all studies focused on PIM interventions directed to older adults (≥ 65 years) that aimed to optimize their pharmacotherapy; 2) controlled intervention studies and case series studies; and 3) all studies published in Portuguese, English, or Spanish between January 1, 2000, and December 31, 2020.

Excluded from this work were reviews, meta-analyses, opinions, letters to the editor that do not provide original data, comments, reports, studies addressing PIM in a specific pathology, and studies targeting a limited and predefined class of PIM.

2.3 Outcomes Measures

Our primary outcome measure was the effectiveness of the PIM interventions through the analysis of the change rate between the mean number of PIM per patient and/or the mean number of patients with PIM before and after an intervention.

2.4 Data Extraction

Two researchers (AP and DR) independently screened all titles and abstracts retrieved from the databases accordingly with the inclusion criteria. To evaluate the eligibility of full-text articles, two researchers (AP and DR) independently screened the full text of the articles. All discrepancies were resolved through discussion with the help of a third researcher (FR).

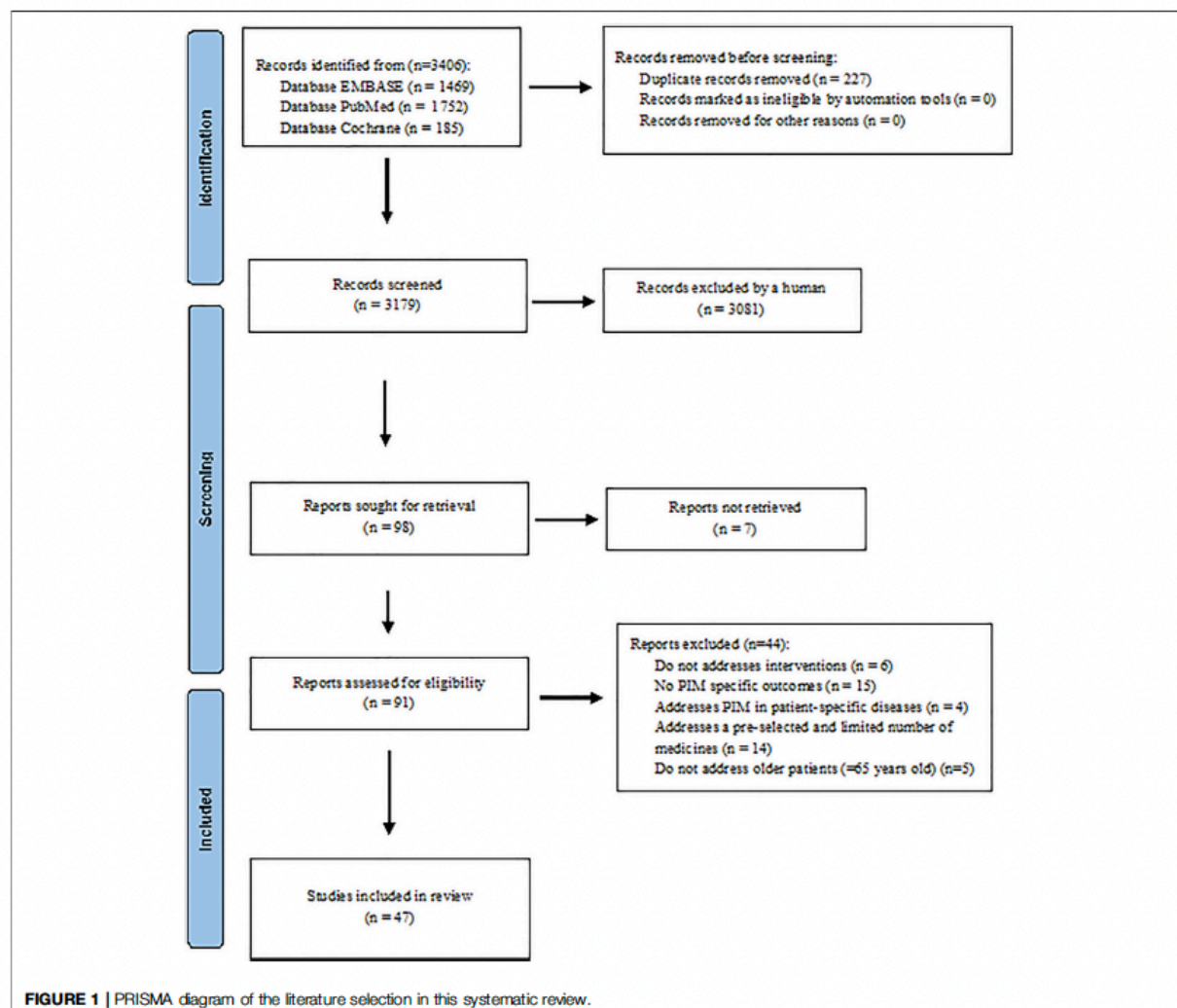
2.5 Quality Assessment

Two researchers (AP and DR) independently evaluated the quality and susceptibility to the bias of the included studies using the “Quality Assessment of Controlled Intervention Studies” and the “Quality Assessment Tool for Case Series Studies” tools, depending on study design (National Heart Laboratory, 2013). All discrepancies were resolved through discussion with a third (FR) or fourth researcher (MH).

2.6 Data Synthesis and Presentation

Two researchers (AP and DR) independently extracted data from the included studies. The data extracted from each article include authors, publication year, study design, country, sample size, patients’ age, type of intervention applied, PIM screening tool, outcome measures, and main results.

To better analyze the extracted data, studies were grouped according to the intervention used. Within the intervention used, studies were grouped according to the setting where the intervention occurs. Five different interventions were identified in the included studies, and their descriptions were based on the following pre-defined definitions: 1) Medication review: “a structured evaluation of a patient’s medicines to optimize



medicines use and improve health outcomes. This entails detecting drug-related problems and recommending interventions” (Griese-Mammen et al., 2018); 2) educational interventions: “a package of interventions aimed to refresh the basic pharmacology competencies of a healthcare professional to change the prescription. The approaches used in the educational interventions included: interactive teaching, mailed educational material combined with individual feedback, and face-to-face visits to physicians” (Kaur et al., 2009); 3) clinical decision support systems (CDSS): “electronic tools that prompt provider behaviors in various areas of patient care, including medication ordering, chronic disease management, health care screening, and vaccination. CDSS can provide physicians, nurses, pharmacists, and other care providers with patient-specific prompts or warnings, treatment guidelines (e.g., order sets), automatic medication dosing calculators, or reports of overdue tests and medications as appropriate” (Bhugra and Cutter, 2001);

4) multifaceted interventions: “any intervention including two or more components.” In this study we classified as a multifaceted approach studies that used a combination of the interventions described above (Squires et al., 2014); and 4) organizational strategies: a combination of methodologies to improve the quality indicators. This type of intervention can include several methodologies, such as diagnostic activity, team building, intergroup relationship, sensitivity training, etc. In this work, organizational strategies include showing charts with the percentage of patients with PIM, an educational session with practices to identify patients with PIM, and frequent reunions to evaluate PIM indicators (Cady and Kim, 2017).

2.7 Statistical Analysis

A qualitative analysis was done if at least two studies had comparable outcomes. The heterogeneity of the studies was

assessed through the comparison between the interventions. The efficacy of the interventions was presented as a change rate between the mean number of PIM per patient and/or the mean number of patients with PIM before and after an intervention.

3 RESULTS

3.1 Study Selection

The search of the databases yielded 3,406 citations (Figure 1). After screening titles and abstracts, 98 articles potentially met the inclusion criteria. Because seven articles were not retrieved, only 91 articles were fully screened. Among these, 42 were excluded because they did not address interventions ($n = 6$), did not report PIM specific outcomes ($n = 15$), addressed PIM in patient-specific diseases ($n = 4$), addressed a pre-selected and/or a limited number of medicines ($n = 14$), and did not address older patients (≥ 65 years old) ($n = 5$) (Supplementary Table S2).

Forty-seven articles (Allard et al., 2001; Brown and Earnhart, 2004; Fick et al., 2004; Spinewine et al., 2007; Wessell et al., 2008; Castelino et al., 2010; Lampela et al., 2010; Gallagher et al., 2011; Keith et al., 2013; Rognstad et al., 2013; Dalleur et al., 2014; Franchi et al., 2014, 2016; Frankenthal et al., 2014; Lopatto et al., 2014; Clyne et al., 2015, 2016; Ilić et al., 2015; Tallon et al., 2015; Campins et al., 2016; Moss et al., 2016; Urfer et al., 2016; Frankenthal et al., 2017; Price et al., 2017; Stevens et al., 2017; Van der Linden et al., 2017; Vanderman et al., 2017; Chan et al., 2018; Etxeberria et al., 2018; Fajreldines et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Najjar et al., 2018; Sennesael et al., 2018; Stuckey et al., 2018; Van Der Linden et al., 2018; Vandenberg et al., 2018; Boersma et al., 2019; Gutiérrez-Valencia et al., 2019; Khera et al., 2019; Liu et al., 2019; McDonald et al., 2019; Moss et al., 2019; Regueiro et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020; Winata et al., 2020) fulfilled the inclusion criteria and were included in this systematic review (Figure 1).

3.2 Characteristics of Included Studies

A description of the characteristics of the included studies is presented in Table 1. Among the included studies, 24 were conducted in Europe (Spinewine et al., 2007; Lampela et al., 2010; Gallagher et al., 2011; Keith et al., 2013; Rognstad et al., 2013; Dalleur et al., 2014; Franchi et al., 2014; Lopatto et al., 2014; Clyne et al., 2015; Ilić et al., 2015; Tallon et al., 2015; Campins et al., 2016; Clyne et al., 2016; Franchi et al., 2016; Urfer et al., 2016; Van der Linden et al., 2017; Etxeberria et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Sennesael et al., 2018; Van Der Linden et al., 2018; Boersma et al., 2019; Gutiérrez-Valencia et al., 2019; Regueiro et al., 2019), 14 in North America (Allard et al., 2001; Brown and Earnhart, 2004; Fick et al., 2004; Wessell et al., 2008; Moss et al., 2016; Price et al., 2017; Stevens et al., 2017; Vanderman et al., 2017; Chan et al., 2018; Stuckey et al., 2018; Vandenberg et al., 2018; Khera et al., 2019; McDonald et al., 2019; Moss et al., 2019), six in Asia (Frankenthal et al., 2014, 2017; Najjar et al., 2018; Liu et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020), two in Oceania (Castelino et al., 2010; Winata et al.,

2020), and one in South America (Fajreldines et al., 2018). The most frequented settings of the included studies were hospital ($n = 26$) (Brown and Earnhart, 2004; Spinewine et al., 2007; Gallagher et al., 2011; Dalleur et al., 2014; Franchi et al., 2014; Tallon et al., 2015; Franchi et al., 2016; Moss et al., 2016; Urfer et al., 2016; Stevens et al., 2017; Van der Linden et al., 2017; Vanderman et al., 2017; Chan et al., 2018; Fajreldines et al., 2018; Najjar et al., 2018; Sennesael et al., 2018; Van Der Linden et al., 2018; Vandenberg et al., 2018; Gutiérrez-Valencia et al., 2019; Liu et al., 2019; McDonald et al., 2019; Moss et al., 2019; Regueiro et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020; Winata et al., 2020) and primary care ($n = 18$) (Allard et al., 2001; Fick et al., 2004; Wessell et al., 2008; Castelino et al., 2010; Lampela et al., 2010; Keith et al., 2013; Rognstad et al., 2013; Lopatto et al., 2014; Clyne et al., 2015; Campins et al., 2016; Clyne et al., 2016; Price et al., 2017; Etxeberria et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Stuckey et al., 2018; Boersma et al., 2019; Khera et al., 2019). The number of participants in the studies ranged from 52 to 124,802. In the included studies, the average age of the participants ranged from 71 to 88.4 years. However, 12 studies did not report an average age of patients, although all of these studies provided an age range: 10 studies included older adults aged ≥ 65 years (Fick et al., 2004; Wessell et al., 2008; Moss et al., 2016; Frankenthal et al., 2017; Price et al., 2017; Stevens et al., 2017; Najjar et al., 2018; Vandenberg et al., 2018; Moss et al., 2019; Vu and Huong, 2019), one study included patients aged ≥ 70 years (Rognstad et al., 2013), and one study included patients aged ≥ 75 years (Lampela et al., 2010).

3.3 Quality of Included Studies

The quality assessment tools results of each study are reported in Table 2. Twenty-five articles fulfilled more than 80% of the exploratory questions (Castelino et al., 2010; Gallagher et al., 2011; Rognstad et al., 2013; Frankenthal et al., 2014; Lopatto et al., 2014; Clyne et al., 2015, 2016; Campins et al., 2016; Price et al., 2017; Stevens et al., 2017; Vanderman et al., 2017; Chan et al., 2018; Etxeberria et al., 2018; Fajreldines et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Sennesael et al., 2018; Gutiérrez-Valencia et al., 2019; Khera et al., 2019; Liu et al., 2019; Moss et al., 2019; Regueiro et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020; Winata et al., 2020). Eighteen studies pointed out clearly potential sources of bias (Brown and Earnhart, 2004; Fick et al., 2004; Spinewine et al., 2007; Wessell et al., 2008; Lampela et al., 2010; Rognstad et al., 2013; Campins et al., 2016; Franchi et al., 2016; Urfer et al., 2016; Frankenthal et al., 2017; Price et al., 2017; Van der Linden et al., 2017; Etxeberria et al., 2018; Gibert et al., 2018; Boersma et al., 2019; Gutiérrez-Valencia et al., 2019; Khera et al., 2019; Moss et al., 2019). Through analysis of Table 2, the main limitations were related to the low sample size and the lack of blinded intervention. Besides that, most of the studies did not do or report follow-up results, so it is not possible to understand if the interventions were effective in the middle/long-term.

3.4 Evidence of Effectiveness

3.4.1 PIM Screening Tools

Thirty-seven studies used validated and published criteria to identify PIM, including Beers criteria ($n = 16$) (Brown and

TABLE 1 | Characteristics of the included studies (*n* = 47).

Author (year)	Country	Study design	Setting	Elderly patients' sample		Comparator	Quality assessment/ (score obtained/total score)
				Sample size	Mean age (SD or IQR)		
Akkawi et al. (2020)	Malaysia	Case series	Hospital	B: 240 A: 240	B: 71.9 (5.8) A: 72.9 (5.7)	Baseline	8/9 ^a
Winata et al. (2020)	Australia	Case series	Hospital (aged care wards)	B: 121 A: 107	B: 83.9 (7.2) A: 83.3 (7.2)	Baseline	8/9 ^a
Boersma et al. (2019)	Netherlands	RCT	Geriatric clinic (outpatients)	C: 59 I: 65	C: 79.0 (6.0) I: 77.8 (5.7)	Usual care	10/14 ^b
Gutiérrez-Valencia et al. (2019)	Spain	Prospective study	Tertiary public hospital (acute geriatric unit)	234	87.6 (4.6)	Baseline	8/9 ^a
Khera et al. (2019)	Canada	Quasi-experimental pretest–posttest	Primary care (community-dwelling patients)	54	81.7 (6.74, 65–95)	Before medication review	8/9 ^a
Liu et al. (2019)	Taiwan	Interventional	Tertiary medical center (emergency department)	B: 243 A: 668	B: 78.2 (7.7) A: 78.1 (7.7)	Before implementation of the intervention	8/9 ^a
McDonald et al. (2019)	Canada	Non-randomized controlled before and after study	Medical clinical teaching units (internal medicine department)	C: 383 I: 417	C: 79 (73–86) I: 81 (74–88)	Usual care	8/14 ^b
Moss et al. (2019)	United States	Case series	Veteran Affairs Medical Center (emergency department)	C: 2,500 I: 3,162	≥65	Untrained cohort	8/9 ^a
Regueiro et al. (2019)	Spain	Quasi-experimental pre-post	University hospital (internal medicine department)	174	82.6 (6.9)	Before implementation of the intervention	8/9 ^a
Vu and Huong (2019)	Vietnam	Case series	General hospital (endocrinology, cardiology, and neurology departments)	B: 211 A: 208	≥65	Baseline	8/9 ^a
Chan et al. (2018)	Canada	Retrospective single-center pre-post cohort	Tertiary hospital (acute care unit)	B: 70 A: 67	B: 88.1 (4.3) A: 88.4 (5.1)	Before implementation of the intervention	7/9 ^a
Etxeberria et al. (2018)	Spain	Case series	Primary health care	503	84.9 (3.8)	Before implementation of the intervention	7/9 ^a
Fajreldines et al. (2018)	Argentina	Case series	Hospital	B: 640 A: 622	B: 80.9 (9.8) A: 79.3 (9.7)	Before implementation of the intervention	8/9 ^a
Hurmuz et al. (2018)	Netherlands	Retrospective longitudinal pretest vs. posttest	Community pharmacy	126	76.0 (7.4)	Before implementation of the intervention	8/9 ^a
Najjar et al. (2018)	Saudi Arabia	Prospective pretest vs. posttest design	Hospital	B: 200 A: 200	≥65	Baseline	6/9 ^a
Gilbert et al. (2018)	France	—	Primary care	172	83.5 (4.9)	Before implementation of the intervention	8/9 ^a
Sennesael et al. (2018)	Belgium	Retrospective interrupted time series study	Teaching hospital (geriatric unit)	120	85 (81–88) ^c	Standard geriatric care	7/9 ^a
Stuckey et al. (2018)	United States	Prospective quality improvement project	Family medicine clinic (residency training outpatients)	34	74 (5)	Before implementation of the intervention	5/9 ^a
Vandenberg et al. (2018)	United States	Quality improvement program	Veteran Affairs Medical Center (community-based outpatient clinic)	>7,000	≥65	Before implementation of the intervention	3/14 ^b
Van Der Linden et al. (2018)	Belgium	Case series	Teaching hospital	B: 29 A: 30	B: 83 (79–86) ^c A: 83 (78–88) ^c	Usual care	8/14 ^b
Frankenthal et al. (2017)	Israel	RCT	Chronic care geriatric facility	C: 126 I: 126	≥65	Usual care	7/14 ^b
Price et al. (2017)	Canada	RCT	Primary care	C: 1,086 I: 1,204	≥65	Baseline rate	11/14 ^b

(Continued on following page)

TABLE 1 | (Continued) Characteristics of the included studies (*n* = 47).

Author (year)	Country	Study design	Setting	Elderly patients' sample		Comparator	Quality assessment/ (score obtained/total score)
				Sample size	Mean age (SD or IQR)		
Stevens et al. (2017)	United States	—	Veteran Affairs Medical Center (emergency department)	—	≥65	—	9/9 ^a
Vandeman et al. (2017)	United States	Retrospective cohort study	Veteran Affairs Medical Center (ambulatory clinics)	B: 1,539 A: 1,490	B: 71.0 (6.72) A: 71.0 (6.65)	Usual care	7/9 ^a
Van der Linden et al. (2017)	Belgium	Prospective controlled trial	Hospital (acute geriatric ward)	C: 81 I: 91	C: 84.5 (4.97) I: 84.5 (4.69)	Usual care	8/14 ^b
Campins et al. (2016)	Spain	RCT	Primary health care center	C: 251 I: 252	C: 78.78 (5.46) I: 79.16 (5.50)	Routine clinical practice	12/14 ^b
Clyne et al. (2016)	Ireland	RCT	Primary care	C: 97 I: 99	C: 76.4 (4.8) I: 77.1 (4.9)	Usual care	11/14 ^b
Franchi et al. (2016)	Italy	RCT	Hospital (internal medicine and geriatric wards)	C: 350 I: 347	C: 83.8 (5.6) I: 83.7 (5.9)	Baseline	9/14 ^b
Moss et al. (2016)	United States	—	Veteran Affairs Medical Center (emergency department)	23,168	≥65	—	6/9 ^a
Urfer et al. (2016)	Switzerland	Case series	Hospital (internal medicine ward)	C: 450 I: 450	C: 79 (73–84) I: 76 (71–83)	Patients hospitalized in some division	8/14 ^b
Clyne et al. (2015)	Ireland	RCT	Primary care	C: 97 I: 99	C: 76.4 (4.8) I: 77.1 (4.9)	Usual care	13/14 ^b
Ilić et al. (2015)	Serbia	Case series	Nursing homes	104	82.6 (2.1)	Before implementation of the intervention	7/9 ^a
Tallon et al. (2015)	Ireland	Case series	Teaching hospital	B: 60 A: 48	B: 75 (70–80) A: 78 (71–83)	Standard care	7/9 ^a
Dalleur et al. (2014)	Belgium	RCT	Teaching hospital	C: 72 I: 74	C: 86 (81–89) I: 84 (81–87)	Usual care	8/14 ^b
Franchi et al. (2014)	Italy	RCT	Hospital (internal medicine ward)	Admission C: 41; I: 40 Discharge C: 33; I: 37	Admission C85.58 (5.99), I: 82.8 (5.59) Discharge, C: 80.92 (4.53), I: 82.49 (4.82)	Only the basic notions of pharmacology	9/14 ^b
Frankenthal et al. (2014)	Israel	RCT	Chronic care geriatric facility	C: 176 I: 183	82.7 (8.7)	Usual care	12/14 ^b
Lopatto et al. (2014)	Italy	—	Health authority database	111,282	75.29 (8.34)	—	7/9 ^a
Keith et al. (2013)	Italy	Multi-phase prospective	Parma local health authority database	C: 81,597 I: 78,482	C: 75.6 (7.3) I: 75.4 (7.2)	Region local health authority database	6/14 ^b
Rognstad et al. (2013)	Norway	RCT	General practice	Control group B: 35,073 After: 35,211 Intervention group B: 46,737 A: 45,310	≥70	Baseline data	11/14 ^b
Gallagher et al. (2011)	Ireland	RCT	Hospital (emergency department)	C: 192 I: 190	C: 77 (71–81.75) I: 74.5 (71–80)	Usual care	13/14 ^b
Castelino et al. (2010)	Australia	Retrospective	Primary care	372	76.1 (7.8)	Before implementation of the intervention	7/9 ^a
Lampela et al. (2010)	Finland	RCT	Primary care	C: 500 I: 500	≥75	Standard care	8/14 ^b
Wessell et al. (2008)	United States	Prospective	Primary care	124,802	≥65	—	6/9 ^a
Spinewine et al. (2007)	Belgium	RCT	Teaching hospital	C: 90 I: 96	C: 81.9 (6.2) I: 82.4 (6.9)	Usual care	10/14 ^b

(Continued on following page)

TABLE 1 | (Continued) Characteristics of the included studies ($n = 47$).

Author (year)	Country	Study design	Setting	Elderly patients' sample		Comparator	Quality assessment/ (score obtained/total score)
				Sample size	Mean age (SD or IQR)		
Brown and Earnhart (2004)	United States	Retrospective, case series	Teaching hospital	99	77.3	—	5/9 ^a
Fick et al. (2004)	United States	RCT	Primary care	C: 185 I: 170	≥65	Usual care	6/14 ^b
Allard et al. (2001)	Canada	RCT	Primary care	C: 130 I: 136	C: 80.7 (4.6) I: 80.4 (4.3)	Usual care	10/14 ^b

A, after; B, before; C, control group; I, intervention group; IQR, interquartile range; RCT, randomized controlled trial; SD, standard deviation.

^aThe National Institutes of Health (NIH) quality assessment tool for case series studies.

^bThe National Institutes of Health (NIH) quality assessment tool of controlled intervention study.

^cMedian age.

TABLE 2 | Quality assessment of included studies through the National Institutes of Health (NIH) quality assessment tools.

Quality assessment of controlled intervention studies				
No	Question	Number of studies ($n = 22$)		
		Yes	No	Other (CD, NA, NR)
1	Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	16	6	0
2	Was the method of randomization adequate (i.e., use of randomly generated assignment)?	11	2	9
3	Was the treatment allocation concealed (so that assignments could not be predicted)?	10	3	9
4	Were study participants and providers blinded to treatment group assignment?	6	11	5
5	Were the people assessing the outcomes blinded to the participants' group assignments?	8	8	6
6	Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	19	2	1
7	Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	13	9	0
8	Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	19	1	2
9	Was there high adherence to the intervention protocols for each treatment group?	22	0	0
10	Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	21	1	0
11	Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	22	0	0
12	Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	12	4	6
13	Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	13	2	7
14	Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	9	0	13
Quality assessment tool for case series studies				
No	Question	Number of Studies ($n = 25$)		
		Yes	No	Other (CD, NA, NR)
1	Was the study question or objective clearly stated?	25	0	0
2	Was the study population clearly and fully described, including a case definition?	24	0	1
3	Were the cases consecutive?	4	6	15
4	Were the subjects comparable?	25	0	0
5	Was the intervention clearly described?	22	3	0
6	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	22	3	0
7	Was the length of follow-up adequate?	4	0	21
8	Were the statistical methods described well?	21	4	0
9	Were the results described well?	24	1	0

Earnhart, 2004; Fick et al., 2004; Wessell et al., 2008; Castellino et al., 2010; Lampela et al., 2010; Franchi et al., 2014; Franchi et al., 2016; Moss et al., 2016, 2019; Stevens et al., 2017; Vanderman

et al., 2017; Chan et al., 2018; Stuckey et al., 2018; Vandenberg et al., 2018; Liu et al., 2019; Vu and Huong, 2019), Screening Tool of Older People's potentially inappropriate Prescriptions

TABLE 3 | Effects of medication review interventions on inappropriate prescribing in older adults ($n = 23$).

Author (year)	Performed by	PIM screening tool	Strategies used	Outcome measures	Significant outcomes
Gutiérrez-Valencia et al. (2019)	Pharm	STOPP criteria version 2	Pharmacist-led medicine optimization strategy	Difference in the number of patients with STOPP criteria and mean number of STOPP criteria per patient, before and after intervention	Patients with STOPP criteria B: 184 (78.6%) vs. A: 139 (59.4%), $p < 0.001$ Mean number of STOPP criteria (SD) B: 1.8 (1.4) vs. A: 1.1 (1.2), $p < 0.001$
Khera et al. (2019)	Pharm	2015 Beers and version 2 of STOPP criteria	Pharmacist-led medication review	Number of medications satisfying explicit criteria of STOPP/Beers for PIM	Mean number of medications from STOPP/Beers criteria per patient (total sample) (SD) B: 1.15 (1.2) vs. A: 0.9 (1.1), $p = 0.006$ Mean number of medications from STOPP/Beers criteria per patient (subjects with at least 1 PIM) (SD) B: 2.0 (0.97) vs. A: 1.6 (0.97), $p = 0.005$
Regueiro et al. (2019)	Investigator	Beers 2012 and STOPP 2008	PIM notification program	PIM number before and after	Not achieved
Chan et al. (2018)	Pharm	2015 Beers criteria	Collaborative medication reviews through a standardized template	Number of PIM that patients were taking at the time of admission and discharge	Not achieved
Fajreldines et al. (2018)	Pharm	STOPP criteria (2008)	Lectures and publications on STOPP criteria and suggestions made by clinical pharm to the physician on each individual prescription	Identification of PIM by the pharmacists before (on the admission and discharge) and after (admission and discharge) intervention	Patients with PIM on admission B: 48.9% vs. A: 47.4% Patients with PIM at discharge B: 46.1% vs. A: 16.7% $p = 0.001$
Hurmuz et al. (2018)	Pharm, Phys	STOPP criteria (version 2)	Medication reviews were initiated by the pharmacist and further carried out in close cooperation with the corresponding general practitioner	Number of PIM and appropriateness of prescribed medicines	Average number of PIM was initially 0.6 (SD = 0.8) per patient and decreased to 0.4, after the intervention (SD = 0.6, $p < 0.05$)
Sennesael et al. (2018)	Pharm	Short version of STOPP criteria (version 2)	Implementation of a screening tool in routine geriatric practice	Proportion of patients with ≥ 1 PIM	Not achieved
Stuckey et al. (2018)	Pharm, Phys	Beers criteria	Distribution of materials, multidisciplinary discussions, and computerized system	Total high-risk medications based on the Beers list	Total high-risk medications B: 42 vs. A: 28, $p < 0.0005$
Van Der Linden et al. (2018)	Investigators	RASP list	Systematic medication review	Number of RASP identified PIM at discharge; number of discontinued RASP PIM during hospital stay	Average number of RASP PIM at discharge (IQR) B: 2.5 (2.0–3.8) vs. A: 1 (0.0–3.0), $p = 0.008$ Mean number of discontinued RASP PIM during hospital stay (SD) B: 0.79 (1.34) vs. A: 2.28 (1.62), $p < 0.001$
Frankenthal et al. (2017)	Study pharm	2008 STOPP criteria	Review of the medications by the study pharmacist	PIM proportion: number of residents with at least 1 PIM according to the STOPP criteria after 24 months	PIM according to STOPP criteria after 24 months C: 61 (48.4%) vs. I: 42 (33.3%), $p = 0.02$
Van der Linden et al. (2017)	Pharm	RASP list	Pharmacist-led medication review and recommendations reported to the treating physician daily	Number of RASP PIM, proportion of discontinued or reduced drugs that was identified by the RASP list	Average number of discontinued or reduced drugs identified by the RASP list (IQR) C: 1 (1–2) vs. I: 2 (1–4), $p = 0.003$
Campins et al. (2016)	Pharm	STOPP criteria (version 2)	A pharmacist evaluated all drugs prescribed to each patient and discussed recommendations for each drug with the patient's physician and then with the	Proportion of prescriptions rated as PIM; rate of acceptance by physicians	Not achieved

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TABLE 3 | (Continued) Effects of medication review interventions on inappropriate prescribing in older adults (n = 23).

Author (year)	Performed by	PIM screening tool	Strategies used	Outcome measures	Significant outcomes
Tallon et al. (2015)	Pharm	MAI	patient. A final decision was agreed by physicians and their patients in a face-to-face visit Collaborative PACT model on the medication appropriateness of acute hospitalized older patients	Appropriateness of prescribing at pre-admission, during admission, and at discharge	PACT significantly improved the MAI score from pre-admission to admission (mean difference 2.4, 95% CI 1.0 to 3.9, $p < 0.005$) and from pre-admission to discharge (mean difference 4.0, 95% CI 1.7 to 6.4, $p < 0.005$) PACT resulted in significantly fewer drugs with 1 or more inappropriate rating at discharge (PACT 15.0%, standard 30.5%, $p < 0.001$)
Dalleur et al. (2014)	Ger	STOPP criteria (2008)	STOPP criteria recommendations from an inpatient geriatric consultation team (IGCT)	Proportion of PIM discontinued	Discontinuation at discharge of PIM present on admission C: 19.3% vs. I: 39.7%, $p = 0.013$
Frankenthal et al. (2014)	Study pharm	STOPP criteria (2008)	Medication review for all residents at study opening and 6 and 12 months later based on STOPP criteria	Number of PIM over time	Number of PIM at baseline C: 114 (64.7%) vs. I: 129 (70.5%) Number of PIM after 6-month follow-up C: 89 (56%) vs. I: 65 (37.4%), $p = 0.001$ Number of PIM after 12-month follow up C: 79 (54.1%) vs. I: 36 (22.5%), $p < 0.001$
Lopatto et al. (2014)	Phys	Maio criteria	Participatory clinical guidelines development, group educational outreach, and dissemination of educational materials combined with peer-to-peer interactive discussion	PIM incidence rate	Not achieved
Keith et al. (2013)	Phys	Maio criteria	Participatory clinical guidelines development, group educational outreach, and dissemination of educational materials combined with peer-to-peer interactive discussion	Quarterly incidence rates of older patients exposed to PIM	Patients exposed to at least 1 PIM 2007 C: 6,315 (7.7%) vs. I: 6,098 (7.7%) 2009 C: 5,111 (6.1%) vs. I: 4,277 (5.3%) $p < 0.001$
Gallagher et al. (2011)	Phys	2008 STOPP criteria	STOPP screening and recommendations to the attending medical team	Patients with ≥ 1 STOPP criteria at discharge	Patients with ≥ 1 STOPP criteria at discharge C: 93 (48.4%); I: 7 (3.7%), $p < 0.001$
Castelino et al. (2010)	Pharm	2003 Beers criteria	Home Medicine Review (HMR) service	Rate of PIM	Not achieved
Lampela et al. (2010)	Phys, N, physiotherapist, nutritionist	1997 Beers criteria (US 2003 update)	Adjustment of a patient's medication when necessary; evaluation of the indications for all drugs in use; clinical examination, including careful evaluation of cognition, mood, orthostatic reactions, and presence of extrapyramidal symptoms; routine blood tests	Numbers of inappropriate drugs or dosages	Not achieved
Spinewine et al. (2007)	Pharm	MAI, Beers (1997), and ACOVE criteria	The appropriateness of treatment was analyzed, and a pharmaceutical care plan was	Appropriateness of prescribing at admission, discharge, and	Intervention patients significantly more likely than control patients to have (Continued on following page)

TABLE 3 | (Continued) Effects of medication review interventions on inappropriate prescribing in older adults ($n = 23$).

Author (year)	Performed by	PIM screening tool	Strategies used	Outcome measures	Significant outcomes
			prepared. Whenever an opportunity for optimization was identified, the pharmacist discussed that opportunity with the prescriber, who could accept or reject the intervention	3 months after discharge using Beers' criteria	improvements in Beers' criteria [OR 0.6 (95% CI 0.3, 1.1)]
Brown and Earnhart (2004)	Pharm	Beers criteria (1997)	Acute Care for Elders (ACE) team improvement on the medication regime of geriatric inpatients	Prevalence of PIM	Rate of PIM at admission 10.1%, and discharge 2.02%, $p < 0.02$
Allard et al. (2001)	Pharm, N, Phys	List of PIM developed by the Quebec Committee on Drug Use in the Elderly	A team comprising 2 physicians, a pharmacist, and a nurse reviewed the list of drugs and the diagnoses of patients and formulated suggestions that were mailed to the patients' physician	Number of PIM; number of subjects with at least 1 PIM	Not achieved

A, after group; B, before group; C, control group; CI, confidence interval; Ger, geriatrician; I, intervention group; IQR, interquartile range; MAI, Medication Appropriateness Index; N, nurse; Pharm, pharmacist; Phys, physician; PACT, pharmaceutical care at Tallaght Hospital; PIM, potentially inappropriate medication; RASP, Rationalization of Home Medication by an Adjusted STOPP list in Older Patient; SD, standard deviation; STOPP, Screening Tool of Older People's potentially inappropriate Prescriptions; US, United States.

(STOPP) criteria ($n = 15$) (Gallagher et al., 2011; Dalleur et al., 2014; Frankenthal et al., 2014; Campins et al., 2016; Urfer et al., 2016; Frankenthal et al., 2017; Price et al., 2017; Fajreldines et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Sennesael et al., 2018; Boersma et al., 2019; Gutiérrez-Valencia et al., 2019; Akkawi et al., 2020; Winata et al., 2020), a combination of Beers and STOPP criteria ($n = 5$) (Ilić et al., 2015; Etcheberria et al., 2018; Najjar et al., 2018; Khera et al., 2019; Regueiro et al., 2019), and Medication Appropriateness Index (MAI) ($n = 1$) (Tallon et al., 2015). Five studies used self-developed or adapted criteria (Allard et al., 2001; Keith et al., 2013; Lopatto et al., 2014; Van der Linden et al., 2017; Van Der Linden et al., 2018), and the remaining studies used a combination of validated (STOPP and/or Beers) and self-developed or adapted criteria.

3.4.2 Interventions Used

After thorough analysis of the studies, five different types of interventions have emerged: medication review, educational interventions, CDSS, multifaceted approaches, and organizational strategies (Tables 3–7, respectively). Twenty-three studies used a medication review approach (Allard et al., 2001; Brown and Earnhart, 2004; Spinewine et al., 2007; Castolino et al., 2010; Lampela et al., 2010; Gallagher et al., 2011; Keith et al., 2013; Dalleur et al., 2014; Frankenthal et al., 2014; Lopatto et al., 2014; Tallon et al., 2015; Campins et al., 2016; Frankenthal et al., 2017; Van der Linden et al., 2017; Chan et al., 2018; Fajreldines et al., 2018; Sennesael et al., 2018; Hurmuz et al., 2018; Stuckey et al., 2018; Van Der Linden et al., 2018; Gutiérrez-Valencia et al., 2019; Khera et al., 2019; Regueiro et al., 2019), an educational intervention was the strategy used in eight studies (Fick et al., 2004; Rognstad et al., 2013; Franchi et al., 2014, 2016; Ilić et al., 2015; Clyne et al., 2016; Etcheberria et al., 2018; Moss et al., 2019), multifaceted approach was present in nine (Clyne et al., 2016; Moss et al., 2016; Gibert et al., 2018; Najjar et al., 2018;

Vandenberg et al., 2018; Boersma et al., 2019; Liu et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020) (i.e., a combination of different interventions), five studies used a CDSS (Urfer et al., 2016; Price et al., 2017; Vanderman et al., 2017; McDonald et al., 2019; Winata et al., 2020), and two used organizational strategies (Wessell et al., 2008; Stevens et al., 2017) (i.e., regulatory policies developed to decrease the number of PIM).

3.4.3 Impact of Medication Review Interventions

Medication review was conducted by different healthcare professionals: physicians (Gallagher et al., 2011; Keith et al., 2013; Lopatto et al., 2014), pharmacists (Brown and Earnhart, 2004; Spinewine et al., 2007; Castolino et al., 2010; Frankenthal et al., 2014; Tallon et al., 2015; Campins et al., 2016; Van der Linden et al., 2017; Chan et al., 2018; Fajreldines et al., 2018; Sennesael et al., 2018; Gutiérrez-Valencia et al., 2019; Khera et al., 2019), pharmacists and physicians (Hurmuz et al., 2018; Stuckey et al., 2018), gerontologists (Dalleur et al., 2014), investigators (Van Der Linden et al., 2018; Regueiro et al., 2019), pharmacist students (Frankenthal et al., 2017), and multidisciplinary teams (Allard et al., 2001; Lampela et al., 2010). Although medication review intervention varies in the included studies, this intervention involved the analysis of the patient's pharmacotherapeutic needs and prescribed drugs, followed by a recommendation to optimize medication.

Six (Brown and Earnhart, 2004; Spinewine et al., 2007; Tallon et al., 2015; Van der Linden et al., 2017; Fajreldines et al., 2018; Gutiérrez-Valencia et al., 2019) of eight medication review interventions conducted by pharmacists at the hospital (Brown and Earnhart, 2004; Spinewine et al., 2007; Tallon et al., 2015; Van der Linden et al., 2017; Chan et al., 2018; Fajreldines et al., 2018; Sennesael et al., 2018; Gutiérrez-Valencia et al., 2019) demonstrate a positive impact on PIM reduction. Among these, in two studies the intervention improved the PIM

TABLE 4 | Effects of educational interventions on inappropriate prescribing in older adults ($n = 8$).

Author (year)	Performed by	Receivers	PIM screening tool	Strategies used	Outcome measures	Significant outcomes
Moss et al. (2016)	Pharm, Phys	Medical residents	Table 2 of 2012 Beers criteria	Enhancing Quality of Prescribing Practices for Veterans Discharged from the Emergency Department (EQUIPPED) provider education through academic detailing, clinical decision support, and provider feedback on prescribing practices	Prescription rate ratio before and after the intervention	The group after the intervention were less likely to prescribe a PIM when compared to the group before the intervention (rate ratio = 0.73, 95% CI = 0.632–0.850; $p < 0.0001$)
Etxeberria et al. (2018)	Research team	Phys	STOPP and Beers criteria	Electronic identification of PIM, training for physicians and structured review of medication	Change in the number of PIM per patient	Number of PIM/patients (SD) B: 0.70 (0.91) vs. A: 0.51 (0.77), $p < 0.0001$
Clyne et al. (2016)	Pharm	Phys (C: 10, I: 11)	Beers, STOPP, McLeod, IPET, ACOVE, and the Prescription Peer Academic Detailing (RxPAD) study—MRC framework	Academic detailing, review of medicines with web-based pharmaceutical treatment algorithms that provide recommended alternative-treatment options, and tailored patient information leaflets	Proportion of patients with PIM and mean number of PIM	Mean number of PIM (SD) C: 1.03 (0.8) vs. I: 0.61 (0.7), $p = 0.01$
Franchi et al. (2016)	Research team	Phys	2012 Beers criteria	E-learning educational program	Reduction in the [PIM prescriptions at hospital discharge (at least 1 PIM)]	Not achieved
Ilić et al. (2015)	Investigator (Phys)	27 Phys	2012 Beers criteria and 2008 STOPP criteria	Lectures and brochures	Inappropriately prescribed drugs	Average number of PIM (Beers) (IQR) B: 11.0 (1.0–43.0) vs. A: 1.0 (1.0–2.0), $p < 0.001$ Average number of PIM (STOPP) (IQR) B: 3.5 (1.0–20.0) vs. A: 1.5 (0.0–6.0), $p < 0.005$ Not achieved
Franchi et al. (2014)	Research Team	Phys (C: 22, I: 54)	2012 Beers criteria	E-learning educational program	Reduction of prescription of PIM	Not achieved
Rognstad et al. (2013)	Phys (peer academic detailers)	Phys (C: 209, I: 256)	13 explicit PIM criteria, assumed to be relevant for the Norwegian general practice setting (based on Beers criteria and The Swedish National Board of Health and Welfare)	Multifaceted educational intervention with feedback and audit	Changes in prescription patterns	Not achieved
Fick et al. (2004)	Research team	Phys (C: 185, I: 170)	1997 Beers criteria for medications to avoid in older adults	Integrated decision support service: 1) a detailed educational brochure listing PIM, 2) a list of suggested PIM alternative medications, and 3) a personally addressed letter that described in detail all the physician's patients who were determined to be in receipt of 1 or more PIM	Rate of providers that prescribed at least 1 PIM	Number of continuously enrolled members with at least 1 PIM declined significantly ($\chi^2 = 13.20$, $p < 0.001$) to 17.9% (3,007/16,818), from a baseline of 19.4% (3,364/17,330)

A, after group; B, before group; C, control group; I, intervention group; Pharm, pharmacist; Phys, physician; PIM, potentially inappropriate medication; SD, standard deviation; STOPP, Screening Tool of Older People's potentially inappropriate Prescriptions.

screening tool score (Spinewine et al., 2007; Tallon et al., 2015). Fajreldines et al. (2018) and Gutiérrez-Valencia et al. (2019) reported that the number of patients with PIM significantly decreased after medication review (19.2% and 30.7%, respectively). Van der Linden et al. (2017) observed a decrease

in the average number of PIM after an intervention. Finally, Brown and Earnhart (2004) conclude that their intervention led to an 8.08% absolute risk reduction.

Among the studies performed by physicians in hospitals, one was conducted at an emergency department of a hospital (Gallagher

TABLE 5 | Effects of clinical decision support system (CDSS) interventions on inappropriate prescribing in older adults ($n = 5$).

Author (year)	PIM screening tool	Strategies used	Outcome measures	Significant outcomes
Winata et al. (2020)	STOPP version 2	Introduction of an electronic medication management system (EMMS)	Number of PIM on admission and discharge per patient; number of patients with ≥ 1 PIM on admission and discharge	Not achieved
McDonald et al. (2019)	Beers and STOPP criteria (version 2), and Choosing Wisely lists	Electronic decision support tool that generates deprescribing opportunities reports	Proportion of patients with 1 or more home medications identified as a PIM and deprescribed at hospital discharge	Not achieved
Price et al. (2017)	STOPP criteria	Electronic medical record with automated STOPP rules	Change in measured PIM rates between the intervention and control groups before the intervention as compared with the difference after the intervention period	Not achieved
Vanderman et al. (2017)	2012 Beers criteria	Medication alert message	Overall PIM, top 10 PIM, and flagged PIM	New top 10 PIM/new total medications B: 1,405/15,539 (12.56%) vs. A: 1,308/15,807 (12.00%), $p = 0.0158$
Urfer et al. (2016)	2008 STOPP criteria	Easy-to-use 5-point checklist: 1) ascertain all current medications used; 2) identify patients at high risk of adverse drug reactions; 3) estimate life expectancy; 4) identify medications which are not indicated and/or are potentially dangerous; and 5) monitor the patient if drugs were stopped or new drugs were added	Proportion of patients prescribed PIM at discharge	Patients with >1 PIM at discharge B: 164 (39.0%) vs. A: 102 (23.7%), $p < 0.001$

A, after group; B, before group; PIM, potentially inappropriate medication; STOPP, Screening Tool of Older People's potentially inappropriate Prescriptions.

et al., 2011), and the remaining two studies used the local health authority databases (Keith et al., 2013; Lopatto et al., 2014). Gallagher et al. (2011) observed a significant reduction in the proportion of patients with at least one PIM in the intervention group (from 43.2% in admission to 3.7%, at discharge). This trend remains stable during the 6 months of follow-up. One study performed a quality improvement program across an Italian region with more than 80,000 older adults and observed that the PIM exposure incidence rate significantly declined 31.4% (from the baseline to the post-intervention period) (Keith et al., 2013).

The intervention performed by a gerontologist in hospitalized patients results in a significant decrease in the number of PIM in patients discharged (PIM discontinuation of 39.7%) (Dalleur et al., 2014). Similar outcomes were achieved in the intervention performed by investigators in hospitalized patients (Van Der Linden et al., 2018).

In primary care, the medication review performed by both physicians and pharmacists results in a significant reduction in the mean number of PIM per patient [from 0.6 to 0.4 (Hurmuz et al., 2018) and from 1.24 to 0.82 (Stuckey et al., 2018)]. In this setting, a multidisciplinary team failed to achieve a significant reduction in the number of PIM, and only one (Khera et al., 2019) of the three pharmacists' interventions (Castelino et al., 2010; Campins et al., 2016; Khera et al., 2019) results in a significant impact in PIM reduction.

Finally, in a chronic care geriatric facility, pharmacy students observed a decline in PIM prescriptions after a follow-up of 12 and 24 months (Frankenthal et al., 2014; Frankenthal et al., 2017).

3.4.4 Impact of Educational Interventions

In the eight included studies (Fick et al., 2004; Rognstad et al., 2013; Franchi et al., 2014, 2016; Ilić et al., 2015; Clyne et al., 2016;

Ettxeberria et al., 2018; Moss et al., 2019) that used educational approaches to reduce PIM, the interventions were performed by the following: a researcher and/or a research team (Fick et al., 2004; Franchi et al., 2014, 2016; Ilić et al., 2015; Ettxeberria et al., 2018), a multifaceted team containing a pharmacist and a physician (Moss et al., 2019) or physicians (peer academic detailers) (Rognstad et al., 2013), or a pharmacist (Clyne et al., 2016). In all studies the target of the educational interventions were physicians. The outcomes of the interventions were measured through the reduction of PIM use or PIM prescriptions. In one of the studies, the included population was polymedicated older adults (Ettxeberria et al., 2018); in the three studies that have a positive impact on PIM, the average number of PIM per patient ranged from 0.7–1.1 before intervention to 0.51–1.5 after the intervention (Ilić et al., 2015; Clyne et al., 2016; Ettxeberria et al., 2018). One study reported that the number of physicians that prescribed at least one PIM declined 17.9% (Fick et al., 2004). Finally, one study reported that after the educational intervention the PIM rate ratio before and after the intervention is 0.73 (Moss et al., 2019).

3.4.5 Impact of Clinical Decision Support System Interventions

Five studies used CDSS to reduce PIM (Urfer et al., 2016; Price et al., 2017; Vanderman et al., 2017; McDonald et al., 2019; Winata et al., 2020). Two of four studies performed in hospitalized patients reported that the implementation of CDSS has a positive impact on PIM deprescription (Urfer et al., 2016; Vanderman et al., 2017). In one study, the introduction of a PIM checklist, in an internal medicine ward, leads to a significant reduction (22.0%) of the risk of

TABLE 6 | Effects of multifaceted interventions on inappropriate prescribing in older adults ($n = 9$).

Author (year)	Educational		CDSS	Medication review	PIM screening tool	Strategies used	Outcome measures	Significant outcomes
	Performed by	Receivers						
Akkawi et al. (2020)	Not reported	Phys, Pharm	X		STOPP version 2	Three educational sessions about PIM and discussion of STOPP criteria, coupled with an introduction of a CDSS	PIM prevalence	Not achieved
Boersma et al. (2019)			X	Phys	STOPP version 1	The intervention consisted of written prescribing recommendations prepared by an independent, clinically experienced research physician using the STRIP Assistant	PIM changes implementation	PIM changes implementations C: 15.3% vs. I: 46.2% ($p < 0.001$)
Liu et al. (2019)			X	Pharm, Phys	Modified and updated 2015 Beers criteria according to common practice and culture in Taiwan	Creation of a multidisciplinary Chi-Mei Integrated Geriatric Emergency Team; creation of a PIM list; computer-based medication reconciliation and integration system to obtain information about medications prescribed	Number of PIM at hospital admission and discharge	Number of PIM on admission B: 173 vs. A: 480, and at discharge B: 88 vs. A: 156. $p < 0.001$
Vu and Huong (2019)	Pharm	Phys		Pharm	2015 Beers criteria	Pharmacists gave a training lecture on the Beers 2015 criteria in 2 h for the medical doctors; the training was also conducted as face-to-face visits. The notebook with the Beers 2015 criteria was provided to the medical doctors	Prevalence of PIM	Prevalence of PIM B: 34.1% vs. A: 23.1%, (odds ratio (OR) = 0.337, 95% CI = 0.207–0.551, $p < 0.001$)
Najjar et al. (2018)	Head of geriatric medicine, 2 Pharms	Pharm		Pharm, Phys	STOPP (version 2) and Beers (2015) criteria	Educational program consisting of 1-h, weekly educational lectures for 1 month, handbook designed was distributed to the physicians at the end of the seminars; collaboration between clinical pharmacists and the prescribers to optimize prescribing: auditing of the physician's orders and providing feedback and recommendations during medical rounds, reminders, and discussions with physicians	Change in the incidence rate of PIM	Incidence rate of PIM B: 61% vs. A: 29.5%, $p < 0.001$

(Continued on following page)

TABLE 6 | (Continued) Effects of multifaceted interventions on inappropriate prescribing in older adults ($n = 9$).

Author (year)	Educational		CDSS	Medication review	PIM screening tool	Strategies used	Outcome measures	Significant outcomes
	Performed by	Receivers						
Gibert et al. (2018)	Research team	20 Phys		Phys	STOPP criteria	STOPP criteria use during primary care GP consultations	Proportion of patients with a reduction of PIM after the intervention	This intervention reduced PIM for 44.9% of the patients ($n = 44$), $p < 0.001$ the intervention, reaching significance ($p = 0.009$) during the postintervention period. PIM prevalence declined at baseline, 22.6% encounters per month were with older veterans taking at least 1 PIM. After the intervention, this proportion had dropped to 16.7% ($p < 0.001$), a 26% relative reduction. Encounters with veterans taking 2 or more PIM showed steady and significant decline, from a baseline of 6.2–4.1% after the intervention ($p < 0.001$), representing a 33.9% relative reduction in multiple PIM prevalence
Vandenberg et al. (2018)	Geriatrician, Pharm, Gerontologist	20 primary care providers, 4 Pharms		Pharm	2012 Beers criteria	A pharmacist-led, one-on-one medication review, to provide rural primary care providers and pharmacists with educational outreach through academic detailing and tools to support safe geriatric prescribing practices, as well as individual audit and feedback on prescribing practice and confidential peer benchmarking	PIM incidence: number of new PIM prescriptions divided by all encounters (opportunities) that a provider had with veterans aged 65 years and older; PIM prevalence—number of encounters with veterans currently taking at least 1 PIM divided by all encounters; multiple PIM prevalence—number of encounters with veterans taking 2 or more PIM divided by all encounters	Not achieved
Moss et al. (2016)	Phys, Geriatricians, Gerontologists, Pharm, N, Clinical application coordinators	73 ED providers (10 physicians, 60 medical residents), 3 advanced practice providers	X		2012 Beers criteria	Provider education; clinical decision support, and provider feedback on prescribing practices	Rate of PIM prescribing over the observation period	Not achieved
Clyne et al. (2015)	Pharm	Phys (C: 11, I: 10)		Phys	Beers, STOPP, McLeod, IPET, ACOVE, and the Prescription Peer Academic Detailing (RxPAD) study—MRC framework	Academic detailing, review of medicines with web-based pharmaceutical treatment algorithms that provide recommended alternative-treatment options, and tailored patient information leaflets	Mean number of PIM	Mean number of PIM (SD) at baseline C: 1.39 (0.6) vs. I: 1.31 (0.6) Mean number of PIM (SD) after intervention completed C: 1.18 (0.1) vs. I: 0.70 (0.1), $p = 0.02$

A, after group; B, before group; C, control group; CDSS, clinical decision support system; CI, confidence interval; ED, emergency department; GP, general practitioner; I, intervention group; N, nurse; Pharm, pharmacist; Phys, physician; PIM, potentially inappropriate medication; SD, standard deviation; STRIP, systematic tool to reduce inappropriate prescribing; STOPP, Screening Tool of Older People's potentially inappropriate Prescriptions.

being prescribed one or more PIM (Urfer et al., 2016). Finally, one study observed that although the total number of newly prescribed PIM did not decrease, the top 10 most common new PIM significantly decreased from 9.0% to 8.3% (Vanderman et al., 2017).

3.4.6 Impact of Multifaceted Interventions

Nine studies used a multifaceted approach as a strategy to decrease the number of PIM (Clyne et al., 2016; Moss et al., 2016; Gibert et al., 2018; Najjar et al., 2018; Vandenberg et al., 2018; Boersma et al., 2019; Liu et al., 2019; Vu and Huong, 2019;

TABLE 7 | Effects of organizational interventions¹ on inappropriate prescribing in older adults ($n = 2$).

Author (year)	PIM screening tool	Strategies used	Outcome measures	Significant outcomes
Stevens et al. (2017)	2012 Beers criteria	Education, informatics-based clinical decision support designed for improved workflow, and individual provider feedback	Average percentage of PIM	Average percentage of PIM per month (SD): Site 1 – B: 11.9% (1.8) vs A: 5.1% (1.5), $p < 0.0001$ Site 2 – B: 8.2% (0.8) vs A: 4.5% (1.0), $p < 0.0001$ Site 3 – B: 8.9% (1.9) vs A: 6.1% (1.7), $p = 0.0007$ Site 4 – B: 7.4% (1.7) vs A: 5.7% (0.8), $p = 0.04$
Wessell et al. (2008)	1997 Beers criteria (US 2003 update)	A quarterly PIM performance report; biannual on-site visits	Change in the prescription rate	Absolute annual decline of 0.018% for always inappropriate medications ($p = 0.03$)

A, After group; B, Before group; PIM, Potentially inappropriate medication; SD, Standard deviation; US, United States.

¹Organizational intervention- a combination of strategies to improve the quality indicators of institutions/organizations and enrolled in the approach all stakeholders, health professionals, and non-health professionals. This intervention uses several approaches, including diagnostic activity (including medication review), Team Building, Intergroup relationship, sensitivity training (including educational sessions).

Akkawi et al., 2020) In two studies, the multifaceted approach consisted in the application of a CDSS followed by a medication review (Boersma et al., 2019; Liu et al., 2019). One study used a combination of educational and CDSS approaches (Akkawi et al., 2020). The remaining studies used, as an approach to decrease the number of PIM, a combination of an educational approach followed by a medication review (Clyne et al., 2016; Moss et al., 2016; Gibert et al., 2018; Najjar et al., 2018; Vandenberg et al., 2018; Vu and Huong, 2019).

Clinical Decision Support System and Medication Review

The combined use of CDSS and medication review strategies led to a significant reduction of the mean number of PIM per patient from 0.7 to 0.23 (Boersma et al., 2019) and an increasing number of PIM changes implementation (intervention: 46.2% vs. control: 15.3%) (Liu et al., 2019).

Educational Intervention and Medication Review

Five of the six studies that used a combination of educational and medication review strategies observed a significant impact on the PIM reduction (Clyne et al., 2016; Gibert et al., 2018; Najjar et al., 2018; Vandenberg et al., 2018; Vu and Huong, 2019). Among these, two studies reported a significant decrease in the mean number of PIM per patient from 0.99–1.18 before intervention to 0.66 to 0.7, after intervention (Clyne et al., 2015; Gibert et al., 2018). Vandenberg et al. (2018) and Vu and Huong (2019) reported that the prevalence of PIM decreased 5.9% and 10.9%, respectively. According to Najjar et al. (2018), the multifaceted approach led to a decrease in the PIM incidence of 31.5%.

Educational Intervention and Clinical Decision Support System

In one study (Akkawi et al., 2020), the multifaceted intervention consists of three educational sessions about PIM and discussion of STOPP criteria, coupled with an introduction of a CDSS. This approach did not achieve significant outcomes.

3.4.7 Impact of Organizational Interventions

One study performed an organizational intervention in four different hospitals and observed a significant decrease in the average percentage of prescribed PIM per month (1.7–6.8) after intervention (Stevens et al., 2017). Another study performed in 99 primary care practices observed that the organizational intervention that includes PIM performance reports, on-site visits, and network meetings was responsible for an absolute annual decline of 0.018% for always inappropriate medication (Wessell et al., 2008).

3.4.8 Impact of Interventions That Have Greater Evidence by Its Design

The analysis of the studies that included a concurrent control and low risk of bias revealed that in the hospital, all the five medication review interventions were effective (Spinewine et al., 2007; Gallagher et al., 2011; Dalleur et al., 2014; Van der Linden et al., 2017; Van Der Linden et al., 2018), two CDSS interventions were effective (Urfer et al., 2016; McDonald et al., 2019), one multifaceted intervention achieved significant impact (Vandenberg et al., 2018), and none of the educational interventions achieved a successful reduction of PIM. In primary care it was observed that all the two multifaceted interventions achieved a significant reduction of PIM (Clyne et al., 2015; Boersma et al., 2019), one (Clyne et al., 2016) of two educational strategies was effective, and none of the medication review and CDSS strategies was well successful.

4 DISCUSSION

Despite the extensive number of studies in the literature on PIM in older patients, only 31 of the included studies reported effective intervention. Among these, 21 presented methodological intervention limitations and could not ensure that the intervention used can be replicated and identical outcomes achieved (Brown and Eamhart, 2004; Fick et al., 2004; Spinewine et al., 2007; Wessell et al., 2008; Gallagher et al.,

2011; Dalleur et al., 2014; Frankenthal et al., 2014; Clyne et al., 2015; Tallon et al., 2015; Urfer et al., 2016; Frankenthal et al., 2017; Van der Linden et al., 2017; Etxeberria et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Van Der Linden et al., 2018; Boersma et al., 2019; Gutiérrez-Valencia et al., 2019; Khera et al., 2019; Liu et al., 2019; Vu and Huong, 2019). Although a meta-analysis was not done, our findings suggested that in the hospital, the most adequate strategy to decrease the number of PIM and/or the patients with at least one PIM was medication review. Concerning primary care setting, the analysis of all the included studies indicated that educational interventions were the most successful. However, when only randomized controlled trial (RCT) studies were analyzed, it did not find greater effectiveness of some interventions over others.

The data of this study also suggested that the inclusion of pharmacists can upgrade the quality of the PIM intervention and effectively promote the well-being of the patients.

Regarding the influence of the number of prescribed medicines per patient in PIM interventions, our data suggested that the success of an intervention is not medicines number-dependent, since the analysis of the successful intervention rate in polymedicated and non-polymedicated patients was similar ($\approx 67\%$).

This work also suggested that most of the studies presented important design limitations, something that limits the grade of their evidence.

Medication review was the most frequent strategy used to improve pharmacotherapy and reduce the number of PIM in hospitalized patients. A reduction in the number of PIM per patient or/and in the number of patients with at least a PIM was achieved for 75% of the medication review interventions (Brown and Earnhart 2004; Spinewine et al., 2007; Gallagher et al., 2011; Keith et al., 2013; Dalleur et al., 2014; Ilić et al., 2015; Tallon et al., 2015; Van der Linden et al., 2017; Chan et al., 2018; Fajreldines et al., 2018; Van Der Linden et al., 2018; Gutiérrez-Valencia et al., 2019). Among the three studies that do not have efficacy in hospitalized patients, the main reasons pointed were as follows: 1) the difficulty to engage physicians to actively participate in the study—they preferred to receive the documentation about drug therapy issues by paper instead of discussing face-to-face the patients' pharmacotherapy (Chan et al., 2018); and 2) the low acceptance of the recommendation by the physicians (Regueiro et al., 2019).

In primary care, 42.9% of the interventional studies (Keith et al., 2013; Hurmuz et al., 2018; Stuckey et al., 2018; Khera et al., 2019) used medication review to improve the pharmacotherapy through the reduction of PIM. The lack of efficacy can be related to 1) the low acceptance rate of recommendations by the physicians (Allard et al., 2001); 2) the PIM list used—for example, Castellino et al. reported that in Australia the medicines listed in Beers criteria were rarely used; 3) the physicians did not use routinely any checklist and do not access computer programs to evaluate hypothetical interactions, and they do not record short-term drug alterations (Lampela et al., 2010); 4) in some cases the patients did not receive the full intervention (Allard et al., 2001); and 6) contamination between control and intervention groups (Campins et al., 2016).

The analysis of all educational interventions performed in primary care revealed that this type of intervention has been

successfully implemented in 75%. However, only one of the two studies that have greater evidence by its design effectively decreased the number of PIM. The success of educational interventions in primary care can be related to the promotion of a specific web training on PIM tools used by physicians in clinical practice, updating the knowledge of physicians in PIM detection (Fick et al., 2004; Clyne et al., 2016; Etxeberria et al., 2018). The lack of efficacy of educational intervention observed in one study can be related to a change in the participants' behavior due to the knowledge that they are taking part in an experiment (Hawthorne effect) (Rognstad et al., 2013).

In hospitalized patients, the poor outcomes achieved by educational interventions can be related to the low interactivity during the education intervention, the lack of knowledge of the clinicians, and the characteristics of the ward included that sometimes make difficult the collection of the data (Franchi et al., 2016).

The implementation of a CDSS in hospitals had a positive impact on 50% of the studies (Urfer et al., 2016; Vanderman et al., 2017). The lack of efficacy of the intervention in the remaining studies can be related to the study design and the fact that the applied criteria are not setting-directed originating a high number of alerts that tend to be ignored by a healthcare professional (McDonald et al., 2019; Winata et al., 2020).

Multifaceted interventions were described as mixed interventions that can reduce the number of PIM (Rahme et al., 2005). In the hospital setting, it was observed that in the two studies that used a combination of educational and medication review strategies, the intervention was well successful (Najjar et al., 2018; Vu and Huong, 2019). In primary care, a combination of educational and medication review strategies results in increased efficacy of the intervention (Clyne et al., 2015; Gibert et al., 2018; Vandenberg et al., 2018).

The results of the included studies suggested that medication review is the most indicated intervention to promote the well-being of the hospitalized patients through the reduction of PIM. The success of medication review strategies at hospital discharge could be related to the fact that the inpatient setting may predispose older adults to new prescriptions and probably unnecessary drugs (Page et al., 2010). Moreover, during the hospitalization physicians tend to resist the change or discontinuation of chronic medication, particularly if the medication is not related to the reason for hospitalization (Page et al., 2010). This high number of prescribed PIM during the hospitalization can be the result of the lack of implemented PIM programs directed to each hospital ward and/or specific condition (Mottet et al., 2018).

To improve the well-being of older adults, besides strategies to reduce PIM, strategies to promote appropriate prescription have also been developed. Medication review is a widely used strategy and with better outcomes to reduce potentially inappropriate prescribing (PIP) in hospitalized older adults. However, in a recent review, Dautzenberg et al. (2021) reported that the heterogeneity between studies does not allow reaching significant conclusion. According to dos Santos et al. (2019), the choice of outcome measures, study design, and

methodological quality of medication review studies make it difficult to analyze the effectiveness of this strategy. The failure of medication review strategies in primary care can be attributed to the lack of time of physicians to perform the medication review (Plácido et al., 2020); also, as a result of this lack of time, even when the medication review was performed, patients' follow-up did not occur (Campins et al., 2016). On the other hand, educational strategies allow the empowerment of primary care physicians who already had enough handling in managing older adults but not the right confidence and knowledge to manage PIM prescription (Maio et al., 2011). Moreover, educational strategies had more impact on prescribing patterns than presenting a physician only with a decision algorithm (Rahme et al., 2005). A previous work observed similar results regarding the effectiveness of educational strategies to reduce PIP in primary care. According to Kunstler et al. (2019), educational strategies are well successful in changing health professional prescribing behavior.

A recent systematic review focused on non-clinical programs to reduce the inappropriate or unnecessary use of medicines observed that interventions consisting of education messages and recommended behavior alternatives were more likely to be successful in reducing the inappropriate use of medicines or medical procedures (Lin et al., 2020). Educational strategies are essential to improve prescription, as observed by Amorim et al. (2021) since physician-related characteristics can influence the number of PIM prescriptions.

Regarding the multifaceted strategies, the scarcity of studies using this approach did not allow clarifying their benefits in PIM reduction.

In the hospital setting, CDSS interventions significantly reduced the PIM number in older adults. Similar results were found in another systematic review (Dalton et al., 2018). The lack of CDSS in primary care can be related to the outdated user interface model (Price et al., 2017).

Regarding the organizational strategies, the studies achieved a significant impact on pharmacotherapy independently of the setting (Wessell et al., 2008; Stevens et al., 2017).

In 47.8% of the included studies, the intervention was performed by a pharmacist or by a multifaceted team that includes at least one pharmacist. Among these studies, the rate that interventions succeeded well was 72.7%. In the remaining studies, the rate of success observed was 62.5%, suggesting that the inclusion of a pharmacist in the PIM interventions team can be beneficial. Previously it was demonstrated that pharmacists are actively engaged in several care-delivery models such as direct patients care and collaborative team-based care, improving pharmacotherapy and ameliorating the patients-related health outcomes (Lee et al., 2015). It was also reported that pharmacists could play an important role in patients' medication review in practice settings such as community pharmacies long-term care facilities, outpatient clinic home care, and hospitals. Moreover, pharmacists-led deprescribing interventions can reduce the number of unnecessary and potentially harmful medications (Silva et al., 2019; Hernández-Prats et al., 2021).

Although this study was performed with scientific rigors, some limitations are present. The search strategy was limited to the

three main health research databases and articles written in English, Portuguese, and Spanish. The included studies were heterogeneous in practice settings, population, size of the samples, and PIM definition that can be variable depending on the screening tool used, which can influence PIM number detected (Thomas and Thomas, 2019; Perpétuo et al., 2021).

Because this review includes studies independently of the quality assessment analysis, an outcomes bias can be aroused. The bias can be attributed to a lack of randomization and blinded interventions and absences/inadequate follow-up period in some studies, compromising a possible scaling up of the interventions.

This study provided valuable data regarding PIM-reduction strategies; however, most of the included studies presented limitations that restrain the extrapolation of the results and a lack of an economic evaluation. Only one study reported that in the intervention group, a significantly lower medication cost was achieved (Frankenthal et al., 2014).

A recent systematic review only found seven articles reporting the economic impact of PIM interventions and suggested that although limited, interventions to optimize medication may outweigh their implementation costs (Laberge et al., 2021).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors meet all four ICJME criteria for authorship. Conceptualization: FR and MH; Data curation: DR, AP, FR, MH, and AF; Formal analysis: DR and AP; Funding acquisition: FR and MH; Investigation: AP and DR; Methodology: FR and MH; Project administration: FR; Resources: FR; Supervision: FR, MH, RM-C, and AF; Validation: FR, AF, and MT-H; Roles/Writing—original draft: AP and DR; Writing—review and editing: FR, MH, RM-C, and AF.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.777655/full#supplementary-material>

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Material

Supplementary Table S1: PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1 and 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2 and 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2 and 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	3 and 4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	3 and 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	3 and 4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	3 and 4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	3 and 4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the	3 and 4

Section and Topic	Item #	Checklist item	Location where item is reported
		model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	3 and 4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary Table S1
Study characteristics	17	Cite each included study and present its characteristics.	4, 5 Table 1 and Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1 and Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5 to 8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	5 to 8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	5 to 8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9 to 11
	23b	Discuss any limitations of the evidence included in the review.	9 to 11
	23c	Discuss any limitations of the review processes used.	11
	23d	Discuss implications of the results for practice, policy, and future research.	11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	12
Competing interests	26	Declare any competing interests of review authors.	12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
 For more information, visit: <http://www.prisma-statement.org/>

Supplementary Table S2: Excluded articles with reason (n=34 44)

No	Authors	Year	Title	Reason for exclusion
1	Balsom et al	2020	Impact of a pharmacist-administered deprescribing intervention on nursing home residents: a randomized controlled trial	Do not address interventions
2	Chivapricha et al	2020	Impact of Geriatric Pharmacy Specialist Interventions to Reduce Potentially Inappropriate Medication Among Hospitalized Elderly Patients at Medical Wards: A Prospective Quasi-Experimental Study	Do not address older patients (≥ 65 years old)
3	Jang et al	2020	Impact of a nationwide prospective drug utilization review program to improve prescribing safety of potentially inappropriate medications in older adults: An interrupted time series with segmented regression analysis	Addresses a pre-selected and/or a limited number of medicines
4	Gedde et al	2020	Less Is More: The Impact of Deprescribing Psychotropic Drugs on Behavioral and Psychological Symptoms and Daily Functioning in Nursing Home Patients. Results From the Cluster-Randomized Controlled COSMOS Trial	Did not report PIM specific outcomes
5	Houliand et al	2020	A Collaborative Medication Review Including Deprescribing for Older Patients in an Emergency	Did not report PIM specific outcomes

			Department: A Longitudinal Feasibility Study	
6	Leguelinel-Blache et al	2020	Impact of pharmacist-led multidisciplinary medication review on the safety and medication cost of the elderly people living in a nursing home: a before-after study	Did not report PIM specific outcomes
7	Schapira et al	2020	A multifactorial intervention to lower potentially inappropriate medication use in older adults in Argentina	Addresses a pre-selected and/or a limited number of medicines
8	Rieckert et al	2020	Use of an electronic decision support tool to reduce polypharmacy in elderly people with chronic diseases: cluster randomised controlled trial	Did not report PIM specific outcomes
9	Alosaimy et al	2019	Effect of a Pharmacist-Driven Medication Management Intervention Among Older Adults in an Inpatient Setting	Do not address interventions
10	Cossette et al	2019	A pharmacist-physician intervention model using a computerized alert system to reduce high-risk medication use in primary care	Addresses a pre-selected and/or a limited number of medicines
11	Parker et al	2019	Effectiveness of using STOPP/START criteria to identify potentially inappropriate medication in people aged ≥ 65 years with chronic kidney disease: a randomized clinical trial	Addresses PIM in patient-specific diseases
12	Prasert et al	2019	Effect of a computerized decision support system on potentially inappropriate medication	Do not address older patients (≥ 65 years old)

			prescriptions for elderly patients in Thailand	
13	Santolaya-Perrin et al	2019	The efficacy of a medication review programme conducted in an emergency department	Did not report PIM specific outcomes
14	Sanz-Tamargo et al	2019	Adaptation of a deprescription intervention to the medication management of older people living in long-term care facilities	Did not report PIM specific outcomes
15	Blanc et al	2018	Prevention of potentially inappropriate medication in internal medicine patients: A prospective study using the electronic application PIM-Check	Did not report PIM specific outcomes
16	Cool et al	2018	Reducing potentially inappropriate drug prescribing in nursing home residents: effectiveness of a geriatric intervention	Do not address older patients (≥ 65 years old)
17	Martin et al	2018	Effect of a Pharmacist-Led Educational Intervention on Inappropriate Medication Prescriptions in Older Adults The D-PRESCRIBE Randomized Clinical Trial	Addresses a pre-selected and/or a limited number of medicines
18	Whitman et al	2018	Pharmacist-led medication assessment and deprescribing intervention for older adults with cancer and polypharmacy: a pilot study	Addresses PIM in patient-specific diseases
19	Cossette et al	2017	Reduction in targeted potentially inappropriate medication use in	Addresses a pre-selected and/or a

			elderly inpatients: a pragmatic randomized controlled trial	limited number of medicines
20	Fried et al	2017	Effect of the Tool to Reduce Inappropriate Medications on Medication Communication and Deprescribing	Did not report PIM specific outcomes
21	Lagrange et al	2017	A context-aware decision-support system in clinical pharmacy: Drug monitoring in the elderly	Did not report PIM specific outcomes
22	Lenander et al	2017	Effects of an intervention (SÄKLÄK) on prescription of potentially inappropriate medication in elderly patients	Addresses a pre-selected and/or a limited number of medicines
23	Cossette et al	2016	Knowledge Translation Strategy to Reduce the Use of Potentially Inappropriate Medications in Hospitalized Elderly Adults	Addresses a pre-selected and/or a limited number of medicines
24	Deliens et al	2016	Drugs prescribed for patients hospitalized in a geriatric oncology unit: Potentially inappropriate medications and impact of a clinical pharmacist	Addresses PIM in patient-specific diseases
25	Kimura et al	2016	Potentially inappropriate medications in elderly Japanese patients: effects of pharmacists' assessment and intervention based on Screening Tool of Older Persons' Potentially Inappropriate Prescriptions criteria ver.2	Do not address interventions
26	Mudge et al	2016	Effects of a pilot multidisciplinary clinic for frequent attending elderly patients on deprescribing	Do not address older patients (≥ 65 years old)

27	Arvisais et al	2015	A Pharmacist–Physician Intervention Model Using a Computerized Alert System to Reduce High-Risk Medication Use in Elderly Inpatients	Addresses a pre-selected and/or a limited number of medicines
28	Alassaad et al	2014	The effects of pharmacist intervention on emergency department visits in patients 80 years and older: subgroup analyses by number of prescribed drugs and appropriate prescribing	Did not report PIM specific outcomes
29	Olson et al	2014	Optimization of Decision Support Tool using Medication Regimens to Assess Rehospitalization Risks	Did not report PIM specific outcomes
30	O’Sullivan et al	2014	The Impact of a Structured Pharmacist Intervention on the Appropriateness of Prescribing in Older Hospitalized Patients	Did not report PIM specific outcomes
31	Peterson et al	2014	Electronic Surveillance and Pharmacist Intervention for Vulnerable Older Inpatients on High-Risk Medication Regimens	Addresses a pre-selected and/or a limited number of medicines
32	Milos et al	2013	Improving the Quality of Pharmacotherapy in Elderly Primary Care Patients Through Medication Reviews: A Randomised Controlled Study	Addresses a pre-selected and/or a limited number of medicines
33	Roughead et al	2013	Bridging evidence-practice gaps: improving use of medicines in elderly Australian veterans	Did not report PIM specific outcomes

34	Lang et al	2012	Interdisciplinary Geriatric and Psychiatric Care Reduces Potentially Inappropriate Prescribing in the Hospital: Interventional Study in 150 Acutely Ill Elderly Patients with Mental and Somatic Comorbid Conditions	Addresses PIM in patient-specific diseases
35	Thorpe et al	2012	The Impact of Family Caregivers on Potentially Inappropriate Medication Use in Noninstitutionalized Older Adults With Dementia	Do not address interventions
36	Beer et al	2011	A pilot randomized controlled trial of deprescribing	Do not address interventions
37	Lapane et al	2011	Evaluation of the Fleetwood Model of Long-Term Care Pharmacy	Addresses a pre-selected and/or a limited number of medicines
38	Mattison et al	2010	Preventing Potentially Inappropriate Medication Use in Hospitalized Older Patients With a Computerized Provider Order Entry Warning System	Addresses a pre-selected and/or a limited number of medicines
39	Stuijt et al	2008	Appropriateness of Prescribing among Elderly Patients in a Dutch Residential Home	Did not report PIM specific outcomes
40	Raebel et al	2007	Randomized Trial to Improve Prescribing Safety in Ambulatory Elderly Patients	Addresses a pre-selected and/or a limited number of medicines

41	Smith et al	2006	The Impact of Prescribing Safety Alerts for Elderly Persons in an Electronic Medical Record	Did not report PIM specific outcomes
42	Briesacher et al	2005	Evaluation of Nationally Mandated Drug Use Reviews to Improve Patient Safety in Nursing Homes: A Natural Experiment	Do not address older patients (≥ 65 years old)
43	Lane et al	2004	Potentially Inappropriate Prescribing in Ontario Community-Dwelling Older Adults and Nursing Home Residents	Addresses a pre-selected and/or a limited number of medicines
44	Harlacher et al	2000	Geriatric assessment in the elderly cancer patient	Do not address interventions

CHAPTER 4

Barriers and facilitators of health professionals in adopting digital health-related tools for medication appropriateness:

A systematic review

IV: Barriers and facilitators of health professionals in adopting digital health-related tools for medication appropriateness: A systematic review

RESUMEN

La salud digital se describe como el uso y desarrollo de todo tipo de tecnologías digitales para mejorar los resultados de salud. Podría utilizarse para prevenir errores de medicación, una prioridad para los sistemas de salud en todo el mundo. Sin embargo, la adopción de estas herramientas sigue siendo lenta. Este estudio tiene como objetivo identificar los factores (actitudes, conocimientos y creencias) que actúan como barreras y/o facilitadores reportados por los profesionales de la salud para la adopción de herramientas digitales relacionadas con la adecuación de la medicación. Se realizó una revisión sistemática buscando en la literatura en las bases de datos científicas MEDLINE PubMed y EMBASE artículos originales sobre datos cualitativos y cuantitativos. Se incluyeron quince artículos y se identificaron, consolidaron y categorizaron un total de 125 barreras y 108 facilitadores en componentes técnicos (n=48), organizacionales (n=12), económicos (n=4), relacionados con el usuario (n=34) y relacionados con el paciente (n=8). Las barreras y facilitadores más comúnmente reportados estaban relacionados con los componentes técnicos, como la necesidad de formación adicional (n=6), el tiempo consumido (n=6) y la facilidad de uso o de aprendizaje para utilizar las herramientas (n=9), respectivamente. En cuanto al análisis del contexto, el acuerdo con las recomendaciones de decisiones clínicas y el impacto en la relación médico-paciente fueron más valorados en atención primaria, mientras que la interfaz de usuario y el diseño del sistema lo fueron en el ámbito hospitalario. Las barreras y facilitadores identificados en este estudio proporcionan información relevante para los desarrolladores y pueden utilizarse como punto de partida para el diseño de herramientas digitales exitosas, específicamente relacionadas con la adecuación de la medicación. Las investigaciones futuras incluyen estudios centrados en la evaluación económica y estudios de caso en profundidad sobre barreras y facilitadores específicos.

Palabras clave: revisión sistemática; adecuación de la medicación; herramientas de salud digital; profesionales de la salud; barreras; facilitadores.

Barriers and facilitators of health professionals in adopting digital health-related tools for medication appropriateness: A systematic review

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Abstract

Objective: Digital health is described as the use and development of all types of digital technologies to improve health outcomes. It could be used to prevent medication errors, a priority for health systems worldwide. However, the adoption of such tools remains slow. This study aims to identify factors (attitudes, knowledge and beliefs) acting as barriers and/or facilitators reported by healthcare professionals (HCPs) for the adoption of digital health-related tools for medication appropriateness.

Methods: A systematic review was performed by searching the literature in the MEDLINE PubMed, and EMBASE scientific databases for original articles regarding qualitative and quantitative data.

Results: Fifteen articles were included and a total of 125 barriers and 108 facilitators were identified, consolidated and categorized into technical ($n = 48$), organizational ($n = 12$), economical ($n = 4$), user-related ($n = 34$), and patient-related ($n = 8$) components. The most often reported barriers and facilitators were technical component-related ones concerning the need for additional training ($n = 6$), the time consumed ($n = 6$), and the easy way of using or learning how to use the tools ($n = 9$), respectively. Regarding setting analysis, agreement with clinical decision recommendations and impact on the doctor-patient relationship were more valued in primary care, while the user interface and system design were in the hospital.

Conclusions: The barriers and facilitators identified in this study provide relevant information to developers and it can be used as a starting point for the designing of successful digital health-related tools, specifically related to medication appropriateness. Future research includes economic evaluation-focused studies and in-depth case studies of specific barriers and facilitators.

Keywords

Systematic review, medication appropriateness, digital health tools, health professionals, barriers, facilitators

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Introduction

Digital health is understood as the use and development of all types of digital technologies to improve health outcomes,¹ encompassing eHealth (information and communication technologies), mHealth (mobile health) and big data.² The widespread use of health information technology has become one of the main strategies to improve the efficiency, accessibility, quality and safety of health systems, clinical decision making, and medication management, helping to avoid errors at ordering and prescribing stages.^{3,4} In fact, in one study, the likelihood of medication errors in hospitals decreased 48% when a prescription drug order was performed through a computerized provider order entry (CPOE) system.⁵

Nowadays, healthcare professionals (HCPs) and patients have access to many digital technology resources involving electronic health records (EHRs), electronic prescribing (ePrescribing), electronic medication administration records (eMARs), remote monitoring, telehealth, websites and applications available for computers, tablets, or smartphones, educational videogames, CPOE, clinical decision support systems (CDSS), bar code medication administration (BCMA), automated medication dispensing cabinets (ADCs) and patient data management systems (PDMs) among others.^{4,6–9} Currently, more than 350,000 health applications are available, and 250 new ones are released every day.¹⁰ Data showed that 58.23% of smartphone users in the United States used and downloaded health-related applications.¹¹ These tools could have several beneficial functionalities such as support for clinical diagnosis or decision making, patient adherence, or simply providing education.¹² It is estimated that the digital health market should reach nearly 660 billion dollars by 2025.¹³ Previous studies found that the implementation of these technologies has been demonstrated to reduce costs by saving time and to improve patients' health outcomes through a reduction of the occurrence of ADR caused by medication errors.^{9,14–18} In addition, the widespread of digital health could help to eliminate health disparities worldwide.¹⁹

Despite the advantages presented above, the adoption of digital health-related tools remains slow.^{20,21} As the digital era emerges, major changes in HCPs' workflow arise, sometimes with a lack of regulation or guidelines, which has led to many HCPs remaining reluctant to adopt digital health technologies.^{22,23} Important knowledge gaps related to digital health education were also identified, reinforcing the need for wider support for HCPs.²⁴ Previously, one study found that only five of 280 diabetes mobile applications evaluated were associated with clinically meaningful improvement, revealing that clinical effectiveness is not always guaranteed.²⁵

Addressing factors that could hamper or promote the adoption of digital health-related tools can help to create

technologies that better meet the needs of HCPs and provide patients with higher-quality care.^{24,26} Therefore, preferences of end-users should be considered for the technology design. HCPs will benefit from clinically meaningful digital solutions, while healthcare systems will need to obtain financial returns or save costs by acquiring digital health technologies.²⁷ Therefore, to improve digital health adherence, an understanding of barriers and facilitators that can influence the adoption and use of digital tools by HCPs is the first step required.

Previous reviews on barriers and facilitators for the implementation of eHealth or mHealth in general,²¹ or the acceptance of medication-related CDSS,²⁸ or in a specific setting^{29,30} showed the following as the most reported barriers and facilitators: time consuming,^{28,29} security and privacy concerns,^{21,23,31} limited knowledge and literacy,^{21,31} weakened communication and interaction with others,^{23,29} and financial support^{21,23,31} as barriers; ease of use,^{21,23,28} and equipment availability and reliability^{21,28,29} as facilitators. However, there is a lack of systematized information on the barriers and facilitators for the use of the various digital tools available to support the appropriate use of medicines. Challenges to the implementation of such technologies should be studied; therefore, with our review, we aim to expand previous findings by covering all types of digital health-related tools for medication appropriateness and to identify factors that are reported by HCPs to act as barriers and/or facilitators in the adoption of digital health-related tools for medication appropriateness. Therefore, outcomes from this systematic review will add more reliable information to the existing body of evidence for developers and all stakeholders involved in the design and creation of successful digital health-related tools.

Material and methods

To provide a comprehensive understanding more useful for clinical decision making and health care decision makers, and to help researchers focus on the most relevant barriers and/or facilitators when developing any types of digital health-related tools, we performed a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines (Table S1).³² The research protocol is registered on PROSPERO (CRD42022363235).

Search strategy

A literature search was conducted on 28 October 2022 on the MEDLINE PubMed and EMBASE scientific databases for articles published since 1 January 2000. The search strategy intended to identify relevant studies addressing barriers and/or facilitators identified by HCPs in adopting

digital health-related tools for medication appropriateness, using the following broad-based search terms strategy: “(barrier OR facilitator OR attitudes OR beliefs OR knowledge) AND (adopt OR adoption OR implementation*) AND (health professional OR health provider OR clinician OR physician OR GP OR general practitioner OR nurse OR pharmacist) AND (digital health-related tool OR digital health tool OR mobile health OR mhealth OR m-health OR electronic health OR ehealth OR e-health OR telehealth OR clinical decision support system OR computerized clinical decision support system) AND (medication appropriateness OR drug appropriateness OR appropriate medication OR inappropriate medication OR inadequate prescription OR quality prescription OR adequate prescription)” (Table S2). The reference list of relevant articles and the author’s files were also searched to identify potential additional articles (snowballing technique).

Study selection

The following inclusion criteria were applied: (i) studies that identify factors (such as attitudes, knowledge, and/or beliefs) acting as barriers (factors hampering) or facilitators (factors promoting) in the adoption of digital health-related tools for medication appropriateness; (ii) studies directed to HCPs in any healthcare context (also including studies in which HCPs are a part of a heterogeneous sample when the data are presented separately for HCPs); (iii) studies that did not have investigating barriers and facilitators to be a mandatory aim; (iv) studies reporting the results of primary data; (v) studies published in Portuguese, English, or Spanish. For this review, an HCP was considered as any individual who requires a degree qualification to practise in their respective healthcare field and to provide healthcare treatments and advice based on formal training and experience.³³

We excluded studies that do not present an analysis of barriers or facilitators as an outcome, reviews, meta-analyses, opinions, letters to the editor that do not provide original data, comments, reports, protocols, duplicate studies and the grey literature. We excluded usability studies, as these look more to analyse system-specific usability problems rather than barriers and facilitators. Studies that analyse electronic prescribing systems which do not address medication appropriateness were also excluded. Studies that identify barriers and facilitators but did not associate them with the intention of HCPs to adopt or use digital health-related tools were excluded.

Two researchers (DR and MR) independently screened all titles and abstracts retrieved from the databases according to the inclusion criteria and evaluated the eligibility of full-text articles. All discrepancies were resolved through discussion with the help of a third researcher (MTH, AF or FR).

Outcome measures

Our primary outcome measure was the data establishing the specific barriers and/or facilitators reported by HCPs in adopting digital health-related tools for medication appropriateness.

Quality assessment

The quality and susceptibility to bias were independently evaluated by two researchers (DR and MR) for each included study. The Mixed Methods Appraisal Tool (MMAT) version 2018 was used to assess the quality of qualitative, quantitative, and mixed methods studies.^{34,35} All discrepancies were resolved through discussion with a third researcher (MTH, AF or FR).

Data extraction

Data were extracted from all studies by two authors (DR and MR) using a data extraction sheet. Data on authors (year), country, study design, setting, sample size, health professionals’ category, methods of data collection, digital health tools, description of tools, types of treatments/drugs, and patients’ subgroups were extracted from each article included. Further data about barriers and facilitators were extracted and analysed.

Data analysis

We defined a barrier as a factor hampering the adoption of digital health-related tools and a facilitator as a factor promoting the adoption of digital health-related tools. Barriers and/or facilitators extracted from the included studies were independently analysed by two researchers, and grouped into the following categories: (i) technical, concerning all barriers and/or facilitators related to digital health tools itself and the associated technology and training; (ii) user-related, including all aspects related to the behaviours, concerns and feelings of HCPs; (iii) economical, aspects associated with costs, funding, financial incentives and/or reimbursement; (iv) organizational, including all barriers and/or facilitators related to the organizational structure and support in which digital health tools are integrated (or where it’s supposed to be); (v) patient-related, including all concerns related to the patient and the quality of care provided. Discrepancies were resolved through discussion with the help of a third researcher. This analysis was conducted for each category concerning barriers and/or facilitators, regardless of the authors’ categorisation. The quotes transcribed in the included studies were also analysed. Subgroup analyses were conducted for the types of barriers and facilitators, and setting (hospital and primary care).

Results

Study selection

The search of the databases yielded 1340 citations by systematically searching the literature in the scientific databases MEDLINE PubMed (n = 1312) and EMBASE (n = 28). After screening titles and abstracts, 13 duplicated articles were removed, and four were added using the snowballing technique. A total of 1327 articles were screened and 87 potentially met the inclusion criteria. Since six articles were not retrieved, only 81 articles were fully screened. Among these articles, 66 were excluded because they did not present an analysis of barriers or facilitators as an outcome (n = 14), did not address medication appropriateness (n = 49), did not present primary data (n = 1), and did not associate barriers and/or facilitators with the intention of HCPs to adopt or use digital health-related tools (n = 2) (Table S3). As a result, 15 articles conducted in 11 countries fulfilled the inclusion criteria and they were included in this systematic review (Figure 1).^{36–50}

Studies characteristics

A general description of the characteristics of the included studies is presented in Table 1. Among them, nine were conducted in Europe,^{36,37,39–42,46,48,50} five in North America,^{43–45,47,49} and one in Asia.³⁸ Most of the studies were qualitative (n = 9),^{36,37,39–41,44,45,47,48} followed by mixed methods studies (n = 4)^{38,42,43,50} and quantitative studies (n = 2).^{46,49} Regarding the setting, the most frequent was primary care (n = 7),^{36,39–41,43,44,46} followed by hospitals (n = 2)^{37,38} or both (n = 1),⁴⁸ ambulatory care (n = 1),⁴⁷ an academic internal medicine residency training clinic (n = 1),⁴⁹ and a paediatric oncology centre (n = 1).⁵⁰ In nine studies, the sample size was composed of a multidisciplinary team of several HCPs,^{36,40–44,47,48,50} three with physicians only,^{37,38,49} two with general practitioners (GPs)^{39,46} and one with nurses.⁴⁵ The sample size ranged from 15 to 98 subjects. Four studies were conducted only through interviews^{36,37,39,44} and four through focus groups;^{40,41,47,48} two resorted to surveys,^{46,49} and the remaining five used a combination of methods.^{38,42,43,45,50}

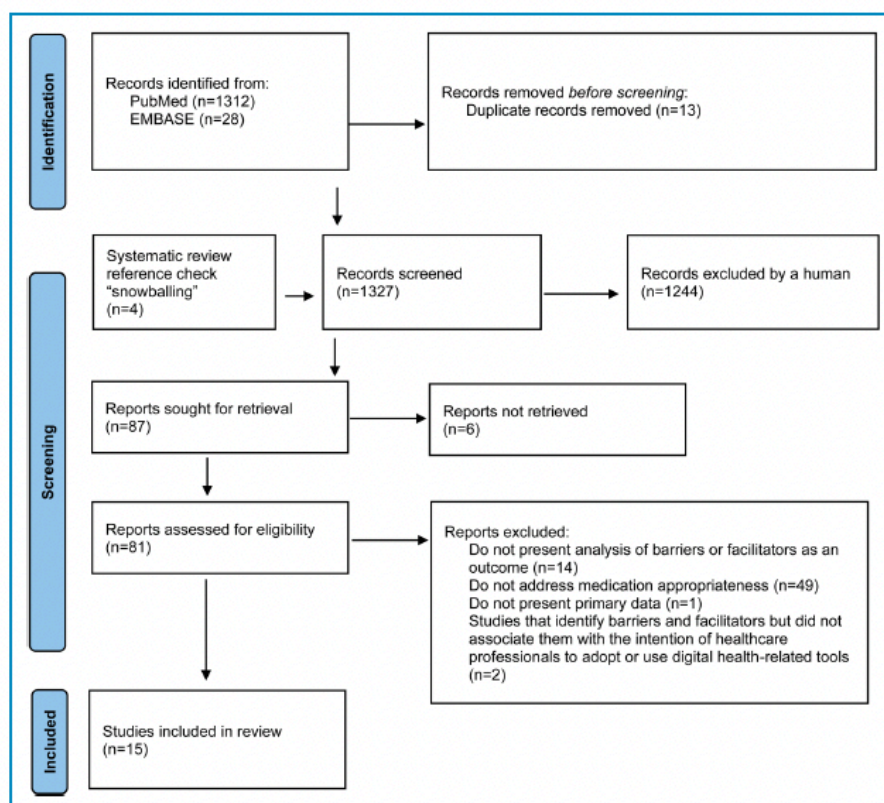


Figure 1. PRISMA diagram of the literature selection in this systematic review.

Table 1. Characteristics of the included studies (n = 15).

Author (year)	Country	Study design	Setting	Sample size	Health professionals' category	Data collection method	Digital health tool	Description of tool	Type of treatment/ drug	Patients' subgroups	Quality assessment/ (score obtained/ total score)
Jeffries et al. (2021) ^a	England	Qualitative	Primary care	29	GP, N, Pharm, and PharmT	Interview	CDSS	Provided a suite of messages that appeared as alerts at the point of prescribing	Not directed to any specific pathology or treatment	Not targeted at any specific population	7/7
Catho et al. (2020)	Switzerland and France	Qualitative	Hospital	29	Phys	Interview	CDSS	Recommendations embedded into the EHR and the CPOE system	Antimicrobial	Not targeted at any specific population	7/7
Jung et al. (2020)	South Korea	Mixed methods	Hospital	61 (quantitative); 15 (qualitative)	Phys	Survey (quantitative); interview (qualitative)	Medication Decision Support System (CDSS)	MDSS in EHR with alert screens; prescription drug monitoring program	Not directed to any specific pathology or treatment	Not targeted at any specific population	15/17
Rieckert et al. (2018)	Germany	Qualitative	Primary care	21	GP	Interview	CDSS	CMR on the screen displaying recommendations regarding missing indications, necessary laboratory tests, evidence-based current medication, dose adjustments, potentially harmful drug-drug interactions, contra-indications, and possible adverse drug events	Several guidelines were used to access medication appropriateness	Older patients (aged 75 and older) taking at least 8 drugs	7/7
Koskela et al. (2016)	Finland	Qualitative	Primary care	21	Phys (9) and N (12)	Focus groups	CDSS	Evidence-based MEDS that provides patient-specific clinical recommendations or warnings in the form of reminders and links to guidelines. Contains CMR where is available guidance for an individual patient on drug therapy	Not directed to any specific pathology or treatment	Not targeted at any specific population	7/7

(continued)

Table 1. Continued.

Author (year)	Country	Study design	Setting	Sample size	Health professionals' category	Data collection method	Digital health tool	Description of tool	Type of treatment/ drug	Patients' subgroups	Quality assessment/ (score obtained/ total score)
Lugtenberg et al. (2015)	Netherlands	Qualitative	Primary care	24	GP and N	Focus groups	CDSS	It provides evidence-based patient-specific advice during consultation in terms of patient data registration, drug prescription and management; in case of a discrepancy between current (guidelines) and advised care, an alert is sent	Cardiovascular risk management, Asthma/COPD, Diabetes mellitus type II, Thyroid disorders, Viral hepatitis and other liver diseases, Atrial fibrillation and Subfertility, Gastro protection and Chronic renal failure	Not targeted at any specific population	7/7
Charani et al. (2013)	UK	Mixed methods	Hospital	81 (quantitative); not reported (qualitative)	Physc and Pharm	Survey (quantitative); Focus groups (qualitative)	Smartphone application	Therapeutic drug monitoring and clinical calculators	Antibiotic	Not targeted at any specific population	13/17
Litvin et al. (2012)	USA	Mixed methods	Primary care	39	Phys (33) and N (6)	Data extracted from the EHR (quantitative); Interview (qualitative)	CDSS	Diagnostic criteria; prompts regarding appropriate antibiotic use; first-line antibiotics recommendations; educational material	Antibiotic for acute respiratory infections	Not targeted at any specific population	14/17
Vedel et al. (2012)	Canada	Qualitative	Primary care	31	Phys, N, and Pharm	Interview	CDSS	Traditional EMR functionalities plus advanced features, such as decision-support tools, patient-centred goal setting, and interdisciplinary functionalities	Not directed to any specific pathology or treatment	Multimorbid patients	7/7
Campion et al. (2011)	USA	Qualitative	Hospital	37	N	Direct observation and interviews	CDSS	Calculates insulin rates using a linear equation explaining	Intensive insulin therapy in the surgical and	Not targeted at any	5/7

(continued)

Table 1. Continued.

Author (year)	Country	Study design	Setting	Sample size	Health professionals' category	Data collection method	Digital health tool	Description of tool	Type of treatment/ drug	Patients' subgroups	Quality assessment/ (score obtained/ total score)
								the recommendations	trauma intensive care units	specific population	
Hor et al. (2010)	Ireland	Cross-sectional (quantitative)	Primary care	98	GP	Survey	CDSS within electronic prescribing	An algorithm that establishes the safety and appropriateness of a prescription, with links to an information system employed to enhance the safety of the prescription. This may include clinical checks which allow alerts to be flagged up to the prescribers on drug-drug interactions or formulary status	Not directed to any specific pathology or treatment	Not targeted at any specific population	6/7
Weingart et al. (2009)	USA	Qualitative	Ambulatory care	25	Phys (21), N (3), and PhysA (1)	Focus groups	Electronic prescribing system	A linked desktop and handheld electronic prescribing system with a variety of drug allergy and interaction alerts, medication pick lists with default dosing, the ability to create favourite prescriptions, formulary tiers tied to patient's insurance type, and the ability to transmit prescriptions to the pharmacy electronically	Not directed to any specific pathology or treatment	Not targeted at any specific population	7/7

(continued)

Table 1. Continued.

Author (year)	Country	Study design	Setting	Sample size	Health professionals' category	Data collection method	Digital health tool	Description of tool	Type of treatment/ drug	Patients' subgroups	Quality assessment/ (score obtained/ total score)
Varonen et al. (2008)	Finland	Qualitative	Primary and secondary care	39	Phys (22 primary care, 17 sary care)	Focus groups	CDSS	Evidence-based MEDS with several updated guidelines	Not directed to any specific pathology or treatment	Not targeted at any specific population	6/7
Schedman et al. (2005)	USA	Not reported (quantitative)	Academic internal medicine residency training clinic	84	Phys	Survey	Computer-based prescription expert system (electronic prescribing system)	Enables electronic maintenance of a medication list, printing and renewing prescriptions, and checks drug-drug and drug-allergy interactions	Not directed to any specific pathology or treatment	Not targeted at any specific population	6/7
Bury et al. (2004)	UK	Mixed methods	Pediatric Oncology Centres and Pediatric Oncology Shared Care Units	36	Clinicians	Survey (quantitative); Interview (qualitative)	Web-based decision support system (CDSS)	A shared electronic record of treatment during continuing therapy, making haematology results, dosage history and other clinical data accessible; provides protocol-based decision support for clinicians when modifying doses of oral chemotherapy – the system advises on any modifications to the level of both oral chemotherapeutic agents for that week and presents an explanation for its proposal	Chemotherapy for Acute Lymphoblastic Leukemia	Children	9/17

CDSS: clinical decision support system; CMR: comprehensive medication review; COPD: chronic obstructive pulmonary disease; CPOE: computerized physician order entry; EHR: electronic health record; EMR: electronic medical record; GP: general practitioner; HCP: healthcare professionals; MDSS: medication decision support system; MEDS: medicine electronic decision support; N: nurse; Pharm: pharmacist; PharmT: pharmacy technicians; Phys: physician; PhysA: physician assistant; UK: United Kingdom; USA: United States of America

*Studies in which HCPs are a part of a heterogeneous sample but it is possible to distinguish their concrete opinions; the sample size reported corresponds only to HCPs.

Table 2. Quality assessment of the included studies through the mixed methods appraisal tool (MMAT) version 2018.

Mixed Methods Appraisal Tool (MMAT) for qualitative studies				
No	Methodological quality criteria	Number of studies (n = 13)		
		Yes	No	Can't tell
1.1	Is the qualitative approach appropriate to answer the research question?	13	0	0
1.2	Are the qualitative data collection methods adequate to address the research question?	12	1	0
1.3	Are the findings adequately derived from the data?	13	0	0
1.4	Is the interpretation of results sufficiently substantiated by data?	10	3	0
1.5	Is there coherence between qualitative data sources, collection, analysis and interpretation?	13	0	0
Mixed Methods Appraisal Tool (MMAT) for quantitative descriptive studies				
No	Methodological quality criteria	Number of studies (n = 6)		
		Yes	No	Can't tell
4.1	Is the sampling strategy relevant to address the research question?	1	5	0
4.2	Is the sample representative of the target population?	3	3	0
4.3	Are the measurements appropriate?	4	2	0
4.4	Is the risk of nonresponse bias low?	4	2	0
4.5	Is the statistical analysis appropriate to answer the research question?	5	1	0
Mixed Methods Appraisal Tool (MMAT) for mixed methods studies				
No	Methodological quality criteria	Number of studies (n = 4)		
		Yes	No	Can't tell
5.1	Is there an adequate rationale for using a mixed methods design to address the research question?	2	2	0
5.2	Are the different components of the study effectively integrated to answer the research question?	4	0	0
5.3	Are the outputs of the integration of qualitative and quantitative components adequately interpreted?	3	1	0
5.4	Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?	4	0	0
5.5	Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?	2	2	0

The most common type of digital health-related tool was CDSS (n = 11),^{36–41,43–45,48,50} followed by electronic prescribing systems (n = 2),^{47,49} CDSS with e-prescribing (n = 1),⁴⁶ and a smartphone application (n = 1).⁴² Three studies were directed for antimicrobial drugs,^{37,42,43} one

was for Potentially Inappropriate Medication (PIM),³⁹ one for chemotherapy,⁵⁰ one for insulin therapy⁴⁵ and one for multiple diseases;⁴¹ the remaining eight studies were not directed to any specific pathology or treatment.^{36,38,40,44,46–49} In one study, the patient subgroup

Table 3. Classification (and acronyms) of barriers.

Classification	Acronym	Total studies (n)	Qualitative studies (n)	Quantitative studies (n)	Mixed methods studies (n)	References
<i>Technical barriers</i>		14	9	2	3	
Alert fatigue	AF	4	4	0	0	36,37,41,47
Bothersome to use	BTU	1	0	0	1	38
Ensure data security	EDS	1	1	0	0	39
Hard to use	HU	1	0	0	1	38
Hardware problems	HP	1	1	0	0	47
Lack of acceptable, standardized product software	LASPS	1	0	1	0	46
Lack of accuracy	LA	1	0	0	1	38
Lack of connection with other medical software	LCOMS	2	2	0	0	39,41
Lack of customizability	LC	2	1	0	1	38,41
Lack of learning capacity of the system	LLCS	1	1	0	0	41
Lack of prioritization of reminders	LPOR	1	1	0	0	40
Lack of protocol reminders	LPR	1	1	0	0	45
Limited value of the alerts	LVA	4	3	0	1	40,41,43,48
The low specificity of alerts	LSA	2	2	0	0	41,47
Need for training	NT	6	2	1	3	36,38,41,43,49,50
Not considering suspended/paused medications	NCSPM	1	1	0	0	40
Not consistent in terms of usability	NCTU	1	0	0	1	38
Not well-integrated functions in the system	NIFS	2	1	0	1	47,50
Outdated medication information	OMI	1	1	0	0	40
Poor user interface and system design	PUISD	5	4	0	1	38,40,41,45,48
Slow the clinical system down	SCSD	1	1	0	0	36
Time-consuming	TC	6	6	0	0	37,39-41,44,45
Unreliable transmission of information	UTI	1	1	0	0	47

(continued)

Table 3. Continued.

Classification	Acronym	Total studies (n)	Qualitative studies (n)	Quantitative studies (n)	Mixed methods studies (n)	References
Unusual to use	UTU	1	1	0	0	39
<i>Organizational barriers</i>		9	7	1	1	
Alters workflow	AW	1	0	0	1	43
Double documentation	DD	1	1	0	0	45
Lack of a strategic plan for implementation	LSPI	1	0	1	0	46
Lack of common instructions in the organization	LCIO	1	1	0	0	40
Lack of internet	LI	3	1	0	2	39,42,43
Limited access to computers and other devices	LACOD	3	0	0	3	42,43,50
Medico-legal issues and liability	MLIL	3	2	0	1	37,45,50
System sustainability	SST	1	1	0	0	44
Use smartphone devices at work	USDW	1	0	0	1	42
<i>Economical barriers</i>		5	3	1	1	
Lack of funding and/or financial incentives	LFFI	5	3	1	1	36,39,46,47,50
<i>User-related barriers</i>		14	9	2	3	
Deters residents from learning the evidence-based guidelines	DRLEBG	1	1	0	0	44
Difficulties navigating the system	DNS	2	1	0	1	47,50
Disagreement with the clinical decision recommendations	DCDR	2	1	0	1	39,43
End-user unfamiliarity with the device and technology	EUUDT	4	3	0	1	37,40,42,44
Fear of misuse of data	FMD	1	1	0	0	39
Forgetting or delay in changing medication	FDCM	1	1	0	0	39
Flexibility to override the system	FOS	1	0	1	0	46
Lack of comfort using the system	LCUS	1	1	0	0	44
Lack of time	LT	3	3	0	0	39,41,47

(continued)

Table 3. Continued.

Classification	Acronym	Total studies (n)	Qualitative studies (n)	Quantitative studies (n)	Mixed methods studies (n)	References
Lack of trust in the system	LTS	3	2	1	0	39,41,46
Less rigorous consideration for individual patients	LRCIP	1	0	0	1	50
Long time to get used	LTGU	1	0	0	1	38
Loss of clinical autonomy	LCA	3	2	1	0	37,46,48
Negative impact on the doctor–patient relationship	NIDPR	4	4	0	0	36,41,44,48
No perceived usefulness	NPU	1	1	0	0	44
Only doctors can access the system	ODCAS	1	1	0	0	40
Preference for hand-written prescriptions	PFHWP	1	0	1	0	49
Pressure to follow the protocol strictly	PFPS	1	0	0	1	50
Previous experience with imperfect/dysfunctional systems	PEIDS	1	1	0	0	48
Reluctance to change	RC	3	2	0	1	37,43,48
Reluctance to discontinue medication prescribed by other specialists	RDMPOS	1	1	0	0	39
Use smartphone devices in the presence of patients	USDPP	1	0	0	1	42
<i>Patient-related barriers</i>		2	1	0	1	
Medication priorities of the patient	MPP	1	1	0	0	39
Patient cooperation in changing medication	PCCM	1	1	0	0	39
Patients with multiple complaints	PMC	1	0	0	1	43

was older adults;³⁹ in one study, it was children;⁵⁰ in one study, it was multimorbid patients.⁴⁴ Twelve studies were not targeted at any specific population.^{36–38,40–43,45–49}

Quality assessment

The quality assessment result of each study is reported in Table 2. Twelve articles fulfilled more than 80% of the exploratory questions.^{36–41,43,44,46–49} Regarding qualitative studies, the main limitation was related to the fact that sometimes the results are not sufficiently substantiated by the data. In quantitative studies, the sampling strategy and

the representativeness of the target population were the major limitations.

Barriers and facilitators related to the use of digital tools on medication appropriateness

In the 15 included studies, 125 barriers and 108 facilitators were identified. After they were consolidated, 59 unique different types of barriers (Table 3) and 47 unique different types of facilitators (Table 4) were obtained. Among the barriers, 24 were classified as technical, 22 were user-related, one was considered economical, nine were

Table 4. Classification (and acronyms) of facilitators.

Classification	Acronym	Total studies (n)	Qualitative studies (n)	Quantitative studies (n)	Mixed methods studies (n)	References
<i>Technical facilitators</i>		13	7	2	4	
Active profile management	APM	1	1	0	0	36
Beneficial calculators	BC	1	1	0	0	40
Easy access to up-to-date information	EAUTDI	2	2	0	0	36,37
Ease of use and learning how to use	EULHU	9	6	1	2	36–38,40,44,47–50
Educational role	ER	3	2	0	1	36,47,50
Enhance medication safety	EMS	2	2	0	0	36,40
The flexibility of the system	FS	1	1	0	0	48
Free of commercial advertisement	FCA	1	1	0	0	39
High sensitivity	HS	1	0	1	0	46
Improve prescribing quality	IPQ	1	0	1	0	46
Independent from the pharmaceutical industry	IPI	1	1	0	0	39
Integrates functions well	IFW	1	1	0	1	38
Pleasant presentation of data	PPD	2	1	0	1	47,50
Practice support	PS	5	4	1	0	36,39,40,47,49
Reduction in medication errors	RME	3	2	1	0	37,46,47
A reliable base of knowledge	RBK	1	1	0	0	48
Simplifies the prescription renewal process	SPRP	1	1	0	0	47
Staff members able to troubleshoot system problems	SMATSP	1	0	0	1	43
System security	SS	1	0	0	1	50
Time-saving and fast	TSF	5	3	1	1	36,37,39,43,49
Training provided	TP	3	2	0	1	37,43,48
Update and complement knowledge	UCK	2	1	0	1	39,42
Useful lab monitoring alerts	ULMA	1	1	0	0	40

(continued)

Table 4. Continued.

Classification	Acronym	Total studies (n)	Qualitative studies (n)	Quantitative studies (n)	Mixed methods studies (n)	References
Useful reminders	UR	4	4	0	0	39,40,47,48
<i>Organizational facilitators</i>		2	0	1	1	
Possibility to accommodate practice workflow	PAPW	1	0	0	1	43
Non-medical clinical staff having access to the system	NMCSAS	1	0	0	1	43
Willingness to invest greater resources in the future	WIGRF	1	0	1	0	46
<i>Economical facilitators</i>		4	4	0	0	
Financial incentives	FI	1	1	0	0	47
Adequate budgeting	AB	1	1	0	0	48
Improve cost effectiveness	ICE	2	2	0	0	36,37
<i>User-related facilitators</i>		12	6	2	4	
Agreement with the clinical decision recommendations	ACDR	2	1	0	1	39,43
Comfort in using it	CFU	1	1	0	0	44
Commitment to use it	CU	4	0	2	2	38,43,46,49
Encourages health professionals to reflect on their practice	EHPRP	3	2	0	1	36,39,50
Familiarity with the system and technology	FST	2	1	1	0	44,46
Improve adherence to policies	IAP	1	0	0	1	42
Improve communication	IC	2	1	0	1	47,50
Increases awareness of prescribing guidelines	IAPG	1	0	0	1	43
Increases clinician confidence	ICC	1	1	0	0	39
Matches expectations	ME	2	1	1	0	44,49
Societal trend	ST	1	1	0	0	44
Trust in the system	TS	6	4	0	2	36-39,45,50
<i>Patient-related facilitators</i>		4	2	1	1	

(continued)

Table 4. Continued.

Classification	Acronym	Total studies (n)	Qualitative studies (n)	Quantitative studies (n)	Mixed methods studies (n)	References
Enhance patient medication safety	EPMS	1	1	0	0	39
Improve communication with the patient	ICP	1	0	0	1	43
Improve patient education	IPE	1	0	0	1	43
Improve quality of care provided	IQC	2	1	1	0	44,49
Patient approval	PA	1	0	1	0	49

organizational, and three were patient-related. Regarding facilitators, 24 were of the technical category, 12 were user-related, three were considered economical, three were organizational, and five were patient-related. Barriers and facilitators according to each study can be found in Table S4.

Technical barriers and facilitators. The most reported technical barriers were the need for training (n=6)^{36,38,41,43,49,50} and time consumed (n=6),^{37,39–41,44,45} closely followed by the poor user interface and system design (n=5),^{38,40,41,45,48} alert fatigue (n=4),^{36,37,41,47} and the limited value of the alerts (n=4).^{40,41,43,48} Less reported ones were the lack of connection with other medical software (n=2),^{39,41} the lack of customizability (n=2),^{38,41} the low specificity of the alerts (n=2),^{41,47} and the lack of well-integrated functions in the system (n=2).^{47,50} The remaining technical barriers were reported only one time.

The most cited technical facilitators were the ease of use and learning how to use (n=9),^{36–38,40,44,47–50} the support given to clinicians (n=5),^{36,39,40,47,49} time saved (n=5),^{36,37,39,43,49} and useful reminders (n=4).^{39,40,47,48} Next, the educational role (n=3),^{36,47,50} reduction in medication errors (n=3),^{37,46,47} and the training provided (n=3) were cited.^{37,43,48} The least described ones were the easy access to up-to-date information (n=2),^{36,37} the possibility to enhance medication safety (n=2),^{36,40} the pleasant presentation of data (n=2),^{47,50} and the opportunity to update and complement knowledge (n=2).^{39,42} The remaining ones were reported only one time.

User-related barriers and facilitators. Regarding user-related barriers, the most reported were end-user unfamiliarity with the device and technology (n=4),^{37,40,42,44} the negative impact on the doctor–patient relationship (n=4),^{36,41,44,48} the lack of time (n=3),^{39,41,47} the lack of trust in the system (n=3),^{39,41,46} the loss of clinical autonomy (n=3)^{37,46,48} and the reluctance to change (n=3).^{37,43,48}

Less reported ones were the difficulties navigating in the system (n=2)^{47,50} and the disagreement with the clinical decision recommendations (n=2).^{39,43} The remaining barriers were reported only one time.

The most reported user-related facilitators were the trust in the system (n=6),^{36–39,45,50} the commitment to use it (n=4)^{38,43,46,49} and the opportunity for HCPs to reflect it in their practice (n=3).^{36,39,50} The less reported ones were the agreement with the clinical decision recommendations (n=2),^{39,43} the familiarity with the system and the technology (n=2),^{44,46} the improvement of communication between HCPs (n=2),^{47,50} and the system meeting expectations (n=2).^{44,49} The remaining user-related facilitators were reported only one time.

Economic barriers and facilitators. Only one economic barrier was reported concerning the lack of funding and/or financial incentives (n=5).^{36,39,46,47,50}

Regarding economic facilitators, the most cited was the improvement of cost-effectiveness (n=2).^{36,37} Financial incentives (n=1)⁴⁷ and adequate budgeting (n=1)⁴⁸ were the least reported ones.

Organizational barriers and facilitators. The most reported organizational barriers were the lack of internet (n=3),^{39,42,43} the limited access to computers and other devices (n=3),^{42,43,50} and medico-legal issues and liability (n=3).^{37,45,50} The remaining ones were only cited once.

Only three organizational facilitators were reported, the possibility to accommodate practice workflow (n=1),⁴³ the possibility of non-medical staff having access to the system (n=1),⁴³ and the willingness to invest greater resources in the future (n=1).⁴⁶

Patient-related barriers and facilitators. Three patient-related barriers were described, the willingness to change according to the medication priorities of the patient (n=1),³⁹ patients' cooperation in changing medication (n=1),³⁹

and the inconvenience to use the system for patients with multiple complaints ($n = 1$).⁴³

The most cited patient-related facilitator was the improved quality of care provided to patients ($n = 2$).^{44,49} The remaining ones were only reported once.

Setting analysis

Alert fatigue, the time consumed, and the ease of use were common technical barriers and facilitators among primary care^{36,39–41,44} and hospitals^{37,38,45} (Table S5). Trust in the system was the common user-related facilitator.^{36–39,45}

However, some differences were also found. Regarding the technical component, HCPs valued the need for training ($n = 3$) in primary care^{36,41,43} and the poor user interface and system design ($n = 2$) was more outlined in hospitals.^{38,45} While in primary care, the lack of internet was an organizational barrier ($n = 2$),^{39,43} medico-legal issues and liability were most reported in hospitals ($n = 2$).^{37,45} Negative impact on the doctor–patient relationship ($n = 3$) and lack of trust in the system ($n = 3$) were user-related barriers in primary care,^{36,39,41,44,46} while in hospitals, HCPs gave more importance to the end-user unfamiliarity with the device and technology ($n = 2$).^{37,42} Finally, besides the trust in the system, HCPs also reported the encouragement to reflect on their practice ($n = 2$),^{36,39} the agreement with the clinical decision recommendations ($n = 2$)^{39,43} and the commitment to use the system ($n = 2$)^{43,46} as user-related facilitators in primary care for the adoption of digital health-related tools.

Discussion

Our review revealed that there are more barriers than facilitators in the adoption of digital health-related tools for medication appropriateness, suggesting that there is a lot of work to be done. The included studies mostly reported barriers and facilitators related to the technical component of the tool, more specifically, the need for additional training and the time consumed as barriers, and the easy way of using or learning how to use it as a facilitator.

HCPs do not want to waste time that could be spent with patients during the consultation with a digital tool that requires too much additional work rather than simplifying it,^{41,51} possibly lowering the quality of care provided.³⁷ Otherwise, there is a propensity for simple systems that require minimal effort to use, view and understand, with an easy way to navigate through them.^{36–38,40,44,47–50} To overcome the need for training and the time needed for technology adoption, user-centred approaches concerning literacy needs, skills, and capabilities should be developed and incorporated into the design of digital health technologies.⁵²

Aligned with our findings, a previous systematic review about barriers and facilitators for the acceptance of

medication-related CDSS identified the time consumed as the most reported barrier, and the ease of use as the most reported facilitator.²⁸ Similar results were found in one study with a specific focus on digital health technology adoption for hypertension management⁵³ and in EHR adoption by physicians.⁵¹ User-friendliness was also reported as one of the most important factors identified by patients and clinicians about digital technology regarding cardiovascular care,⁵⁴ and as the most important predictor of the implementation of eHealth services and digital health technologies.^{21,55} Our results corroborate with a recently published overview of systematic reviews, which found that infrastructure and technical issues are a source of concern for HCPs in utilizing digital health technologies.⁵⁶ To surpass such constraints, digital tool developers should guarantee that user interfaces are intuitive, and technical support is properly supplied.⁵⁷ Investment in infrastructure upgrades may also be necessary to improve equipment and network connections.

Regarding user-related barriers and facilitators, end-user unfamiliarity with the device and technology was reported as a barrier to the adoption of new technologies. Reluctance to change and the lack of trust in the system were also important barriers reported by HCPs since they may be accustomed to traditional methods, resisting to embrace digital technology.⁵⁸ User-friendly interfaces and well-designed digital tools that guarantee long-term sustainability and maintenance are essential for HCPs to integrate these tools into their daily practice, even without extensive technical knowledge.^{19,27} Besides, as a facilitator, the recommendations provided by these technologies can represent an opportunity for HCPs to reflect them in their practice and to consider alternative treatment options, leading to more informed decision making and making their practice even more patient-centred.⁵⁹

The improved quality of care provided to the patient was also reported as one patient-related facilitator. On the other hand, inconvenience to use such tools in patients with multiple complaints was reported as one patient-related barrier, maybe due to the complexity of their health conditions and the need for a more comprehensive assessment and care plan.⁶⁰ Therefore, a digital tool must be flexible. Sometimes patients can also resist to medication changes; however, digital health technologies could help to improve treatment adherence and completion.⁶¹ Reaching patient cooperation requires effective communication and education by HCPs.

Concerning the organizational domain, medico-legal issues and liability were reported as barriers. This could be related with misdiagnosis or errors such as providing inaccurate information, diagnostic suggestions, or treatment recommendations which could lead to patient harm, implying that digital tools may face liability claims.⁶² Otherwise, the growing recognition of significant benefits that technology can bring to healthcare increases the willingness to invest greater resources in digital health-related tools.⁵⁸

The barriers and facilitators identified in our review aligned with existing models and frameworks theorizing user adoption of new technologies including: the Theory of Planned Behaviour (TPB),^{63,64} in which perceived behavioural is determined by the perceived availability of resources, opportunities and skills (like user unfamiliarity with the device and technology, or difficulties navigating through the system); the Theory of Interpersonal Behaviour (TIB)^{64,65} and the Social Cognitive Theory (SCT),^{64,66} with emotions, social and environment factors and habits being identified as the main factors influencing the intention to use (such as societal trend and the increase in clinicians' own confidence); the Technology Acceptance Model (TAM),^{64,67} reflected in the perceived ease of use and attitude toward use; the Motivational Model (MM),^{64,68} being the improvement of the quality of care provided a motivation factor for the adoption of the digital tool for medication appropriateness.

Regarding the setting, most differences between primary care and hospitals are related to the technical component of the digital tool and user-related barriers and facilitators. In primary care, medication-related digital tools provide information to HCPs at the point of care for decision making and direct intervention.⁶⁹ Therefore, agreement with the clinical decision recommendations and the impact on the doctor-patient relationship are very important factors.⁷⁰ Besides, the relationship between HCPs and patients is one of the main factors influencing the delivery of good therapy and high-quality care.⁷¹ In hospitals, medication-related digital technology is directed towards therapeutic drug monitoring and clinical calculators,^{42,45} explaining why user interfaces and system design were more valued. A previous systematic review focused on hospital setting identified hardware and network problems, such as malfunctions and cumbersome access procedures, slow systems, and poor functionality as key barriers for the implementation of electronic systems for the prescribing, dispensing and administration of medicines.²⁹ Also, it had already been reported that HCPs working in hospitals have the perception that CDSS may be used against them in the event of medico-legal controversies.⁷² Clear documentation and legal protection when using digital tools is advised.

The studies included in this review are reported in different years, with up to 20 year of difference, and it is possible to perceive that some barriers and facilitators remain over time. Although there is a recommendation from the United Nations^{73,74} and World Health Organization (WHO)¹ for health digitalization, this study demonstrates that the lack of funding and financial incentives continues to be an important barrier that has not yet been overcome,^{36,50} as also reported by other studies.⁷⁵⁻⁷⁷ Funding challenges could be related to the cost of purchasing the system, expensive equipment, installation charges and staff training costs, among others.^{36,39,46,47,50,76} Unfortunately, an insufficient level of sustainable funding

is an enormous obstacle to implementing digital health technologies.^{21,78,79} Knowledge about digital health outcomes is essential to overcome this barrier,¹ with designing and planning for longitudinal cost analysis at the outset.⁸⁰ Therefore, investment should be directed towards reducing these barriers and enhancing the facilitators when developing tools and with interventions adapted to cultural and sociodemographic differences. Regarding facilitators, HCPs continue to give the same importance to the ease of use of systems, the capacity to trust in digital tools, and the encouragement to reflect on their practice.^{36,50} Having a system that easily adapts to the needs and capabilities of HCPs is a timeless quality. Trust in digital health technologies can be positively influenced by a variety of factors, such as the system's capacity to provide the information needed at the point of prescribing, the ability to provide accurate messages, and the credible source of recommendations available in the system.^{36-39,45,50,81} Digital health systems can be a source of information that could support reflective practice and behaviour change of HCPs,⁸² and make the decision to prescribe a more conscious process.^{36,39,50} This is closely related to the educational role technical facilitator also identified in this study, since the alert information provided may educate the HCP about a potential interaction or prompt him/her to look up more information or confer with a colleague.^{36,47,50}

Over the last 20 years, most of the studies were conducted in Europe, showing that the impact of digital tools for medication appropriateness on health was not well documented, especially in African countries. Despite reports of the use of mobile phones, and information and communication technologies to improve public health in developing countries,⁸³ its application remains slow and inequitable, far from being high.⁸⁴ This could be related to the lack of HCPs in these countries, the high cost of technology implementation, unstable power supply, the excessive burden of diseases⁸⁵ or the limited access to digital technologies.^{85,86} However, according to the WHO Global Strategy on Digital Health, there is an urgent need to invest and overcome the major obstacles felt by developing countries in engaging and accessing digital health technologies.¹ Therefore, a commitment and engagement with stakeholders are needed to advance digital health in these countries.

The data of this study also suggested that CDSS are the most used type of digital health-related tool for medication appropriateness, often making use of web applications, and in EHR or CPOE systems, maybe because several studies have shown that the use of these systems decreased the incidence of medical errors, improving the quality of care provided and patient safety.^{80,87-89} The high use of CDSS can also be explained by its capacity to develop multiple functions beyond medication reconciliation, such as computerized guidelines, order sets, patient data reports, documentation templates, and clinical workflow tools.⁸⁰

They can also be found in different ways such as desktops, tablets, smartphones, biometric monitoring, and wearable health technology. Furthermore, CDSS can be cost-effective for health systems.⁸⁰

With this study, we intend to give relevant information to developers and to all stakeholders for the creation and implementation of digital health-related tools for medication appropriateness. The strengths of this review also include the cross-checking of the reference lists of the included studies to avoid missing papers, and the independent and duplicate process of the screening, data extraction, and quality assessment. Besides, we made a reflection on differences regarding types of barriers and facilitators, and between settings. However, some limitations are also present. Firstly, a search in grey literature was not performed. However, we believe that it does not influence our results since the grey literature is not peer reviewed and is not indexed in major bibliographic resources. Secondly, the search strategy was limited to articles written only in English, Portuguese, and Spanish. Besides, the included studies were heterogeneous concerning digital health-related tools, although most studies used CDSS; the description can be variable in each study. Furthermore, medication appropriateness is generally understood as a guarantee that a specific medication is chosen as the most suitable, effective, and safety option aligned with the individual patient's specific clinical and healthcare needs, minimizing adverse effects and improving therapeutic outcomes.^{90,91} However, authors of the different studies included in this systematic review may have a different definition.

Despite the limitations presented, we believe that our main findings are pertinent. The data collected assessed the barriers and facilitations identified by HCPs for the adoption of medication-related digital tools, adding reliable information for all stakeholders, from developers to policy-makers, allowing them to develop and implement useful and friendly health technologies, and to contribute to the improvement of services and healthcare.

Conclusion

The barriers and facilitators identified in this study can be used as a starting point by developers and all stakeholders involved in the design and creation of successful digital health-related tools. The results suggest that the main barriers are related to usability and technical issues, user attitudes and perceptions, and infrastructure challenges; adherence to digital tools can be facilitated by practice support, user-friendly design and functionality, and quality improvement. The implementation of such tools should mostly follow a technical and user-centred approach, being easy-to-use essentially for HCPs without being time-consuming.

Future research is needed on economic evaluation-focused studies to surpass barriers and to better invest

resources in medication-related digital tool development and implementation. In-depth case studies of specific barriers and facilitators should also be conducted.

Contributorship

Research idea was conceived and conceptualization was performed by Daniela A. Rodrigues, Maria Roque, Ramona Mateos-Campos, Adolfo Figueiras Guzmán, Maria Teresa Herdeiro and Fátima Roque. Material preparation, data collection and analysis were performed by Daniela A. Rodrigues and Maria Roque. The first draft of the manuscript was written by Daniela A. Rodrigues. All authors reviewed, edited, and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Barriers and facilitators of health professionals in adopting digital health-related tools for medication appropriateness: a systematic review.

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Supplementary Information (SI)

Table S1: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 1-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 3 and 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 3 and 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pages 4 and 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 4 and 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 4 and 5

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 4 and 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 3 and 4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 4 and 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 3-5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pages 5 and 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 5
Study characteristics	17	Cite each included study and present its characteristics.	Pages 5 and 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 7 and 15
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 7 and 15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 20-23
	23b	Discuss any limitations of the evidence included in the review.	Page 23
	23c	Discuss any limitations of the review processes used.	Page 23
	23d	Discuss implications of the results for practice, policy, and future research.	Pages 20-24
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 24
Competing interests	26	Declare any competing interests of review authors.	Page 24
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary material

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Table S2: EMBASE and PubMed full search strategy.

EMBASE ALL<1 January 2000 to 28 October 2022>		
Search date: 28 October 2022		
#	Searches	Results
1	(barrier OR facilitator OR attitudes OR beliefs OR knowledge) AND (adopt OR adoption OR implementation*) AND (health professional OR health provider OR clinician OR physician OR GP OR general practitioner OR nurse OR pharmacist) AND (digital health related tool OR digital health tool OR mobile health OR mhealth OR m-health OR electronic health OR ehealth OR e-health OR telehealth OR clinical decision support system OR computerized clinical decision support system) AND (medication appropriateness OR drug appropriateness OR appropriate medication OR inappropriate medication OR inadequate prescription OR quality prescription OR adequate prescription)	28
PubMed ALL<1 January 2000 to 28 October 2022>		
Search date: 28 October 2022		
#	Searches	Results
1	(barrier OR facilitator OR attitudes OR beliefs OR knowledge) AND (adopt OR adoption OR implementation*) AND (health professional OR health provider OR clinician OR physician OR GP OR general practitioner OR nurse OR pharmacist) AND (digital health related tool OR digital health tool OR mobile health OR mhealth OR m-health OR electronic health OR ehealth OR e-health OR telehealth OR clinical decision support system OR computerized clinical decision support system) AND (medication appropriateness OR drug appropriateness OR appropriate medication OR inappropriate medication OR inadequate prescription OR quality prescription OR adequate prescription)	1312

Table S3: Excluded articles with reason (n=66).

No	Authors	Year	Title	Reason for exclusion
	Abuzaid et al	2022	Assessment of the Willingness of Radiologists and Radiographers to Accept the Integration of Artificial Intelligence into Radiology Practice	Do not address medication appropriateness
	Aquino et al	2022	Patients' and Providers' Perspectives on and Needs of Telemonitoring to Support Clinical Management and Self-care of People at High Risk for Preeclampsia: Qualitative Study	Do not address medication appropriateness
	Brünn et al	2022	Use of an Electronic Medication Management Support System in Patients with Polypharmacy in General Practice: A Quantitative Process Evaluation of the AdAM Trial	Do not present analysis of barriers or facilitators as an outcome
	Kidd et al	2022	Improving assessment and progress monitoring in alcohol use disorder: An implementation evaluation of the instant assessment and personalised feedback system (iAx)	Do not address medication appropriateness
	Liu et al	2022	Clinician Acceptance of Order Sets for Pain Management: A Survey in Two Urban Hospitals	Do not address medication appropriateness
	Michiels-Corsten et al	2022	MediQuit - an electronic deprescribing tool: a pilot study in German primary care; GPs' and patients' perspectives	Do not present analysis of barriers or facilitators as an outcome
	Moss et al	2022	Physicians' Views on Utilization of an Electronic Health Record-Embedded Calculator to Assess Risk for Venous Thromboembolism among Medical Inpatients: A Qualitative Study	Do not address medication appropriateness
	Novakowski et al	2022	Health worker perspectives of Smart Triage, a digital triaging platform for quality improvement at a referral hospital in Uganda: a qualitative analysis	Do not address medication appropriateness
	Regge et al	2022	Encouraging Digital Patient Portal Use in Ambulatory Surgery: A Mixed Method Research of Patients and Health Care Professionals Experiences and Perceptions	Do not address medication appropriateness

Soobiah et al	2022	Understanding Engagement and the Potential Impact of an Electronic Drug Repository: Multi-Methods Study	Do not address medication appropriateness
Sibbald et al	2022	Electronic Diagnostic Support in Emergency Physician Triage: Qualitative Study With Thematic Analysis of Interviews	Do not address medication appropriateness
Silvestri et al	2022	Desired Characteristics of a Clinical Decision Support System for Early Sepsis Recognition: Interview Study Among Hospital-Based Clinicians	Do not address medication appropriateness
Smith et al	2022	Exploring cancer patients', caregivers', and clinicians' utilisation and experiences of telehealth services during COVID-19: A qualitative study	Do not address medication appropriateness
Thield et al	2022	Adoption of a Postoperative Pain Self-Report Tool: Qualitative Study	Do not address medication appropriateness
Zaagsma et al	2022	'It really is quite a different ballgame'. A qualitative study into the work experiences of remote support professionals	Do not address medication appropriateness
Zaslavsky et al	2022	Patient Digital Health Technologies to Support Primary Care Across Clinical Contexts: Survey of Primary Care Providers, Behavioral Health Consultants, and Nurses	Do not present analysis of barriers or facilitators as an outcome
Halwani et al	2021	Implementation of e-health innovative technologies in North Lebanon hospitals	Do not address medication appropriateness
Henkhaus et al	2021	Barriers and facilitators to use of a mobile HIV care model to re-engage and retain out-of-care people living with HIV in Atlanta, Georgia	Do not address medication appropriateness
Li et al	2021	Users' Perceptions Toward mHealth Technologies for Health and Well-being Monitoring in Pregnancy Care: Qualitative Interview Study	Do not address medication appropriateness
Muehlensiepen et al	2021	Opportunities and Barriers of Telemedicine in Rheumatology: A Participatory, Mixed-Methods Study	Do not address medication appropriateness

Nikolian et al	2021	A National Evaluation of Surgeon Experiences in Telemedicine for the Care of Hernia and Abdominal Core Health Patients	Do not address medication appropriateness
Pillay et al	2021	Doctor-perceived-barriers to telephone clinics at KwaZulu-Natal hospitals during the COVID-19 pandemic	Do not address medication appropriateness
Sarradon-Eck et al	2021	Attitudes of General Practitioners Toward Prescription of Mobile Health Apps: Qualitative Study	Do not address medication appropriateness
Taber et al	2021	Social dynamics of a population-level dashboard for antimicrobial stewardship: A qualitative analysis	Do not present analysis of barriers or facilitators as an outcome
Vilendrer et al	2021	An App-Based Intervention to Support First Responders and Essential Workers During the COVID-19 Pandemic: Needs Assessment and Mixed Methods Implementation Study	Do not address medication appropriateness
Ash et al	2020	Clinical Decision Support for Worker Health: A Five-Site Qualitative Needs Assessment in Primary Care Settings	Do not address medication appropriateness
Farokhzadian et al	2020	Nurses' experiences and viewpoints about the benefits of adopting information technology in health care: a qualitative study in Iran	Do not address medication appropriateness
Gui et al	2020	Physician champions' perspectives and practices on electronic health records implementation: challenges and strategies	Do not address medication appropriateness
Matsumoto et al	2020	Rheumatology Clinicians' Perceptions of Telerheumatology Within the Veterans Health Administration: A National Survey Study	Do not address medication appropriateness
Mulder-Wildemors et al	2020	Reducing Inappropriate Drug Use in Older Patients by Use of Clinical Decision Support in Community Pharmacy: A Mixed-Methods Evaluation	Studies that identify barriers and facilitators but did not associate them with the intention of healthcare professionals to adopt or use digital health-related tools
Kozikowski et al	2019	Care Team Perspectives and Acceptance of Telehealth in Scaling a Home-Based Primary Care Program: Qualitative Study	Do not address medication appropriateness

Morris et al	2019	Clinician Perspectives on mRehab Interventions and Technologies for People with Disabilities in the United States: A National Survey	Do not address medication appropriateness
Almutairi et al	2018	Physicians' Perceptions of Electronic Prescribing with Electronic Medical Records in Kuwaiti Primary Healthcare Centres	Do not address medication appropriateness
Johansson-Pajala et al	2018	Registered nurses' use of computerised decision support in medication reviews	Do not present analysis of barriers or facilitators as an outcome
Krog et al	2018	Barriers and facilitators to using a web-based tool for diagnosis and monitoring of patients with depression: a qualitative study among Danish general practitioners	Do not address medication appropriateness
Orengo-Aguayo et al	2018	Enhancing the Delivery of an Empirically-Supported Trauma-Focused Treatment for Adolescents: Providers' Views of the Role of Technology and Web-Based Resources	Do not address medication appropriateness
Beam et al	2017	Examining Perceptions of Computerized Physician Order Entry in a Neonatal Intensive Care Unit	Do not present analysis of barriers or facilitators as an outcome
Berkowitz et al	2017	Prescribing an App? Oncology Providers' Views on Mobile Health Apps for Cancer Care	Do not address medication appropriateness
DeMuro et al	2017	How Stakeholder Assessment of E-Prescribing Can Help Determine Incentives to Facilitate Management of Care: A Delphi Study	Do not present primary data
Mills et al	2017	Hospital staff views of prescribing and discharge communication before and after electronic prescribing system implementation	Do not present analysis of barriers or facilitators as an outcome
Morilla et al	2017	Implementing technology in healthcare: insights from physicians	Do not address medication appropriateness
Mozaffar et al	2017	Exploring the roots of unintended safety threats associated with the introduction of hospital ePrescribing systems and candidate avoidance and/or mitigation strategies: a qualitative study	Studies that identify barriers and facilitators but did not associate them with the intention of

			healthcare professionals to adopt or use digital health-related tools
Cresswell et al	2016	Establishing data-intensive healthcare: the case of Hospital Electronic Prescribing and Medicines Administration systems in Scotland	Do not address medication appropriateness
Peeters et al	2016	Use and Uptake of eHealth in General Practice: A Cross-Sectional Survey and Focus Group Study Among Health Care Users and General Practitioners	Do not address medication appropriateness
Rosenkrantz et al	2016	Technology-Assisted Virtual Consultation for Medical Imaging	Do not address medication appropriateness
Gangnon et al	2015	Connecting primary care clinics and community pharmacies through a nationwide electronic prescribing network: A qualitative study	Do not address medication appropriateness
Gider et al	2015	Evaluation of electronic prescription implications in Turkey: an investigation of the perceptions of physicians	Do not present analysis of barriers or facilitators as an outcome
Missiakos et al	2015	Identifying effective computerized strategies to prevent drug-drug interactions in hospital: A user-centered approach	Do not present analysis of barriers or facilitators as an outcome
Lakbala et al	2014	Physicians' perception and attitude toward electronic medical record	Do not address medication appropriateness
Levine et al	2014	Novel telemedicine technologies in geriatric chronic non-cancer pain: primary care providers' perspectives	Do not address medication appropriateness
Makam et al	2013	The good, the bad and the early adopters: providers' attitudes about a common, commercial EHR	Do not address medication appropriateness
Meulendijk et al	2013	General practitioners' attitudes towards decision-supported prescribing: an analysis of the Dutch primary care sector	Do not present analysis of barriers or facilitators as an outcome
Lehnbom et al	2013	A qualitative study of Swedes' opinions about shared electronic health records	Do not address medication appropriateness

Thomas et al	2013	Early experience with electronic prescribing of controlled substances in a community setting	Do not address medication appropriateness
Silow-Carroll et al	2012	Using electronic health records to improve quality and efficiency: the experiences of leading hospitals	Do not address medication appropriateness
Kim et al	2011	Attitude of Korean primary care family physicians towards telehealth	Do not address medication appropriateness
Loscertales et al	2011	Facilitators in the implantation of telemedicine services. Perspective of professionals involved in its design and implementation	Do not address medication appropriateness
Paré et al	2011	Clinicians' perceptions of organizational readiness for change in the context of clinical information system projects: insights from two cross-sectional surveys	Do not address medication appropriateness
Hains et al	2009	Standardizing care in medical oncology: are Web-based systems the answer?	Do not address medication appropriateness
Kralewski et al	2008	Factors influencing physician use of clinical electronic information technologies after adoption by their medical group practices	Do not address medication appropriateness
Zaidi et al	2008	The role of perceptions of clinicians in their adoption of a web-based antibiotic approval system: do perceptions translate into actions?	Do not present analysis of barriers or facilitators as an outcome
Blaya et al	2007	A web-based laboratory information system to improve quality of care of tuberculosis patients in Peru: functional requirements, implementation and usage statistics	Do not address medication appropriateness
Grossman et al	2007	Physicians' experiences using commercial e-prescribing systems	Do not address medication appropriateness
Kramer et al	2007	Implementation of an electronic system for medication reconciliation	Do not present analysis of barriers or facilitators as an outcome

Chisolm et al	2006	The role of computerized order sets in pediatric inpatient asthma treatment	Do not present analysis of barriers or facilitators as an outcome
Barrett et al	2005	Physician perspectives on a pilot prescription monitoring program	Do not present analysis of barriers or facilitators as an outcome

Table S4: Barriers and facilitators according to each study.

Author (year)	Barriers					Facilitators				
	Technical	Organizational	Economical	User-related	Patient-related	Technical	Organizational	Economical	User-related	Patient-related
Jeffries et al (2021)	SCSD NT AF	-	LFFI	NIDPR	-	EMS EULHU PS APM TSF EAUTDI ER	-	ICE	TS EHPRP	-
Catho et al (2020)	AF TC	MLIL	-	EUUDT RC LCA	-	EULHU TSF TP RME EAUTDI	-	ICE	TS	-
Jung et al (2020)	AF LA PUISD LC HU NT NCTU BTU	-	-	LTGU	-	EULHU IFW	-	-	CU TS	-
Rieckert et al (2018)	UTU LCOMS EDS TC	LI	LFFI	LT DCDR LTS RDMPOS FDCM	MPP PCCM	UCK UR TSF PS FCA IPI	-	-	TS ACDR EHPRP ICC	EPMS
Koskela et al (2016)	PUISD OMI LVA LPOR AF NCSPM TC	LCIO	-	ODCAS EUUDT	-	EULHU EMS ULMA UR BC PS	-	-	-	-

Lugtenberg et al (2015)	NT LVA AF PUISD LSA LC LLCS LCOMS TC	-	-	LTS NIDPR LT FMD	-	-	-	-	-
Charani et al (2013)	-	LI LACOD USDW	-	EUUDT USDPP	-	UCK	-	-	IAP -
Litvin et al (2012)	LVA NT	LI LACOD AW	-	RC DCDR	PMC	SMATSP TP TSF	NMCSAS PAPW	-	CU ACDR IAPG ICP IPE
Vedel et al (2012)	TC	SST	-	EUUDT NPU NIDPR DRLEBG LCUS	-	EULHU	-	-	FST ME ST CFU IQC
Campion et al (2011)	LPR PUISD TC	DD MLIL	-	-	-	-	-	-	TS -
Hor et al (2010)	LASPS	LSPI	LFFI	LCA FOS LTS	-	HS IPQ RME	WIGRF		FST CU
Weingart et al (2009)	HP NIFS AF LSA UTI	-	LFFI	LT DNS	-	PPD SPRP RME EULHU ER UR PS	-	FI	IC -
Varonen et al (2008)	LVA PUISD	-	-	PEIDS NIDPR LCA RC	-	FS RBK EULHU UR TP	-	AB	- -

Schectman et al (2005)	NT	-	-	PFHWP	-	TSF PS EULHU	-	-	CU ME	IQC PA
Bury et al (2004)	NIFS NT ER	LACOD MLIL	LFFI	DNS LRCIP PFPS	-	EULHU SS PPD	-	-	TS EHPRP IC	-

Table S5: Most frequent reported barriers and facilitators according to the setting.

<i>Primary care</i>		<i>Hospital</i>	
Technical barriers	Technical facilitators	Technical barriers	Technical facilitators
AF TC NT	EULHU TSF OS	AF TC PUISD	EULHU
Organizational barriers	Organizational facilitators	Organizational barriers	Organizational facilitators
LI	-	MLIL	-
Economical barriers	Economical facilitators	Economical barriers	Economical facilitators
LFFI	-	-	-
User-related barriers	User-related facilitators	User-related barriers	User-related facilitators
NIDPR LTS	TS EHPRP ACDR CU	EUUDT	TS

CHAPTER 5

Comparing AGS Beers 2019, STOPP version 2, and EU(7)-
PIM list in Portuguese older adults in primary health care

V. Comparing AGS Beers 2019, STOPP version 2, and EU(7)-PIM list in Portuguese older adults in primary health care

RESUMEN

Este estudio tiene como objetivo identificar la prevalencia de Medicamentos Potencialmente Inapropiados (PIM) en adultos mayores según los criterios de Beers de 2019, los criterios de la versión 2 de la Herramienta de Evaluación de Prescripciones en Personas Mayores (STOPP v2) y la lista portuguesa EU(7)-PIM, y también analizar la concordancia entre estos criterios. Se realizó un estudio retrospectivo entre 1200 adultos mayores portugueses (≥ 65 años), usuarios de atención primaria de salud. Se recopilaron datos demográficos, clínicos y farmacológicos relacionados con el período comprendido entre abril de 2021 y agosto de 2022. Se realizó un análisis comparativo entre los tres criterios de identificación de PIM, y se determinó la concordancia según el coeficiente de correlación de concordancia de Lin. La edad media fue de 76,3 años (DE 7,7), y el 57,6% de los adultos mayores eran mujeres. Nuestros hallazgos indican tasas de prevalencia variables entre estos criterios, con el 63,8% (IC 95%: 61,0–66,6%), 66,8% (IC 95%: 64,1–69,5%) y el 50,1% (IC 95%: 47,2–53,0%) de los adultos mayores que toman al menos un PIM según la lista EU(7)-PIM, los criterios de Beers 2019 y los criterios STOPP v2, respectivamente. La mayor prevalencia observada fue para los inhibidores de la bomba de protones según la lista EU(7)-PIM (30,1%, IC 95%: 27,6–32,9) y los criterios de Beers (30,1%, IC 95%: 27,6–32,9), y para alprazolam según los criterios STOPP v2 (10,1%, IC 95%: 8,4–11,9%). Se observó una baja concordancia entre los criterios ($< 0,834$). El coeficiente de concordancia más alto se encontró entre la lista EU(7)-PIM y los criterios de Beers (0,833), y el más bajo entre la lista EU(7)-PIM y los criterios STOPP (0,735). Este estudio revela tasas de prevalencia variables de PIM en adultos mayores, según la evaluación con diferentes criterios, y destaca la necesidad de intervenciones específicas y mejoras en las prácticas de prescripción. En el futuro, los estudios deberían centrarse en la aparición de resultados negativos en adultos mayores asociados con el consumo de PIM.

Palabras clave: medicamentos potencialmente inapropiados; adultos mayores; atención primaria de salud; Criterios Beers AGS 2019; Criterios STOPP v2; lista EU(7)-PIM.



Comparing AGS Beers 2019, STOPP version 2, and EU(7)-PIM list in Portuguese older adults in primary health care

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Abstract

Purpose This study aims to identify PIM prevalence in older adults according to the 2019 Beers criteria, Screening Tool of Older Person's Prescriptions version 2 (STOPP v2) criteria, and the Portuguese EU(7)-PIM list and also to analyze the concordance between these criteria.

Methods A retrospective study was conducted among 1200 Portuguese older adults (≥ 65 years old), users of primary health care. Demographic, clinical, and pharmacological data were collected concerning the period between April 2021 and August 2022. A comparative analysis was performed between the three PIM identification criteria, and the concordance was determined according to the Lin concordance correlation coefficient.

Results The mean age was 76.3 (SD 7.7) years old and 57.6% of the older adults were females. Our findings indicate varying prevalence rates among these criteria with 63.8% (95% CI 61.0–66.6%), 66.8% (95% CI 64.1–69.5%), and 50.1% (95% CI 47.2–53.0%) of the older adults take at least one PIM according to the EU(7)-PIM list, Beers 2019, and STOPP v2 criteria, respectively. The highest prevalence observed was for proton pump inhibitors according to EU(7)-PIM list (30.1%, 95% CI 27.6–32.9) and Beers criteria (30.1%, 95% CI 27.6–32.9) and alprazolam according to STOPP v2 criteria (10.1%, 95% CI 8.4–11.9%). A poor concordance between criteria was observed (<0.834). The highest concordance coefficient was found between the EU(7)-PIM list and the Beers criteria (0.833), and the lowest between the EU(7)-PIM list and STOPP criteria (0.735).

Conclusion This study reveals varying prevalence rates of PIM in older adults, as assessed by different criteria, and highlights the need for targeted interventions and improved prescribing practices. In the future, studies should focus on the occurrence of negative outcomes in older adults associated with PIM consumption.

Keywords Potentially inappropriate medications · Older adults · Primary health care · AGS 2019 Beers criteria · STOPP v2 criteria · EU(7)-PIM list

Introduction

Medicines are the most common medical intervention, and its consumption is an important and fundamental component of older adults' care [1]. However, some medications

may become potentially inappropriate medications (PIM) in older people [2], when the risk of adverse effects exceeds the clinical benefit [2, 3]. In fact, it was shown that PIM and frailty interact with each other, having a bidirectional association [4].

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Over the last years, there is an increase on the development of interventions to support prescribing and medication use in older people [5–7], and several criteria for PIM identification have been developed. The first published criteria were the Beers criteria in 1991 [8], updated in 2002 [9], becoming American Geriatrics Society (AGS) responsibility in 2011, and updated again in 2012 [10], 2015 [11], 2019 [12], and 2023 [13]. On the other hand, the Screening Tool of Older Person's Prescriptions (STOPP) criteria were created in 2008 according to European prescription standards [14], with the version 2 (v2) being published in 2015 [15] and version 3 (v3) in 2023 [16]. Also in 2015, a panel of experts from seven European countries (Germany, Finland, Estonia, Holland, France, Spain, and Sweden) developed the EU(7)-PIM list, an explicit criteria tool that allows the identification and comparison of PIM in these countries [17]. Beers criteria were operationalized in Portugal in 2008 [18]. In 2020, the EU(7)-PIM list was operationalized for the Portuguese reality [19], and the STOPP criteria in 2022 [20]. The Beers and STOPP criteria were the basis for developing most of the other criteria that currently exist [3].

According to a recent systematic review, the worldwide overall pooled prevalence of PIM use was 36.7%, varying between 47.0% in Africa, 46.9% in South America, 37.2% in Asia, 35.0% in Europe, 29.0% in North America, and 23.6% in Oceania [21]. Moreover, high PIM prevalence could impose a high economic burden on the older population and society [2]. Primary health care is responsible for the first contact between patients and the health care system and where the most prescriptions for older adults occur [22–24], so research on the use of PIM in this setting is of great interest. One systematic review performed in primary care settings identified factors that contribute to potentially inappropriate prescriptions among older adults which include a greater number of medications and a higher number of comorbidities, while physical comorbidities and psychiatric comorbidities were identified as patient-related clinical risk factors [25]. In Portugal, according to the 2015 Beers Criteria, PIM prevalence in primary care was 68.6% [26]. A nationwide study identified a PIM-defined daily dose frequency of 9.2% according to the EU(7)-PIM list, which was relatively higher in the center region [27]. According to the EU(7)-PIM list and the Beers criteria, PIMs were also present in 12.8% of the adverse drug reactions reported to the Portuguese pharmacovigilance system [28]. Concerning Portuguese institutionalized older adults, one study discovered that 79.3% took PIMs according to the 2019 Beers criteria, and a positive association between polypharmacy and PIM was found ($p < 0.001$) [29]. Regarding nursing home residents, PIM was observed in 86.4% [30]. Recently, one study also found that the number of PIMs at discharge was higher

than at admission in Portuguese geriatric inpatients of an internal medicine service [31].

Although some studies have been carried out in Portugal that show a high percentage of PIMs, to our knowledge, there are no studies comparing the most used criteria in primary health care. So, the aim of this study was to identify the prevalence of PIM in older adults in primary care health of the center region of Portugal, according to the 2019 Beers criteria, STOPP v2 criteria, and the Portuguese EU(7)-PIM list, and to analyze the concordance between these criteria.

Methods

Study design and study population

A retrospective study was performed to characterize the PIM profile among Portuguese older adults (≥ 65 years old), users of primary health care at the Regional Health Administration (Administração Regional de Saúde (ARS)) of Centro (ARSC) of Portugal. This study is part of a project that obtained ethics approval from ARSC (P33-2021). The ARSC has 488,824 older adult users enrolled in their primary health centers. The sample size included 1200 randomly selected older adults actively enrolled in ARSC primary health care facilities in the last month of the period under review, aged 65 or over in the last month of the period under review, and who had at least two primary care consultations in the period under review. This study followed the STROBE checklist for cross-sectional studies (Table S1) [32].

Data source

Data were provided by the Shared Services of the Health Ministry (Serviços Partilhados do Ministério da Saúde) concerning the period between April 2021 and August 2022 and included the following: sex (female or male), age, health problems (according to the International Classification of Primary Care, 2nd edition – ICPC2), clinical laboratory test results, dispensed medicines, dosage, and dosage form.

Data collection

All medicines were analyzed by a Pharmacy PhD student (DAR) who applied three criteria (Beers 2019, STOPP v2, and the Portuguese EU(7)-PIM list) for PIM identification. The classification was revised by two pharmacologists.

Three tools were used for PIM identification: (a) the Portuguese version of the EU(7)-PIM list [19], (b) the 2019 Beers criteria, and [12] (c) the STOPP v2 criteria [15]. Given the information available, it was not possible to apply all criteria. Concerning the EU(7)-PIM list, were

excluded from the analysis drugs in which the classification as PIM is (i) duration of treatment-dependent ($n = 2$), (ii) therapeutic scheme-dependent ($n = 1$), (iii) duration of treatment and dose-dependent ($n = 3$), and (iv) posology-dependent ($n = 5$) (Table S2). Regarding Beers criteria, drugs whose PIM classification required information on gastroparesis ($n = 1$), first-line therapy ($n = 1$), and clinical indication ($n = 3$) were excluded from the analysis since this information was not available (Table S3). At least, according to STOPP criteria, drugs whose PIM classification required information on treatment ($n = 3$), clinical indication ($n = 3$), duration of treatment ($n = 1$), normal systolic ventricular function ($n = 1$), New York Heart Association (NYHA) Class III or IV heart failure ($n = 1$), first-line therapy ($n = 5$), contraindication or clear intolerance to other drugs ($n = 2$), concurrent significant bleeding risk ($n = 1$), coronary stent(s) inserted in the previous 12 months ($n = 1$), first deep venous thrombosis ($n = 1$), first pulmonary embolus ($n = 1$), glaucoma ($n = 3$), (m) sleep disorder ($n = 1$), posology ($n = 1$), acute or chronic respiratory failure ($n = 1$), trying other drugs before ($n = 2$), and intact uterus ($n = 1$) were excluded from the analysis since this information was not available (Table S4).

Statistical analysis

All medicines were coded using the Anatomical and Therapeutic Classification (ATC) system. The results were presented as frequencies and percentages for categorical variables and as means (SD) for numerical variables. Statistical and descriptive analysis was conducted using the Statistical Package for Social Sciences (IBM® SPSS® Statistics version 25). PIM prevalence was defined as the number of older adults taking at least one PIM. A comparative analysis was performed between the three PIM identification criteria, and the concordance was determined according to the Lin concordance correlation coefficient. The findings were represented using their corresponding 95% confidence intervals (CIs).

Results

Study population characteristics

Descriptive statistics of older adults' characteristics are described in Table 1. From the 1200 older adults included in this study, 57.6% were females, and the mean age was 76.3 (SD 7.7) years old. Within the 7921 dispensed drugs, the 2742 ICPC2 symptoms and/or complaints and the 11635 ICPC2 diagnoses and diseases, 426, 228, and 298,

were different from each other, respectively. The mean number of medicines per older adult was 6.6 drugs (SD 4.2). Atorvastatin (31.4%) was the most dispensed drug followed by paracetamol (20.5%), pantoprazole (16.4%), furosemide (15.1%), and simvastatin (14.3%). The mean number of symptoms and/or complaints per older adult was 2.3 (SD 3.0). The most common observed were sleep disturbance (11.8%), low back symptom/complaint (9.3%), knee symptom/complaint (6.5%), tobacco abuse (5.9%), vertigo/dizziness (5.5%), incontinence urine (5.5%), feeling anxious/nervous/tense (5.4%), and cough (5.4%). The mean number of diagnoses and diseases per older adult was 9.7 (SD 5.6). Lipid disorder (62.8%) was the most common condition affecting older adults followed by hypertension uncomplicated (57.8%), overweight (39.7%), back syndrome with radiating pain (26.1%), diabetes non-insulin dependent (25.6%), obesity (24.8%), osteoarthritis of the knee (23.5%), and depressive disorder (20.3%).

PIM prevalence and frequency according to the EU(7)-PIM list, Beers criteria, and STOPP criteria

According to the Portuguese EU(7)-PIM list, 1467 PIMs were detected, 63.8% (95% CI 61.0–66.6%) of the participants took at least one PIM, and the mean number of PIM per older adult was 1.2 (SD 1.3) (Table 2). Overall, the most consumed PIMs were proton pump inhibitors (PPIs) (30.1%, 95% CI 27.6–32.9%), alprazolam (10.1%, 95% CI 8.4–11.9%), and diazepam (5.7%, 95% CI 4.4–7.1%) (Tables 3 and S5).

Concerning Beers criteria, we have identified a total of 1824 PIMs, with 66.8% (95% CI 64.1–69.5%) of the older adults taking at least one PIM and with a mean number of PIM per older adult of 1.5 (SD 1.5) (Table 2). The most consumed PIMs were PPIs (30.1%, 95% CI 27.6–32.9%), furosemide (15.1%, 95% CI 13.1–17.2%), and alprazolam (10.1%, 95% CI 8.4–11.9%) (Tables 3 and S6). Through the application of Table 2 of Beers 2019 criteria (medications that are potentially inappropriate in most older adults), 916 PIMs were detected, with PPIs with the highest value of PIM frequency (39.5%), followed by alprazolam (13.2%) and diazepam (7.4%) (Table S7). Regarding Table 3 of Beers 2019 criteria (medications that are potentially inappropriate in older adults with certain conditions), 157 PIMs were identified (Table S8). The application of Table 4 of Beers 2019 criteria resulted in 856 medications that should be used with caution in older adults, with furosemide presenting the highest value of PIM frequency (21.1%) (Table S9). According to Table 5 of Beers 2019 criteria (potentially clinically important drug-drug interactions that should be avoided in older adults), 206 potentially drug-drug interactions

Table 1 Descriptive statistics of older adults' characteristics ($n = 1200$)

Sex		$n = 1200$
Male		509 (42.4%)
Female		691 (57.6%)
Age (years), mean (SD)		76.3 (SD 7.7)
Dispensed medicines		
Total number		7921
Mean (SD)		6.6 (SD 4.2)
Range (minimum and maximum)		0–25
ATC code of the 5 most dispensed medicines (5th level, chemical substance)		
C10AA05	Atorvastatin	377 (31.4%)
N02BE01	Paracetamol	246 (20.5%)
A02BC02	Pantoprazole	197 (16.4%)
C03CA01	Furosemide	181 (15.1%)
C10AA01	Simvastatin	172 (14.3%)
ICPC2 symptoms/complaints		
Total number		2742
Mean (SD)		2.3 (SD 3.0)
Range (minimum and maximum)		0–24
Most observed ICPC2 symptoms/complaints		
P06	Sleep disturbance	142 (11.8%)
L03	Low back symptom/complaint	112 (9.3%)
L15	Knee symptom/complaint	78 (6.5%)
P17	Tobacco abuse	71 (5.9%)
N17	Vertigo/dizziness	66 (5.5%)
U04	Incontinence urine	66 (5.5%)
P01	Feeling anxious/nervous/tense	65 (5.4%)
R05	Cough	65 (5.4%)
ICPC2 diagnoses and diseases		
Total number		11,635
Mean (SD)		9.7 (SD 5.6)
Range (minimum and maximum)		0–35
Most observed ICPC2 diagnoses and diseases		
T93	Lipid disorder	753 (62.8%)
K86	Hypertension uncomplicated	693 (57.8%)
T83	Overweight	476 (39.7%)
L86	Back syndrome with radiating pain	313 (26.1%)
T90	Diabetes non-insulin-dependent	307 (25.6%)
T82	Obesity	298 (24.8%)
L90	Osteoarthritis of knee	282 (23.5%)
P76	Depressive disorder	244 (20.3%)

ATC Anatomical Therapeutic Chemical (ATC) Classification, ICPC2 International Classification of Primary Care, 2nd edition, SD standard deviation

were identified (Table S10). Any combination of three or more of central nervous system-active drugs had the highest interaction frequency (52.9%). Concerning Table 6 of Beers criteria, 17 medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults were identified, being edoxaban the most frequent (41.2%) (Table S11). The frequency of drugs with strong anticholinergic properties through the application of Table 7 of Beers 2019 criteria was 154,

with cyclobenzaprine being the most frequent (26.0%) (Table S12).

For STOPP criteria, a total of 980 PIM was obtained, 50.1% (95% CI 47.2–53.0%) of the older adults take at least one PIM and the mean number of PIM per older adult was 0.8 (SD 1.1) (Table 2). According to these criteria, alprazolam was the most consumed PIM (10.1%, 95% CI 8.4–11.9%), followed by tramadol and paracetamol (7.8%, 7.8%, 95% CI 6.4–9.5%) and lorazepam (6.1%, 6.1%, 95%

Table 2 PIMs identified according to the EU(7)-PIM list, Beers 2019, and STOPP v2 criteria

EU(7)-PIM list		Beers 2019			STOPP v2		
No. of PIMs*	1467	1824	980				
Mean PIM/ older adult (SD)	1.2 (SD 1.3)	1.5 (SD 1.5)	0.8 (SD 1.1)				
	<i>n</i>	%	95% CI	<i>n</i>	%	95% CI	95% CI
No. of older adults with at least 1 PIM	766	63.8%	61.1–66.6%	802	66.8%	64.1–69.5%	47.2–53.0%
No. of older adults with 1 PIM	369	30.8%	28.2–33.5%	298	24.8%	22.4–27.4%	27.0–32.2%
No. of older adults with 2 PIMs	208	17.3%	15.2–19.6%	219	18.3%	16.1–20.6%	10.8–14.7%
No. of older adults with 3 PIMs	112	9.3%	7.8–11.1%	139	11.6%	9.8–13.5%	4.5–7.2%
No. of older adults with 4 PIMs	47	3.9%	2.9–5.2%	85	7.1%	5.7–8.7%	0.7–2.1%
No. of older adults with ≥ 5 PIMs	30	2.5%	1.7–3.6%	61	5.1%	3.9–6.5%	0.4–1.5%

CI confidence interval, PIM potentially inappropriate medications

Asterisk (*) symbol means an older adult can have more than one PIM

Table 3 The three most consumed PIMs according to the EU(7)-PIM list, Beers 2019, and STOPP v2 criteria

Position	EU(7)-PIM list			Beers 2019			STOPP v2		
	PIM	n	% PIM	PIM	n	% PIM	PIM	n	% PIM
1	Proton pump inhibitors	362	a) 24.7% b) 30.1% (95% CI 27.6–32.9%)	Proton pump inhibitors	362	a) 19.9% b) 30.1% (95% CI 27.6–32.9%)	Alprazolam	121	a) 12.3% b) 10.1% (95% CI 8.4–11.9%)
2	Alprazolam	121	a) 8.3% b) 10.1% (95% CI 8.4–11.9%)	Furosemide	181	a) 9.9% b) 15.1% (95% CI 13.1–17.2%)	Tramadol and paracetamol	94	a) 8.8% b) 7.8% (95% CI 6.4–9.5%)
3	Diazepam	68	a) 4.6% b) 5.7% (95% CI 4.4–7.1%)	Alprazolam	121	a) 6.6% b) 10.1% (95% CI 8.4–11.9%)	Lorazepam	73	a) 6.9% b) 6.1% (95% CI 4.8–7.6%)

CI confidence interval, PIM potentially inappropriate medications

a) percentage of PIMs per tool, b) percentage of PIMs per older adult ($n=1200$)

CI 4.8–7.6%) (Tables 3 and S12). Besides, 85 duplicate drug classes were identified according to Section A.3 of the STOPP criteria.

PIM frequency according to the anatomical group and concordance between criteria

According to Table 4, drugs that act on the nervous system were the most identified as PIM for all the three criteria. However, some differences were found regarding PIM frequency according to the anatomical group. From the 1231 dispensed medicines belonging to the alimentary tract and metabolism group, 34.1% and 30.0% were considered PIM according to the EU(7)-PIM list and Beers criteria, but only 1.5% by the STOPP criteria. Major differences can also be found in the dispensed drugs belonging to the blood and blood-forming organs group, with 35.5% and

24.0% considered PIM according to the EU(7)-PIM list and Beers criteria, but only 3.5% by the STOPP criteria. Concerning the cardiovascular system, the major difference was found in the Beers criteria which considered 12.1% of the drugs dispensed as PIM, unlike the EU(7)-PIM list (4.9%) and STOPP criteria (3.0%). For the systemic hormonal preparations (excluding sex hormones and insulins) group, PIMs were found according to Beers (0.6%) and STOPP criteria (1.7%). Otherwise, drugs belonging to the anti-infectives for systemic use group were identified as PIM by the EU(7)-PIM list (0.5%) and Beers criteria (0.3%). Regarding the respiratory system, drugs were considered PIM only by the EU(7)-PIM list (2.2%). A poor concordance between criteria was found according to Lin's concordance correlation coefficient (Table 5). The highest concordance coefficient was found between the EU(7)-PIM list and the Beers criteria, and the lowest

Table 4 PIM frequency according to the anatomical group

ATC code (1st level, anatomical main group)	Dispensed medicines	EU(7)-PIM list (%)	Beers 2019 (%)	STOPP v2 (%)
Alimentary tract and metabolism (A)	1231	420 (34.1%)	369 (30.0%)	18 (1.5%)
Blood and blood-forming organs (B)	396	140 (35.3%)	95 (24.0%)	14 (3.5%)
Cardiovascular system (C)	2482	121 (4.9%)	299 (12.1%)	74 (3.0%)
Dermatologicals (D)	129	0	0	0
Genito urinary system and sex hormones (G)	269	35 (13.0%)	35 (13.0%)	9 (3.4%)
Systemic hormonal preparations, excl. Sex hormones and insulins (H)	172	0	1 (0.6%)	3 (1.7%)
Anti-infectives for systemic use (J)	394	2 (0.5%)	1 (0.3%)	0
Antineoplastic and immunomodulating agents (L)	8	0	0	0
Musculo-skeletal system (M)	619	263 (42.5%)	167 (27.0%)	240 (38.8%)
Nervous system (N)	1762	479 (27.2%)	857 (48.6%)	622 (35.3%)
Antiparasitic products, insecticides, and repellents (P)	8	0	0	0
Respiratory system (R)	314	7 (2.2%)	0	0
Sensory organs (S)	137	0	0	0
Various (V)	0	0	0	0

Table 5 LIN concordance correlation coefficient

PIM criteria	CCC (95% CI)
EU(7)-PIM list vs. Beers	0.833 (0.648–0.925)
EU(7)-PIM list vs. STOPP	0.735 (0.366–0.904)
Beers vs. STOPP	0.800 (0.568–0.914)

between the EU(7)-PIM list and STOPP criteria. The three criteria have in common 31 unique PIMs (Fig. 1). The EU(7)-PIM list had 50 PIMs in common with the Beers criteria and 41 with the STOPP criteria. Beers and STOPP criteria shared 51 PIMs.

Discussion

This is the first study, to our knowledge, comparing PIM prevalence according to the three different criteria applied simultaneously to the same sample of older adults in primary care in Portugal. PIM prevalence was high, but it was different according to each criterion applied. According to our results, the 2019 Beers criteria are the most sensitive tool to detect PIMs when compared to the EU(7)-PIM list and the STOPP v2 criteria (66.8%, 95% CI 64.1–69.5% vs. 63.8%, 95% CI 61.1–66.6% vs. 50.1%, 95% CI 47.2–53.0%, respectively). A poor concordance between criteria was found which means there was minimal overlap between the criteria.

Several studies have also shown a high PIM prevalence in older adult primary care users, ranging from 23.6 to 75.9% [33–39]. The Beers criteria are usually the tool that

identifies most PIMs in older population when several screening tools are compared to each other [33, 36–38]. Perhaps because this tool considers a drug as PIM-based (i) in the older adult medication profile, (ii) in their diseases or syndromes, and (iii) in their levels of kidney function [12]. Besides, the criteria also contain a list of drugs for which there is some cause of concern but for which the evidence is yet insufficient [12]. The STOPP criteria identified the lowest number of PIMs, maybe because for this tool to be applied, many patients' clinical information is required, and that information was not available equally in all settings [40]. In fact, according to one study performed in nursing homes, sufficient information was available for only 32.5% of the potential STOPP criteria situations [40].

The high mean number of medicines per older adult (6.6, SD 4.2) and the high PIM prevalence presented in this study suggest that polypharmacy can be an important predictor for PIM occurrence, as identified in previous studies [41–43]. According to a recent systematic review, the prevalence of polypharmacy among older adults is 46.0% [44]. Additional reasons may include the presence of multiple comorbidities [45], with our results also revealing a high mean number of conditions per older adult (9.7, SD 5.6). Like our study, hypertension and dyslipidemia are among the most common conditions found in older adults [46].

Different PIMs were identified by the criteria applied. As in our study, PPIs are often recognized as one of the most inappropriately consumed drug classes [47, 48]. They have the indication to treat gastroesophageal reflux disease (GERD), Barrett's esophagus/intestinal metaplasia, functional dyspepsia, *Helicobacter pylori* eradication, and pathological hypersecretory conditions such as Zollinger–Ellison syndrome [49, 50]. However, none of these conditions was identified as one of the most prevalent in our sample, which highlights the potential inappropriate consumption of PPIs in the older population. In addition, long-term use of PPIs is very frequent in older adults [51] and has been associated with several adverse effects, such as dementia; osteoporosis; increased risk of micronutrient deficiencies (calcium, iron, magnesium, vitamin B12); increased risk of *Clostridium difficile*, *Campylobacter*, *Salmonella*, and community-acquired pneumonia infection; kidney disease; and myocardial infarction [52].

Alprazolam was the only common top-dispensed PIM for all criteria. Consistently with several studies, benzodiazepines are one of the most common PIMs identified [53] and widely used by Portuguese older adults. In fact, some studies conclude that alprazolam was the most found PIM in Portuguese samples of institutionalized older adults [29, 54]. The high consumption of benzodiazepines may be related with sleep disturbance and feelings of anxiety

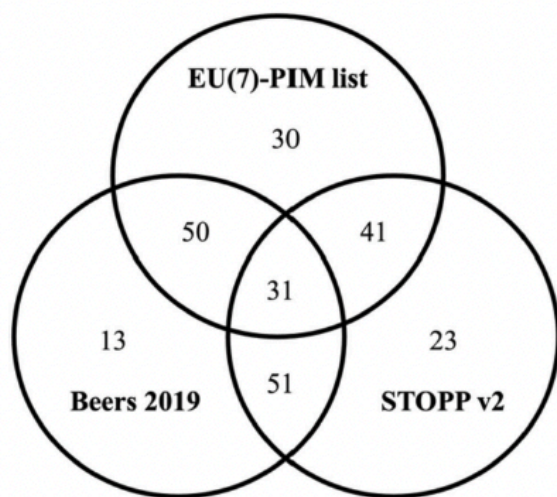


Fig. 1 PIM number according to the EU(7)-PIM list, Beers criteria, and STOPP criteria

and nervousness which were identified as two of the most prevalent symptoms/complaints in our sample (11.8% and 5.4%, respectively). In fact, anxiety disorders are one of the most prevalent mental health illnesses in the older population [55].

Central nervous system-active drugs had the highest interaction frequency (52.9%), regarding potentially drug–drug interactions identified through the application of Table 5 of Beers criteria. This result is in line with an international consensus list of potentially clinically significant drug–drug interactions in older people [56]. Besides, drugs acting in the central nervous system are commonly implicated in potentially serious interactions over time [57].

Considering medications that should be avoided or have their dosage reduced according to the levels of kidney function in older adults through the application of Table 6 of Beers criteria, edoxaban had the higher PIM frequency (41.2%). Direct Oral Anticoagulants (DOACs), such as edoxaban, significantly reduce the occurrence of stroke and embolism in older adults with atrial fibrillation [58], being a more effective and safer alternative to warfarin [59], possibly explaining their high consumption among this population. However, according to Beers 2019 criteria, there is a lack of evidence of efficacy or safety in patients with a CrCl < 30 mL/min, so dose reduction is advised if CrCl 15–50 mL/min and should be avoided if CrCl < 15 or > 95 mL/min [12]. Besides, there is less advantage of DOACs over vitamin K antagonists (VKAs), the more the renal function declines [60].

Cyclobenzaprine, a muscle relaxant, was the most identified drug with strong anticholinergic properties (26.0%) in our study through the application of Table 7 of Beers criteria. In other studies, cyclobenzaprine was also among the most found potentially inappropriate anticholinergic medications in older adults [61, 62]. Sometimes, muscle relaxants are inappropriately used as an alternative to conventional pain medications by older adults [63], and cyclobenzaprine was associated with an increased risk of injury in older adults [64].

The poor concordance between criteria could be related to the applicability of different requirements of each screening tool and the different information available in each setting. The EU(7)-PIM list and the STOPP criteria presented the lowest concordance value, maybe because the EU(7)-PIM list classification as PIM only considers the current medication profile of older adults, including dose and duration of treatment [17], while STOPP criteria also considers previous medication, current and past medical conditions, and laboratory data [15, 40]. In Portugal, one study also compared the same criteria but in older inpatients of an internal medicine ward, with the Beers criteria also identifying the highest number of patients with at least one PIM (92.0%), although with a lower concordance between criteria (< 63.4%) [65].

A previous study in Brazil found high concordance among the 2015 Beers criteria, STOPP v2, the EU(7)-PIM list, and Taiwan criteria [37]. However, the 2019 update made to the 2015 Beers criteria includes the removal of 2 medications, the addition of 3, and the modification to the recommendations related to 6 medications/medication classes [11, 12], probably decreasing concordance with other criteria.

This study contributes with valuable data on the most prevalent PIMs and the concordance between different criteria, which will be useful for the development of interventions designed to improve PIM prescription. The main limitations of this study are the reasons why older adults are taking these drugs are not known, and the exclusion of some criteria of the three screening tools that could not be applied may have underestimated the PIM number.

Conclusion

Our study reveals high PIM prevalence in Portuguese primary health care older adults, with varying prevalence rates according to different criteria, emphasizing the need for targeted interventions and improved prescribing practices. Future studies should focus on the occurrence of negative outcomes in the older adults associated with PIM consumption, and more interventions are needed to reduce PIM use in this population.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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Supplementary Material

Table S1: STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies.

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table S2: EU(7)-PIM excluded PIM with reasons (n=11).

ATC code	EU(7)-PIM	Reason of exclusion
A07DA03	Loperamide (>2 days)	(a) the classification as PIM is duration of treatment-dependent
no ATC, treatment concept PIM	Insulin, sliding scale	(b) the classification of PIM is therapeutic scheme-dependent
J01XE01	Nitrofurantoin (>1 week)	(a) the classification as PIM is duration of treatment-dependent
M01AE01	Ibuprofen (>3 x 400 mg/d or for a period longer than one week)	(c) the classification as PIM is duration of treatment and dose-dependent
M01AE02	Naproxen (>2 x 250 mg/d or for a period longer than one week)	(c) the classification as PIM is duration of treatment and dose-dependent
N05AD01	Haloperidol (>2 mg single dose; >5mg/d)	(c) the classification as PIM is duration of treatment and dose-dependent
N05AH03	Olanzapine (>10 mg/d)	(d) the classification as PIM is posology-dependent
N05BA04	Oxazepam (>60 mg/d)	(d) the classification as PIM is posology-dependent
N05BA06	Lorazepam (>1 mg/d)	(d) the classification as PIM is posology-dependent
N05CD09	Brotizolam (> 0,125 mg/d)	(d) the classification as PIM is posology-dependent
N05CF02	Zolpidem (> 5mg/d)	(d) the classification as PIM is posology-dependent

Table S3: Beers 2019 criteria excluded with reasons (n=5).

Table 2. 2019 American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults		
Organ System, Therapeutic Category, Drug(s)	Criteria - Recommendation	Reason of exclusion
Metoclopramide	Avoid, unless for gastroparesis with duration of use not to exceed 12 weeks except in rare cases	Information about gastroparesis not available
Digoxin for first-line treatment of atrial fibrillation or of heart failure	Avoid this rate control agent as first-line therapy for atrial fibrillation. Avoid as first-line therapy for heart failure.	Information about first-line therapy not available
Peripheral alpha-1 blockers for treatment of hypertension Doxazosin Prazosin Terazosin	Avoid use as an antihypertensive	Information about clinical indication not available
Desmopressin	Avoid for treatment of nocturia or nocturnal polyuria	Information about clinical indication not available
Nitrofurantoin	Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression	Information about clinical indication not available

Table S4: STOPP v2 criteria excluded with reasons (n=28).

Section A: Indication of medication		Reason of exclusion
1	Any drug prescribed without an evidence-based clinical indication.	Information about clinical indication not available
2	Any drug prescribed beyond the recommended duration, where treatment duration is well defined.	Information about duration of treatment not available
Section B: Cardiovascular System		Reason of exclusion
1	Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit)	Information about normal systolic ventricular function not available
2	Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).	Information about NYHA Class III or IV heart failure not available
5	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem).	Information about first-line therapy not available
6	Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).	Information about first-line therapy not available

10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people).	Information about clear intolerance of, or lack of efficacy with, other classes of antihypertensives not available
Section C: Antiplatelet/Anticoagulant Drugs		Reason of exclusion
3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).	Information about concurrent significant bleeding risk not available
4	Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy).	Information about coronary stent(s) inserted in the previous 12 months not available
8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit).	Information about first deep venous thrombosis not available
9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).	Information about first pulmonary embolus not available
Section D: Central Nervous System and Psychotropic Drugs		Reason of exclusion
1	TriCyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).	Information about glaucoma not available
2	Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	Information about first-line therapy not available
7	Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity).	Information about treatment for extra-pyramidal side-effects of neuroleptic medications not available
9	Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).	Information about other non-pharmacological treatments failure not available

10	Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).	Information about sleep disorder not available
12	Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).	Information about first-line therapy not available
Section E: Renal System. The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR (refer to summary of product characteristics datasheets and local formulary guidelines)		Reason of exclusion
1	Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m ² (risk of digoxin toxicity if plasma levels not measured).	Information about specific dosage for each patient not available
Section G: Respiratory System		Reason of exclusion
3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).	Information about glaucoma not available
4	Benzodiazepines with acute or chronic respiratory failure i.e. pO ₂ < 8.0 kPa ± pCO ₂ > 6.5 kPa (risk of exacerbation of respiratory failure).	Information about acute or chronic respiratory failure not available
Section H: Musculoskeletal System		Reason of exclusion
3	Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief).	Information about trying paracetamol before not available
4	Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects).	Information about monotherapy for rheumatoid arthritis not available
5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).	Information about intra-articular injections for mono-articular pain not available
6	Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	Information about contraindication to a xanthine-oxidase inhibitor not available

Section I: Urogenital System		Reason of exclusion
1	Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).	Information about glaucoma not available
Section J: Endocrine System		Reason of exclusion
5	Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).	Information about intact uterus not available
Section L: Analgesic Drugs		Reason of exclusion
1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).	Information about first-line therapy not available
3	Long-acting opioids without short-acting opioids for break-through pain (risk of persistence of severe pain).	Information about trying short-acting opioids before not available

Table S5: Total number of PIM dispensed, according to the EU(7)-PIM list.

ATC code	PIM EU(7)-PIM list	PIM frequency n=1467	PIM %
A02BC	Proton pump inhibitors (PPI) (>8 weeks)	362	24.7%
A03FA01	Metoclopramide	24	1.6%
A10BB01	Glibenclamide	2	0.1%
A10BB12	Glimepiride	2	0.1%
A10BF01	Acarbose	3	0.2%
A10BG03	Pioglitazone	1	0.1%
A10BH01	Sitagliptine	18	1.2%
A10BH02	Vildagliptine	8	0.6%
B01AA07	Acenocoumarol	4	0.3%
B01AC05	Ticlopidine	8	0.6%
B01AC07	Dipyridamole	1	0.1%
B01AE07	Dabigatran etexilate	13	0.9%
B01AF01	Rivaroxaban	48	3.3%
B01AF02	Apixaban	57	3.9%
B03AA	Iron supplements / Ferrous sulfate (>325 mg/d)	9	0.6%
C01AA05	Digoxin	19	1.3%
C01AA08	Metildigoxin	2	0.1%
C01BC03	Propafenone	12	0.8%

C01BD01	Amiodarone	14	1.0%
C01EB15	Trimetazidine	10	0.7%
C01EB17	Ivabradine	2	0.1%
C02AC06	Rilmenidine	7	0.5%
C02CA04	Doxazosin	3	0.2%
C03DA01	Spirolactone (>25 mg/d)	3	0.2%
C04AX17	Vinburnine	1	0.1%
C07AA05	Propranolol	20	1.4%
C07AA07	Sotalol	2	0.1%
C08CA05	Nifedipine (sustained release)	13	0.9%
C08DA01	Verapamil	5	0.3%
C08DB01	Diltiazem	8	0.6%
G04BD02	Flavoxat	13	0.9%
G04BD04	Oxybutynine (non-sustained release)	5	0.3%
G04BD08	Solifenacin	5	0.3%
G04BD09	Trospium	12	0.8%
J01MA17	Prulifloxacin	2	0.1%
M01AB05	Diclofenac	44	3.0%
M01AB08	Etodolac	38	2.6%
M01AB11	Acemetacin	58	4.0%
M01AB16	Aceclofenac	7	0.5%
M01AC01	Piroxicam	2	0.1%
M01AC06	Meloxicam	1	0.1%
M01AE03	Ketoprofen	7	0.5%
M01AH01	Celecoxib	9	0.6%
M01AH05	Etoricoxib	37	2.5%
M03BX01	Baclofen	1	0.1%
M03BX02	Tizanidine	4	0.3%
M03BX08	Cyclobenzaprine	40	2.7%
M04AC01	Colchicin	15	1.0%
N02AX02	Tramadol (sustained release)	16	1.1%
	Tramadol (non-sustained release)	4	0.3%
N02CC	Triptanes	1	0.1%
N03AA02	Phenobarbital	2	0.1%
N03AB02	Phenytoin	1	0.1%
N03AE01	Clonazepam	16	1.1%
N03AF01	Carbamazepine	3	0.2%
N03AX11	Topiramate	4	0.3%
N04AA01	Trihexyphenidyl	1	0.1%
N04AA02	Biperiden	1	0.1%
N04BC04	Ropinirole	2	0.1%
N04BC08	Piribedil	2	0.1%

N04BC09	Rotigotine	1	0.1%
N04BD01	Selegiline	1	0.1%
N05AA01	Chlorpromazine	1	0.1%
N05AA06	Cyamemazine	2	0.1%
N05AN01	Lithium	1	0.1%
N05AX08	Risperidone (>6 weeks)	8	0.6%
N05AX12	Aripiprazole	1	0.1%
N05BA01	Diazepam	68	4.6%
N05BA05	Dipotassium clorazepate	7	0.5%
N05BA08	Bromazepam	32	2.2%
N05BA09	Clobazam	3	0.2%
N05BA12	Alprazolam	121	8.3%
N05BA18	(Ethyl-) Loflazepate	23	1.6%
N05BA22	Cloazolam	9	0.6%
N05BB01	Hydroxyzine	18	1.2%
N05CD01	Flurazepam	2	0.1%
N05CD04	Estazolam	4	0.3%
N05CD05	Triazolam	1	0.1%
N05CD08	Midazolam	4	0.3%
N05CD11	Loprazolam (>0.5 mg/d)	1	0.1%
N06AA04	Clomipramine	9	0.6%
N06AA06	Trimipramine	1	0.1%
N06AA09	Amitriptyline	24	1.6%
N06AA16	Dosulepin	2	0.1%
N06AA21	Maprotiline	2	0.1%
N06AB03	Fluoxetine	36	2.5%
N06AB05	Paroxetine	17	1.2%
N06AB08	Fluvoxamine	2	0.1%
N06AX12	Bupropion	7	0.5%
N06AX16	Venlafaxine	18	1.2%
R06AX22	Ebastine	7	0.5%

Table S6: Total number of PIM dispensed, according to Beers 2019 criteria (excluding Beers criteria Table 5).

ATC code	PIM Beers 2019 criteria	PIM frequency n=1824	PIM %
A02BC	Proton pump inhibitors	362	19.9%
A03FA01	Metoclopramide	3	0.2%
A10BB01	Glibenclamide	2	0.1%
A10BB12	Glimepiride	2	0.1%
B01AC06	Acetylsalicylic acid	45	2.5%
B01AC07	Dipyridamole	1	0.1%

B01AE07	Dabigatran etexilate	7	0.4%
B01AF01	Rivaroxaban	34	1.9%
B01AF02	Apixaban	1	0.1%
B01AF03	Edoxaban	7	0.4%
C01BD01	Amiodarone	6	0.3%
C03BA04	Chlortalidone	23	1.3%
C03BA11	Indapamide	52	2.9%
C03CA01	Furosemide	181	9.9%
C03DA01	Spironolactone	35	1.9%
C08DA01	Verapamil	1	0.1%
C08DB01	Diltiazem	1	0.1%
G04BD02	Flavoxate	13	0.7%
G04BD04	Oxybutynin	5	0.3%
G04BD08	Solifenacin	5	0.3%
G04BD09	Trospium	12	0.7%
H02AB13	Deflazacort	1	0.1%
J01EE01	Sulfamethoxazole and trimethoprim	1	0.1%
M01AB05	Diclofenac	22	1.2%
M01AB08	Etodolac	21	1.2%
M01AB11	Acemetacin	5	0.3%
M01AC01	Piroxicam	1	0.1%
M01AC06	Meloxicam	1	0.1%
M01AE01	Ibuprofen	23	1.3%
M01AE02	Naproxen	51	2.8%
M01AE03	Ketoprofen	2	0.1%
M01AX17	Nimesulide	1	0.1%
M03BX08	Cyclobenzaprine	40	2.2%
N02AB03	Fentanyl	1	0.1%
N02AJ06	Codeine and paracetamol	1	0.1%
N02AJ13	Tramadol and paracetamol	12	0.7%
N02AX02	Tramadol	20	1.1%
N02AX06	Tapentadol	1	0.1%
N03AX14	Levetiracetam	3	0.2%
N03AA02	Phenobarbital	2	0.1%
N03AE01	Clonazepam	16	0.9%
N03AF01	Carbamazepine	3	0.2%
N04AA01	Trihexyphenidyl	1	0.1%
N05AA01	Chlorpromazine	1	0.1%
N05AA06	Cyamemazine	2	0.1%
N05AD01	Haloperidol	3	0.2%
N05AD03	Melperone	3	0.2%
N05AH03	Olanzapine	8	0.4%
N05AH04	Quetiapine	31	1.7%

N05AL03	Tiapride	3	0.2%
N05AL05	Amisulpride	14	0.8%
N05AX08	Risperidone	9	0.5%
N05AX12	Aripiprazole	1	0.1%
N05BA01	Diazepam	68	3.7%
N05BA04	Oxazepam	16	0.9%
N05BA05	Potassium clorazepate	7	0.4%
N05BA06	Lorazepam	73	4.0%
N05BA08	Bromazepam	2	0.1%
N05BA12	Alprazolam	121	6.6%
N05BA18	Ethyl loflazepate	2	0.1%
N05BA22	Cloxacolam	2	0.1%
N05BB01	Hydroxyzine	18	1.0%
N05CD01	Flurazepam	2	0.1%
N05CD04	Estazolam	4	0.2%
N05CD05	Triazolam	1	0.1%
N05CD09	Brotizolam	1	0.1%
N05CF02	Zolpidem	19	1.0%
N06AA04	Clomipramine	9	0.5%
N06AA06	Trimipramine	1	0.1%
N06AA09	Amitriptyline	24	1.3%
N06AA16	Dosulepin	2	0.1%
N06AA21	Maprotiline	2	0.1%
N06AB03	Fluoxetine	36	2.0%
N06AB04	Citalopram	4	0.2%
N06AB05	Paroxetine	17	0.9%
N06AB06	Sertraline	77	4.2%
N06AB08	Fluvoxamine	2	0.1%
N06AB10	Escitalopram	71	3.9%
N06AX05	Trazodone	68	3.7%
N06AX11	Mirtazapine	46	2.5%
N06AX16	Venlafaxine	18	1.0%
N06AX21	Duloxetine	8	0.4%
N06AX26	Vortioxetine	1	0.1%

Table S7: PIM identified through the application of the Table 2 of Beers 2019 criteria (medications that are potentially inappropriate in most older adults).

ATC code	PIM independent of diagnosis or condition	PIM frequency n=916	PIM %
A02BC	Proton pump inhibitors	362	39.5%
A10BB01	Glibenclamide	2	0.2%
A10BB12	Glimepiride	2	0.2%

B01AC07	Dipyridamole	1	0.1%
C01BD01	Amiodarone	6	0.7%
M01AB05	Diclofenac	21	2.3%
M01AB08	Etodolac	20	2.2%
M01AC01	Piroxicam	1	0.1%
M01AC06	Meloxicam	1	0.1%
M01AE01	Ibuprofen	21	2.3%
M01AE02	Naproxen	48	5.2%
M03BX08	Cyclobenzaprine	40	4.4%
N03AA02	Phenobarbital	2	0.2%
N03AE01	Clonazepam	16	1.8%
N04AA01	Trihexyphenidyl	1	0.1%
N05AD01	Haloperidol	1	0.1%
N05BA01	Diazepam	68	7.4%
N05BA04	Oxazepam	16	1.8%
N05BA05	Potassium clorazepate	7	0.8%
N05BA06	Lorazepam	73	8.0%
N05BA12	Alprazolam	121	13.2%
N05BB01	Hydroxyzine	18	2.0%
N05CD01	Flurazepam	2	0.2%
N05CD04	Estazolam	4	0.4%
N05CD05	Triazolam	1	0.1%
N05CF02	Zolpidem	19	3.0%
N06AA06	Trimipramine	1	0.1%
N06AA09	Amitriptyline	24	2.6%
N06AB05	Paroxetine	17	1.9%

Table S8: PIM identified through the application of the Table 3 of Beers 2019 criteria (medications that are potentially inappropriate in older adults with certain conditions).

ATC code	PIM considering disease and syndrome interactions	Diagnose	PIM frequency n=157
A03FA01	Metoclopramide	Parkinson disease	3
C08DA01	Verapamil	Heart failure	1
C08DB01	Diltiazem	Heart failure	1
H02AB13	Deflazacort	Delirium	1
		Dementia or cognitive impairment	
M01AB05	Diclofenac	Heart failure	3
		History of gastric or duodenal ulcers	
		Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	
M01AB08	Etodolac	Heart failure	3
		History of gastric or duodenal ulcers	

		Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	
		Heart failure	
M01AB11	Acemetacin	History of gastric or duodenal ulcers	5
		Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	
		Heart failure	
M01AC01	Piroxicam	History of gastric or duodenal ulcers	1
		Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	
		Heart failure	
M01AE01	Ibuprofen	History of gastric or duodenal ulcers	3
		Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	
		Heart failure	
M01AE02	Naproxen	History of gastric or duodenal ulcers	11
		Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	
		Heart failure	
M01AE03	Ketoprofen	History of gastric or duodenal ulcers	2
		Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	
		Heart failure	
M01AX17	Nimesulide	History of gastric or duodenal ulcers	1
		Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	
M03BX08	Cyclobenzaprine	Lower urinary tract symptoms, benign prostatic hyperplasia	6
N02AB03	Fentanyl	History of falls or fractures	1
N02AJ06	Codeine and paracetamol	History of falls or fractures	1
N02AJ13	Tramadol and paracetamol	History of falls or fractures	12
N02AX02	Tramadol	History of falls or fractures	3
N02AX06	Tapentadol	History of falls or fractures	1
		Dementia or cognitive impairment	
N05AD01	Haloperidol	Parkinson disease	1
		Syncope	
		Dementia or cognitive impairment	
N05AH03	Olanzapine	Parkinson disease	4
		Lower urinary tract symptoms, benign prostatic hyperplasia	
N05AH04	Quetiapine	Dementia or cognitive impairment	8
		Dementia or cognitive impairment	
N05AX08	Risperidone	Parkinson disease	3

N05BA01	Diazepam	Delirium	6
		Dementia or cognitive impairment	
		History of falls or fractures	
N05BA04	Oxazepam	Delirium	1
		Dementia or cognitive impairment	
		History of falls or fractures	
N05BA05	Potassium clorazepate	Delirium	1
		Dementia or cognitive impairment	
		History of falls or fractures	
N05BA06	Lorazepam	Delirium	10
		Dementia or cognitive impairment	
		History of falls or fractures	
N05BA08	Bromazepam	Delirium	2
		Dementia or cognitive impairment	
		History of falls or fractures	
N05BA12	Alprazolam	Delirium	8
		Dementia or cognitive impairment	
		History of falls or fractures	
N05BA18	Ethyl loflazepate	Delirium	2
		Dementia or cognitive impairment	
		History of falls or fractures	
N05BA22	Clonazepam	Delirium	2
		Dementia or cognitive impairment	
		History of falls or fractures	
N05BB01	Hydroxyzine	Lower urinary tract symptoms, benign prostatic hyperplasia	2
N05CD01	Flurazepam	Delirium	1
		Dementia or cognitive impairment	
		History of falls or fractures	
N05CD09	Brotizolam	Delirium	1
		Dementia or cognitive impairment	
		History of falls or fractures	
N05CF02	Zolpidem	Delirium	2
		Dementia or cognitive impairment	
		History of falls or fractures	
N06AA09	Amitriptyline	Syncope	8
		History of falls or fractures	
		Lower urinary tract symptoms, benign prostatic hyperplasia	
N06AB03	Fluoxetine	History of falls or fractures	4
N06AB05	Paroxetine	History of falls or fractures	7
		Lower urinary tract symptoms, benign prostatic hyperplasia	

N06AB06	Sertraline	History of falls or fractures	8
N06AB10	Escitalopram	History of falls or fractures	9
N06AX05	Trazadone	Syncope	1
		History of falls or fractures	
N06AX11	Mirtazapine	Syncope	5
		History of falls or fractures	
N06AX16	Venlafaxine	History of falls or fractures	1
N06AX21	Duloxetine	History of falls or fractures	1

Table S9: PIM identified through the application of the Table 4 of Beers 2019 criteria (medications that should be used with caution).

ATC code	Drugs to be used with caution in older adults	PIM frequency n=856	PIM %
B01AC06	Acetylsalicylic acid	45	5.3%
B01AE07	Dabigatran etexilate	7	0.8%
B01AF01	Rivaroxaban	29	3.4%
C03BA04	Chlortalidone	23	2.7%
C03BA11	Indapamide	52	6.1%
C03CA01	Furosemide	181	21.1%
C03DA01	Spironolactone	34	4.0%
J01EE01	Sulfamethoxazole and trimethoprim	1	0.1%
N02AX02	Tramadol	20	2.3%
N03AF01	Carbamazepine	3	0.4%
N05AA01	Chlorpromazine	1	0.1%
N05AA06	Cyamemazine	2	0.2%
N05AD01	Haloperidol	3	0.4%
N05AD03	Melperone	3	0.4%
N05AH03	Olanzapine	8	0.9%
N05AH04	Quetiapine	31	3.6%
N05AL03	Tiapride	3	0.4%
N05AL05	Amisulpride	14	1.6%
N05AX08	Risperidone	9	1.1%
N05AX12	Aripiprazole	1	0.1%
N06AA04	Clomipramine	9	1.1%
N06AA06	Trimipramine	1	0.1%
N06AA09	Amitriptyline	24	2.8%
N06AA16	Dosulepin	2	0.2%
N06AA21	Maprotiline	2	0.2%
N06AB03	Fluoxetine	36	4.2%
N06AB04	Citalopram	4	0.5%
N06AB05	Paroxetine	17	2.0%
N06AB06	Sertraline	77	9.0%

N06AB08	Fluvoxamine	2	0.2%
N06AB10	Escitalopram	71	8.3%
N06AX05	Trazadone	68	7.9%
N06AX11	Mirtazapine	46	5.4%
N06AX16	Venlafaxine	18	2.1%
N06AX21	Duloxetine	8	0.9%
N06AX26	Vortioxetine	1	0.1%

Table S10: Potentially drug-drug interactions identified through the application of the Table 5 of Beers 2019 criteria (potentially clinically important drug-drug interactions that should be avoided in older adults).

Object drug and class	Interacting drug and class	Interactions	
		frequency n=206	PIM %
Opioids	Benzodiazepines	28	13.6%
	Gabapentin, pregabalin	13	6.3%
Anticholinergic	Anticholinergic	14	6.8%
Antidepressants (TCAs, SSRIs, and SNRIs)	Any combination of three or more of these CNS-active drugs	109	52.9%
Antipsychotics			
Antiepileptics			
Benzodiazepines and nonbenzodiazepine, benzodiazepine			
receptor agonist hypnotics (ie, "Z-drugs")			
Opioids			
Corticosteroids, oral or parenteral	NSAIDs	38	18.5%
Peripheral α -1 blockers	Loop diuretics	2	1.0%
Warfarin	Amiodarone	1	0.5%
	NSAIDs	1	0.5%

Table S11: Medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults identified through the application of the Table 6 of Beers 2019 criteria.

ATC code	Medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults	PIM frequency n=17	PIM %
B01AF01	Rivaroxaban	5	29.4%
B01AF02	Apixaban	1	5.9%
B01AF03	Edoxaban	7	41.2%
C03DA01	Spironolactone	1	5.9%

N03AX14	Levetiracetam	3	17.7%
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Table S12: PIM identified through the application of the Table 7 of Beers 2019 criteria (drugs with strong anticholinergic properties).

ATC code	Drugs with strong anticholinergic properties	PIM frequency n=154	PIM %
G04BD02	Flavoxate	13	8.4%
G04BD04	Oxybutynin	5	3.3%
G04BD08	Solifenacin	5	3.3%
G04BD09	Trospium	12	7.8%
M03BX08	Cyclobenzaprine	40	26.0%
N04AA01	Trihexyphenidyl	1	0.7%
N05AA01	Chlorpromazine	1	0.7%
N05AH03	Olanzapine	8	5.2%
N05BB01	Hydroxyzine	18	11.7%
N06AA04	Clomipramine	9	5.8%
N06AA06	Trimipramine	1	0.7%
N06AA09	Amitriptyline	24	15.6%
N06AB05	Paroxetine	17	11.0%

Table S13: Total number of PIM dispensed, according to STOPP v2 criteria.

ATC code	PIM STOPP v2	PIM frequency n=980	PIM %
A02BC02	Pantoprazole	4	0.4%
A02BC05	Esomeprazole	3	0.3%
A03FA01	Metoclopramide	3	0.3%
A10BA02	Metformin	4	0.4%
A10BB01	Glibenclamide	2	0.2%
A10BB12	Glimepiride	2	0.2%
B01AC04	Clopidogrel	3	0.3%
B01AC05	Ticlopidine	8	0.8%
B01AC18	Triflusal	1	0.1%
B03AB09	Ferric proteinsuccinylate	1	0.1%
B03AD03	Ferrous sulfate and folic acid	1	0.1%
C01DA14	Isosorbide mononitrate	1	0.1%
C03BA04	Chlortalidone	7	0.7%
C03BA11	Indapamide	3	0.3%
C03CA01	Furosemide	28	2.9%
C03DA01	Spironolactone	19	1.9%
C07AA05	Propranolol	2	0.2%

C07AA07	Sotalol	1	0.1%
C07AB07	Bisoprolol	3	0.3%
C08CA01	Amlodipine	2	0.2%
C08CA13	Lercanidipine	1	0.1%
C09AA03	Lisinopril	1	0.1%
C09AA04	Perindopril	3	0.3%
C09AA05	Ramipril	1	0.1%
C09CA04	Irbesartan	1	0.1%
C09CA08	Olmesartan medoxomil	1	0.1%
G04BD02	Flavoxate	2	0.2%
G04BD04	Oxybutynin	2	0.2%
G04BD08	Solifenacin	1	0.1%
G04BD09	Trospium	4	0.4%
H02AB13	Deflazacort	2	0.2%
H02BX01	Methylprednisolone, combinations	1	0.1%
M01AB05	Diclofenac	25	2.6%
M01AB08	Etodolac	23	2.4%
M01AB11	Acemetacin	34	3.5%
M01AB16	Aceclofenac	3	0.3%
M01AB55	Diclofenac, combinations	3	0.3%
M01AC01	Piroxicam	2	0.2%
M01AC06	Meloxicam	1	0.1%
M01AE01	Ibuprofen	32	3.3%
M01AE02	Naproxen	54	5.5%
M01AE03	Ketoprofen	4	0.4%
M01AH01	Celecoxib	6	0.6%
M01AH05	Etoricoxib	23	2.4%
M01AX17	Nimesulide	4	0.4%
M03BX08	Cyclobenzaprine	11	1.1%
M05BA04	Alendronic acid	7	0.7%
M05BA06	Ibandronic acid	2	0.2%
M05BB03	Alendronic acid and colecalciferol	6	0.6%
N02AA55	Oxycodone and naloxone	1	0.1%
N02AB03	Fentanyl	5	0.5%
N02AJ13	Tramadol and paracetamol	94	9.6%
N02AX02	Tramadol	15	1.5%
N02AX06	Tapentadol	17	1.7%
N05AA01	Chlorpromazine	1	0.1%
N05AD01	Haloperidol	3	0.3%
N05AD03	Melperone	3	0.3%
N05AH03	Olanzapine	8	0.8%
N05AH04	Quetiapine	31	3.2%
N05AL03	Tiapride	3	0.3%

N05AL05	Amisulpride	14	1.4%
N05AX08	Risperidone	9	0.9%
N05AX12	Aripiprazole	1	0.1%
N05BA01	Diazepam	68	6.9%
N05BA04	Oxazepam	16	1.6%
N05BA05	Potassium clorazepate	7	0.7%
N05BA06	Lorazepam	73	7.5%
N05BA08	Bromazepam	32	3.3%
N05BA09	Clobazam	3	0.3%
N05BA12	Alprazolam	121	12.4%
N05BA18	Ethyl loflazepate	23	2.4%
N05BA22	Cloxazolam	9	0.9%
N05BB01	Hydroxyzine	18	1.8%
N05CD01	Flurazepam	2	0.2%
N05CD04	Estazolam	4	0.4%
N05CD05	Triazolam	1	0.1%
N05CD08	Midazolam	4	0.4%
N05CD09	Brotizolam	5	0.5%
N05CD11	Loprazolam	1	0.1%
N05CF02	Zolpidem	19	1.9%
N06AA04	Clomipramine	1	0.1%
N06AA09	Amitriptyline	5	0.5%
N06AB05	Paroxetine	4	0.4%
N07CA02	Cinnarizine	1	0.1%

CHAPTER 6

Usability of APIMedOlder: A Web Application to Manage Potentially Inappropriate Medication in Older Adults

VI. Usability of APIMedOlder: A Web Application to Manage Potentially Inappropriate Medication in Older Adults

RESUMEN

Considerando el aumento de la proporción de la población mayor a nivel mundial, también surge la demanda de recursos del sistema de salud. Estas herramientas optimizan la toma de decisiones clínicas, evitando así la iatrogenia y contribuyendo a una mejor calidad de vida para la población mayor. En respuesta, creamos una aplicación web en línea, APIMedOlder, que proporciona acceso a los profesionales de la salud, permitiéndoles acceder a los criterios de identificación de medicación potencialmente inapropiada a través de una herramienta útil con un perfil simplificado, lo que facilita su aplicabilidad en la práctica clínica. Este estudio tiene como objetivo evaluar la usabilidad de la aplicación web en línea APIMedOlder por parte de los profesionales de la salud. Se distribuyó un cuestionario, basado en la Escala de Usabilidad del Sistema (System Usability Scale, SUS), entre 15 profesionales de la salud (cinco farmacéuticos, cuatro médicos, tres técnicos de farmacia y tres enfermeros) para explorar completamente el sitio web. En general, la evaluación de los profesionales de la salud sobre la usabilidad de la aplicación web en línea APIMedOlder fue calificada como “Mejor imaginable” (puntuación media de 87,17 puntos), con puntuaciones individuales que oscilan entre 75 y 100 puntos. Se logró una consistencia interna de $\alpha = 0,881$ (IC 95%: 0,766 - 0,953). Los ítems específicos del cuestionario que contribuyeron a esta alta puntuación incluyeron facilidad de uso, eficiencia en el aprendizaje e integración de funciones. La evaluación general de la herramienta desarrollada fue positiva, reconociendo esta aplicación en línea como fácil de usar y con funciones bien integradas.

Palabras clave: ancianos; sistemas de apoyo a la decisión clínica; prescripción inapropiada/prevenición y control; internet; errores de medicación/prevenición y control; lista de medicamentos potencialmente inapropiados.

Usability of APIMedOlder: A Web Application to Manage Potentially Inappropriate Medication in Older Adults

Usabilidade da APIMedOlder: Uma Aplicação Web para a Gestão de Medicamentos Potencialmente Inapropriados em Idosos

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ABSTRACT

Introduction: Considering the increase in the proportion of the older population worldwide, the demand for health system resources also arises. These tools optimize clinical decision-making, thus avoiding iatrogenesis and thus contributing to a better quality of life for the older population. In response, we created an online web application, the APIMedOlder, that provides access to healthcare professionals to allow healthcare professionals to access potentially inappropriate medication identification criteria through a useful tool with a simplified profile, allowing its applicability in clinical practice. This study aims to assess the usability of the APIMedOlder online web application by healthcare professionals.

Methods: A questionnaire, based on the System Usability Scale, was distributed among 15 healthcare professionals (five pharmacists, four physicians, three pharmacy technicians, and three nurses), to fully explore the website.

Results: Overall, healthcare professionals' evaluation of the usability of the APIMedOlder online web application was rated as "Best imaginable" (mean score of 87.17 points), with individual scores ranging from 75 to 100 points. Internal consistency of $\alpha = 0.881$ (CI 95%: 0.766 - 0.953) was achieved. Specific questionnaire items contributing to this high score included ease of use, learning efficiency, and integration of functions.

Conclusion: The overall evaluation of the developed tool was positive, with this online application being recognized as being easy to use and having well-integrated functions.

Keywords: Aged; Decision Support Systems, Clinical; Inappropriate Prescribing/prevention & control; Internet; Medication Errors/prevention & control; Potentially Inappropriate Medication List

RESUMO

Introdução: Tendo em conta o aumento da proporção da população idosa em todo o mundo, surge também a demanda por recursos dos sistemas de saúde. Estas ferramentas otimizam a decisão clínica, evitando iatrogenia, contribuindo assim para uma melhor qualidade de vida dos idosos. Em resposta, criámos uma aplicação *web online*, APIMedOlder, para proporcionar acesso por parte dos profissionais de saúde aos critérios de identificação de medicamentos potencialmente inapropriados através de uma ferramenta útil com um perfil simplificado, permitindo a sua aplicabilidade na prática clínica. Este estudo tem como objetivo a avaliação da usabilidade da aplicação *web online* APIMedOlder por parte dos profissionais de saúde.

Métodos: Foi distribuído um questionário, baseado na Escala de Usabilidade do Sistema, a 15 profissionais de saúde (cinco farmacêuticos, quatro médicos, três técnicos de farmácia e três enfermeiros), de forma a explorar completamente a aplicação *web*.

Resultados: No geral, a avaliação dos profissionais de saúde sobre a usabilidade da aplicação *web online* APIMedOlder foi classificada como "Best imaginable" (pontuação média de 87,17 pontos), com pontuações individuais a variar entre 75 e 100 pontos. Foi alcançada uma consistência interna de $\alpha = 0.881$ (IC 95%: 0,766 - 0,953). Os itens específicos do questionário que contribuíram para esta pontuação incluíram facilidade de uso, eficiência de aprendizagem e integração de funções.

Conclusão: A avaliação geral da ferramenta desenvolvida foi positiva, tendo sido reconhecida como fácil de utilizar e com funções bem integradas.

Palavras-chave: Erros de Medicação/prevenção e controlo; Idoso; Internet; Lista de Medicamentos Potencialmente Inapropriados; Prescrição Inapropriada/prevenção e controlo; Sistemas de Apoio à Decisão Clínica

Key-messages

- APIMedOlder online web application is a useful tool that provides access to health professionals to Potentially Inappropriate Medication identification criteria.
- Overall evaluation of the APIMedOlder tool by healthcare professionals was positive.
- Usability testing results can lead to a more user-friendly, efficient, and enjoyable tool.
- The relatively small sample size may limit the generalizability of findings.

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INTRODUCTION

The global population is living longer and aging fast,¹ which increases the risk of suffering from chronic diseases and exposes older adults to the occurrence of polypharmacy.² Besides, age-related pharmacokinetic and pharmacodynamic changes potentiate the use of potentially inappropriate medication (PIM) in older people.^{3,4} Potentially inappropriate medication are drugs that should be avoided in older adults since the risk of potential adverse events may outweigh the clinical benefit, particularly when safer or more effective alternatives are recommended for use in this population.⁵⁻⁷

As the proportion of the older population increases, the demand for health system resources also rises.⁸⁻¹⁰ Technology-based solutions have the potential to take healthcare systems into the 21st century, and therefore to disseminate information and knowledge all around the world.¹¹ Digital health technologies are important tools for healthcare professionals since they offer ready access to information and resources designed to help save time.¹² E-health tools can improve care by allowing access to health resources and healthcare by electronic means.¹³ Therefore, e-health technology can be used to help healthcare professionals optimize clinical decision-making and prevent iatrogenesis,^{14,15} thereby contributing to improving older patients' quality of life. Moreover, digital information can be easily updated in line with the new evidence.¹⁶

Recently, some studies have been carried out in Portugal that showed a high percentage of use of PIM.¹⁷⁻²¹ In older individuals living in residential facilities from different geographical regions of the country the average number of PIM according to the Beers 2015 criteria was 4.8 ± 2.0 .²¹ In a sample of older inpatients of an internal medicine ward, 79.7%, 92.0%, and 76.5%, used at least one PIM according to the EU(7)-PIM list, Beers, and STOPP criteria, respectively.¹⁷ The use of PIM was also observed in 86.4% (mean $\pm$ SD per patient = 2.30 ± 0.10) of a sample of nursing homes' older adult residents, in 2020 and according to the EU(7)-PIM list.¹⁸ The prescriptions of PIM for all older adults in mainland Portugal were analyzed between 2019 and 2021, and the results showed that the defined daily dose (DDD) of PIM represented 9.20% of the total DDD-prescribed medicines in the same period.¹⁹ Moreover, the

use of PIM was found in 12.8% of the adverse drug reactions reported to the Portuguese pharmacovigilance system in 2019 in older patients ≥ 65 years old, and 10.6% of the suspected medicines identified were classified as PIM.²⁰

According to a recent systematic review that assessed the impact of interventions designed to reduce the prescription of PIM, no studies have been published in Portugal reinforcing the need to develop interventions in this field.²² Moreover, the implementation of clinical decision support system interventions showed a positive impact on the reduction of PIM.²² In response, we have developed a web application, the APIMedOlder,²³ addressed to healthcare professionals, that intends to be applicable in clinical practice and is a useful tool with a simplified profile.

The usability level is a fundamental characteristic to evaluate the success of a website,²⁴ which is defined as the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use.²⁵ Therefore, the aim of this study was to assess the usability of the APIMedOlder online web application.

METHODS

Study design

A usability study was conducted through several steps as represented in the flowchart (Fig. 1). After ethics committee approval, the participants were invited to take part in the study and signed an informed consent form. After being provided within the URL of the APIMedOlder application, the participants had complete autonomy to thoroughly explore it. After familiarizing themselves with the tool, healthcare professionals answered the System Usability Scale questionnaire.

Description of the web application

The APIMedOlder website was developed as part of a research project funded by the Fundação para a Ciência e a Tecnologia (FCT) (PTDC/MED-FAR/31598/2017), aiming to prevent the use of PIM in older adults through the development of a clinical decision support system. The APIMedOlder web application is embedded into the project's website, which includes details about the research

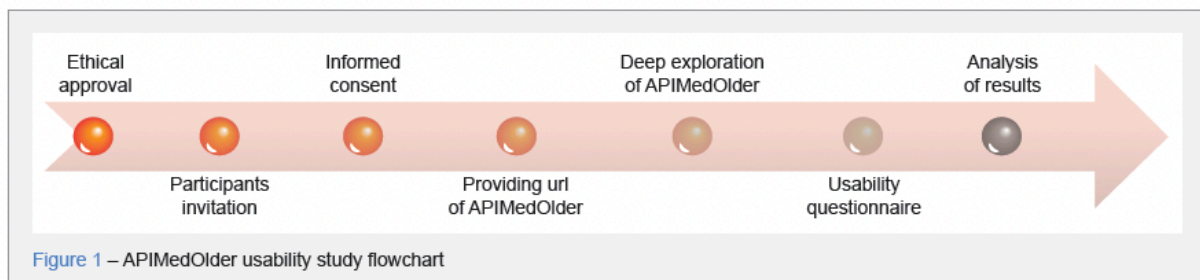


Figure 1 – APIMedOlder usability study flowchart

project, the research team, scientific publications, and a contacts section. This web application allows the healthcare professional to identify a particular drug as a PIM or not according to the Portuguese version of the EU(7)-PIM list.²⁶ The search can be performed using the International Nonproprietary Name (INN) or the Anatomical Therapeutic Chemical (ATC) code of a specific drug. If a drug is reported as a PIM, the main reason, dose adjustment/special considerations of use and alternative drugs and/or therapies are presented to the user. It is also optimized for mobile phones and tablet devices. APIMedOlder aims to be a useful tool with a simplified profile, allowing its applicability in clinical practice.

Participants

A non-probabilistic method of convenience sampling was used to ensure easier access to the participants. So, fifteen healthcare professionals, a sample size normally recommended in this type of studies,^{27,28} without any involvement in the design or development of the web application, were recruited via e-mail between June and October 2022, to explore the web application on their mobile phones, personal computers, or tablets with an internet connection (Fig. 2). They were instructed to integrate this tool into their daily practice during a defined period (one week) and use it with their patients (test in real real-life setting). According to the General Data Protection Regulation-Directive 95/46/EC (GDPR), the security, anonymity, and confidentiality of all data provided by the participants were guaranteed. Participation in the study was voluntary, and informed consent

was obtained from all participants to allow for the use of their e-mail addresses to inform them about the study aims and to provide access to the website's URL and the usability questionnaire. Additionally, in order to gain a better insight into the participants' perspectives, they were invited to make additional and optional comments or suggestions at the end of the questionnaire.

Usability test

The SUS was developed in 1986 by John Brooke.²⁹ It is an inexpensive tool and has become a standard questionnaire for the assessment of perceived usability since it allows the evaluation of a wide variety of products and services, such as hardware, software, mobile devices, websites, and applications.³⁰ It is composed of 10 statements, each having a 5-point Likert scale that ranges from 1 "Strongly Disagree" to 5 "Strongly Agree".²⁹ Its translation for European Portuguese was validated in 2015.³¹ Considering that the statements alternate between positive (items 1,3,5,7, and 9) and negative (items 2,4,6,8, and 10), care must be taken to calculate the SUS score.³² For positive items, the score contribution is the scale position minus 1, and for negative items, the contribution is 5 minus the scale position. Then, the sum of the scores of all items is multiplied by 2.5 to obtain the overall score.²⁹ The final score ranges from 0 to 100 and higher scores indicate better usability. Better products score in the high 70s to upper 80s, with superior products scoring better than 90, while products with SUS scores below 70 should be considered for improvement and with less than 50 should be cause for significant concern.³² Based

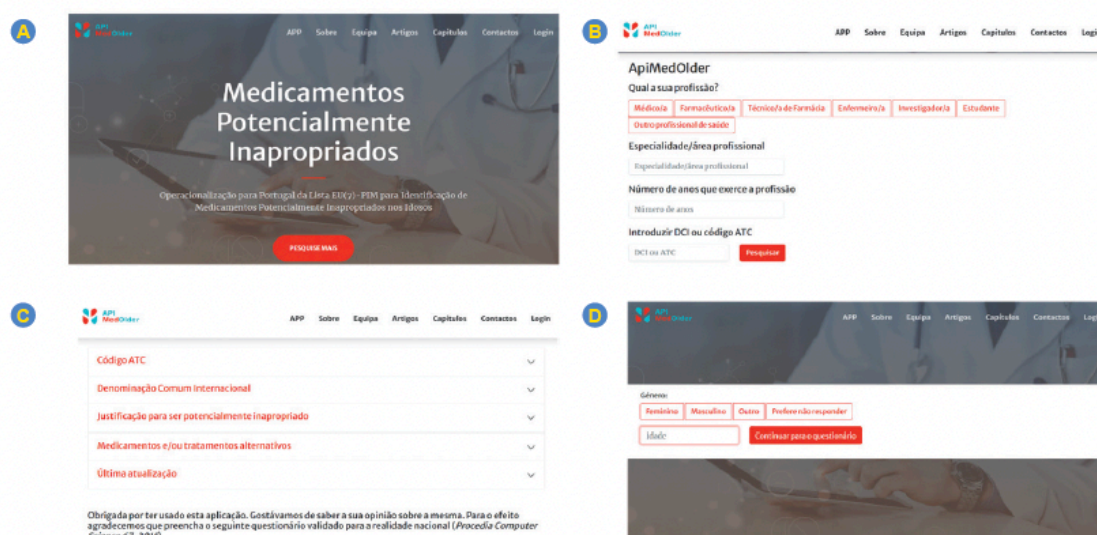


Figure 2 – APIMedOlder screenshots: (A) website main menu; (B) web application main menu; (C) PIM information page; (D) SUS questionnaire access page

on the total usability scores, a qualitative scale was applied to assign adjectives to the overall experience in using the platform, through a classification adjective anchored with numerical equivalents of 1 through 7, from “Worst Imaginable” corresponding to usability scores from 0 - 25, to “Best Imaginable” with scores from 86 - 100, respectively.³²

Statistical analysis

Descriptive statistical analyses were conducted to determine if the online application was overall well-designed and highly usable through the SUS. To measure the internal consistency of the applied survey, Cronbach’s alpha (CI 95%) was calculated using the Statistical Package for Social Sciences (SPSS 20, IBM Corp., New York, NY, USA). This value can range from 0 to 1 and evaluate how well the 10 statements correlate with the hypothetical statements regarding the concept of usability.

RESULTS

Fifteen healthcare professionals (five pharmacists, four physicians, three pharmacy technicians and three nurses) were recruited via e-mail. They were aged between 23 and 45 years old (86.67% were women) and from different regions of Portugal.

The final scores ranged from 75 to 100 points, and the mean value was 87.17 with a standard deviation of 9.70. The overall perception of healthcare professionals on the online web application APIMedOlder is presented in Table 1.

The reliability analysis was performed and the absolute ratings (i.e., transformed responses for statements 2, 4, 6,

8, and 10 so all scales have 1 as “Strongly Disagree” and 5 as the “Strongly Agree”) for the 10 statements were used to compute Cronbach’s alpha, achieving an internal consistency of $\alpha = 0.881$ (CI 95%: 0.766 - 0.953).

All the positive items (1, 3, 5, 7 and 9) revealed scores above 4.30 with standard deviation values ranging from 0.49 to 0.60. Regarding negative items (2, 4, 6, 8 and 10), scores below 1.73 with standard deviation values between 0.40 and 0.85 were obtained.

Overall, the mean evaluation of this study corresponded to the “Best Imaginable”. The individual results for adjective ratings are presented in Table 2.

DISCUSSION

This study evaluated the recently created web application APIMedOlder and collected feedback from healthcare professionals to optimize this tool according to the obtained results.

Overall, the SUS results showed that the APIMedOlder web application provided users with good usability with a mean value of 87.17, and most of the questions expressed highly positive results. This is in line with other e-health tools’ medication-related usability studies.³³⁻³⁸ The positive items presented an average score above 4.30 points, reflecting the desire to use the APIMedOlder web application frequently, its easy usage and quick learning of how to use it, the well-integrated functions, and the confidence in using it. The negative items also presented good results with scores below 1.73, showing that the web application was not perceived as complex or inconsistent. Since the

Table 1 – Overall perception of healthcare professionals on the online web application APIMedOlder (results by item)

Item EN (PT)	Mean score (1 - 5)	Standard deviation
1. I think that I would like to use this system frequently. (Acho que gostaria de utilizar este produto com frequência.)	4.33	0.60
2. I found the system unnecessarily complex. (Considereí o produto mais complexo do que necessário.)	1.73	0.85
3. I thought the system was easy to use. (Achei o produto fácil de utilizar.)	4.53	0.50
4. I think that I would need the support of a technical person to be able to use this system. (Acho que necessitaria de ajuda de um técnico para conseguir utilizar este produto.)	1.27	0.44
5. I found the various functions in this system were well integrated. (Considereí que as várias funcionalidades deste produto estavam bem integradas.)	4.40	0.49
6. I thought there was too much inconsistency in this system. (Achei que este produto tinha muitas inconsistências.)	1.67	0.60
7. I would imagine that most people would learn to use this system very quickly. (Suponho que a maioria das pessoas aprenderia a utilizar rapidamente este produto.)	4.47	0.50
8. I found the system very cumbersome to use. (Considereí o produto muito complicado de utilizar.)	1.33	0.47
9. I felt very confident using the system. (Senti-me muito confiante a utilizar este produto.)	4.33	0.60
10. I needed to learn a lot of things before I could get going with this system. (Tive que aprender muito antes de conseguir lidar com este produto.)	1.20	0.40

Table 2 – Descriptive statistics of the System Usability Scale (SUS) scores for adjective ratings

Adjective	Count	Mean SUS score	Standard deviation
Worst imaginable	0	-	-
Awful	0	-	-
Poor	0	-	-
Ok	0	-	-
Good	0	-	-
Excellent	7	78.93	3.98
Best imaginable	8	94.38	7.15

Correspondence between adjective scale and total SUS score: Best Imaginable [85.59 – 100.00]; Excellent [72.76 – 85.58]; Good [62.02 – 72.75]; OK [39.18 – 62.01]; Poor [25.01 – 39.17]; Awful [Not Applicable]; Worst Imaginable [0.00 – 25.00].³²

SUS is composed only of closed questions, the participants were allowed to make additional comments to complement this study. However, no major suggestions arose during the questionnaire filling. Nonetheless, the two respondents who wrote a comment emphasized their satisfaction with APIMedOlder.

For this usability analysis, the SUS tool was chosen since it is a free, easy-to-setup and administer to participants, reliable tool that has been available for approximately 30 years and can be easily retrieved and scored quickly.^{29,30} Besides, SUS can measure the usability of a wide variety of systems, and its psychometric properties, such as reliability, validity, and sensitivity, are well established.^{32,40-42} This tool has also proven to be flexible and not affected by minor wording changes.³² Moreover, SUS has been strongly recommended for researchers and practitioners over other similar tools, such as the Usability Metric for User Experience (UMUX), UMUX-Lite, or the Standardized User Experience Percentile Rank Questionnaire (SUPR-Q), since it presents several advantages.^{32,39,43,44}

To make the measure more meaningful, a single-item adjective scale was added and serves as a good supplement to the SUS since Likert scale scores correlate extremely well,⁴⁵ with this study reaching the maximum classification of “Best Imaginable”.

The Cronbach's alpha test was performed to measure the reliability of the survey applied, and in this study, an internal consistency of $\alpha = 0.881$ was obtained. This value shows that the items are highly correlated with each other since a maximum Cronbach's alpha value of 0.90 has been recommended.^{46,47}

Besides the good level of usability perceived, the positive feedback obtained through this study could be related to several factors. When questions from everyday practice arise, healthcare professionals frequently use the internet to obtain information.^{48,49} However, the huge amount of online medical information available may be overwhelming.⁵⁰ Therefore, APIMedOlder can be a reliable source of information that can be easily obtained. The APIMedOlder online website is also optimized for several devices, such

as computers, mobile phones, and tablets, promoting quick and easy access to the information, allowing healthcare professionals to closely follow the therapeutic regimen of older people and a faster detection of PIM. So, this type of technology can enable quick and efficient management of medical conditions.⁵¹ In the primary healthcare context, such technology can also contribute to reducing consultation time and improving patient health outcomes in the long term.⁵² Besides, health information technology has been shown to decrease medication errors⁵³ and APIMedOlder presents a varied list of therapeutic alternatives and recommendations for the use of specific drugs, also providing the opportunity to ensure personalized medical care and guarantee older people's healthcare demands.⁵¹ Therefore, incorporating APIMedOlder in primary health care will allow family physicians to better manage treatment for older patients. However, the application of the criteria provided does not replace the clinical judgment and individual assessment of healthcare professionals regarding prescribing appropriateness.

According to datareportal.com,⁵⁴ there were 8.63 million internet users in Portugal in January 2022 (85.00% of the total population in the same period) with an increase of 245 thousand (+ 2.90%) since 2021. Therefore, mobile technologies represent an excellent opportunity to quickly access information and to improve the range and quality of services provided by healthcare professionals.⁵⁵

Regarding limitations, the small sample of participants in this study ($n = 15$) could restrain the extrapolation of the results. However, according to the literature, a sample size of three to 20 participants is typically valid,²⁷ with five to 10 participants being considered as a sensible baseline range. With 10 users, the lowest percentage of problems detected was 80%, and with 20 users was 95%.²⁸ While there is not a specific number of participants required to uncover all usability problems, the rule of 16 ± 4 can often yield significant insights in user testing.⁵⁶ In addition, it is important to note that, while the SUS provided valuable insights into the usability of APIMedOlder, it may not have captured all dimensions, such as concerns, trust, comfort, and agreement with

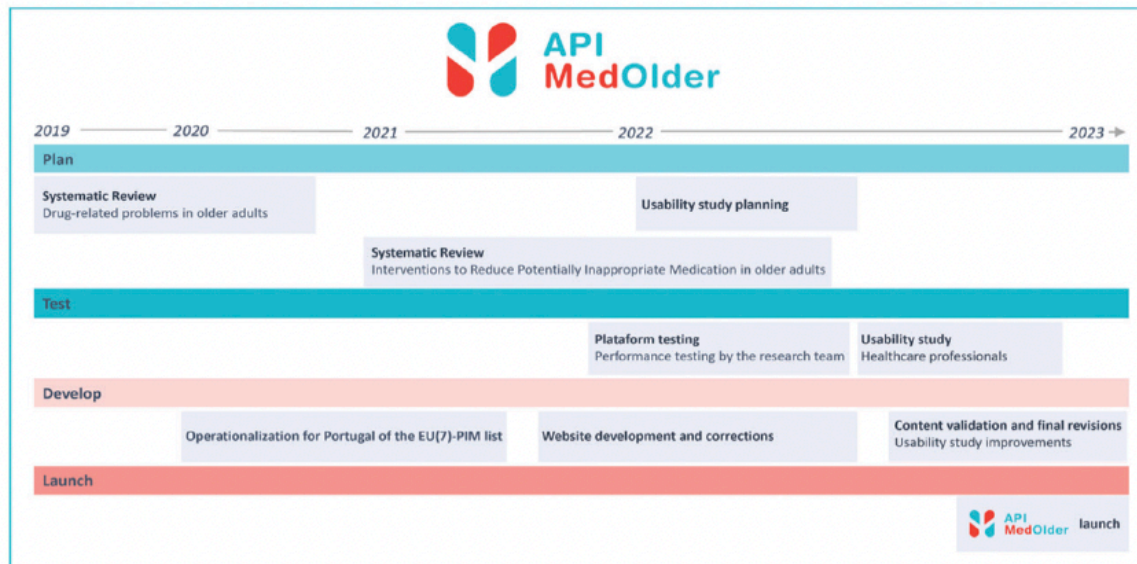


Figure 3 – APIMedOlder development roadmap

recommendations.⁵⁷ Therefore, future studies should consider incorporating these additional dimensions in order to provide a more comprehensive evaluation of APIMedOlder.

The development of the APIMedOlder website followed a well-established plan (Fig. 3) and following this usability study, a randomized-cluster control trial will be conducted at the local health unit in the Centre of Portugal. Educational interventions will be organized in sessions with family physicians, through outreach visits and will include (i) information about PIM and its impact on health outcomes in older patients; (ii) PIM prescription data in Portugal (iii) factors previously identified as underlying PIM prescribing; (iv) barriers/facilitators previously identified as influencing the use of digital health tools; and (v) presentation of the APIMedOlder application with a deep exploration of its functionalities. The interventions will be structured to engage family physicians in using the APIMedOlder application in their clinical practice, ensuring safe medication prescribing practices for older patients.

Future research directions may involve updating the EU(7)-PIM list and the APIMedOlder application and performing longitudinal studies to assess the impact of using APIMedOlder in clinical practice and explore the possibility of integrating this tool into existing electronic health record systems both in primary and secondary care settings. This could facilitate healthcare professionals' access to information about PIM during medication prescribing and review. Furthermore, future studies could explore the effectiveness of educational interventions targeting pharmacists and nurses in improving patient follow-up and medication management.

CONCLUSION

The APIMedOlder web application was designed to help healthcare professionals with prescribing PIM and medication review, improving older patient safety through the development of a clinical decision support system tool that is easy to use and applicable in clinical practice.

The overall evaluation of the developed tool was positive, and this study validated the research for the next phase.

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AUTHOR CONTRIBUTIONS

DAR: Study design, data collection and analysis, writing of the manuscript.

AIP, RMC, AF, MTH, FR: Study design, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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CHAPTER 7

Exploring the impact of APIMedOlder web-based application:
a retrospective analysis of searches made by healthcare
professionals

VII. Exploring the impact of APIMedOlder web-based application: a retrospective analysis of searches made by healthcare professionals

RESUMEN

Prescribir medicamentos a pacientes mayores es un desafío, ya que muchos fármacos son potencialmente inapropiados para esta población. La implementación de intervenciones mediante sistemas de apoyo a la toma de decisiones clínicas ha mostrado un impacto positivo en la reducción de Medicamentos Potencialmente Inapropiados (PIM). Por ello, hemos desarrollado una aplicación web en línea que ofrece acceso gratuito a los profesionales de la salud para la identificación de PIM, basada en la lista EU(7)-PIM. Este estudio tiene como objetivo describir qué han buscado los usuarios de APIMedOlder durante el último año. Se realizó un estudio retrospectivo utilizando datos de búsquedas realizadas por los usuarios en el sitio web APIMedOlder entre el 16 de noviembre de 2022 y el 16 de noviembre de 2023. Durante este período, se realizaron 400 búsquedas, de las cuales el 42.8% correspondieron a PIM. La mayoría de las búsquedas fueron realizadas por farmacéuticos (39.0%), seguidos de médicos (26.5%), estudiantes (23.5%), técnicos de farmacia (4.8%), enfermeros (3.5%), investigadores (1.5%) y otros (1.3%). Los medicamentos más buscados fueron omeprazol (4.5%), quetiapina (3.5%), furosemida (3.0%), alprazolam (2.8%) y paracetamol (2.5%). Las búsquedas realizadas por farmacéuticos se centraron principalmente en omeprazol (7.1%) y provinieron en su mayoría del ámbito de la farmacia comunitaria (44.2%). En cuanto a los médicos, los medicamentos más buscados fueron oxicodona y tramadol (6.6%), con una mayor representación de médicos de atención primaria (50.9%). Las búsquedas realizadas por estudiantes se enfocaron principalmente en quetiapina (6.4%), y la mayoría de los estudiantes eran de la carrera de enfermería (53.2%). Otros profesionales de la salud representaron una menor proporción de búsquedas (11.1%), lo que refleja una participación menos frecuente, pero diversa. Aunque esta aplicación web aún no se ha difundido ampliamente entre los profesionales de la salud, algunas búsquedas ya demuestran su potencial para reducir la prescripción de PIM en adultos mayores.

Palabras clave: APIMedOlder: medicamentos potencialmente inapropiados; adultos mayores, profesionales de la salud; búsquedas.



Exploring the Impact of APIMedOlder Web-Based Application: A Retrospective Analysis of Searches Made by Healthcare Professionals

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Abstract. Prescribing medication to older patients is a challenge as many drugs are potentially inappropriate for this population. The implementation of clinical decision support systems interventions showed a positive impact on Potentially Inappropriate Medications (PIM) reduction. Therefore, we have developed an online web application offering free access to health professionals for PIM identification criteria based on the EU(7)-PIM list. This study aims to describe what users of APIMedOlder have been searching for the last year. A retrospective study was performed using data from searches carried out by users on the online website APIMedOlder between 16 November 2022 and 16 November 2023. During this period, 400 searches were made, of which 42.8% corresponded to PIM. Most of the searches were made by pharmacists (39.0%), followed by physicians (26.5%), students (23.5%), pharmacy technicians (4.8%), nurses (3.5%), researchers (1.5%), and others (1.3%). The most searched drugs were omeprazole (4.5%), quetiapine (3.5%), furosemide (3.0%), alprazolam (2.8%), and paracetamol (2.5%). The searches made by pharmacists mostly focused on omeprazole (7.1%) and were mostly from the community pharmacy setting (44.2%). Regarding physicians, the most searched drugs were oxycodone and tramadol (6.6%) and were mostly from

general practitioners (50.9%). Searches made by students mostly centered on quetiapine (6.4%). Most students were from a nursing degree (53.2%). Other health professionals accounted for a smaller proportion of searches (11.1%), reflecting a lesser but diverse user engagement. Although this web-based application is not yet widely publicized among health professionals, some searches already demonstrate its potential to reduce PIM prescription in older adults.

Keywords: APIMedOlder · Potentially inappropriate medications · Older adults · Healthcare professionals · Searches

1 Introduction

Aging population represents a challenge for healthcare professionals, particularly in the field of medication management [1]. Prescribing drugs for the older population require careful consideration, as many medications have the potential for adverse effects that are exacerbated by age-related physiological changes [2, 3]. In this context, Potentially Inappropriate Medications (PIM) in older adults arise, defined as drugs that should be avoided since the potential for adverse events outweighs the clinical benefits, especially when safer or more effective alternatives are available [4–6].

The use of PIMs in older populations can lead to detrimental consequences for their health, such as an increased risk of adverse drug reactions, falls, cognitive impairment, and hospitalizations [7–9]. Moreover, the use of PIM can possibly exacerbate existing health conditions, potentially compromising the overall quality of life for older adults [10, 11].

Recently, a systematic review found that the worldwide PIM pooled prevalence of nearly 371.2 million older participants was 36.7% [12]. In Europe this prevalence stands at 35.0% [12]. Regarding Portugal, PIM prevalence ranged from 56.6 to 92.0%, explained by the different methodologies used and study settings analyzed in each study [13–16]. A PIM Defined Daily Dose (DDD) frequency of 9.20% was achieved, in mainland Portugal with higher values in Alentejo and Centro regions and lower in the North [17]. Furthermore, a study aimed to identify PIM within the adverse drug reactions reported in the Portuguese pharmacovigilance system, found that PIMs were found in 12.8% of them [18].

The widespread occurrence of PIMs poses a significant challenge to older population health and well-being. Therefore, recognizing and addressing PIM in the older population become crucial. Developing targeted strategies for identification, intervention, and education can contribute to mitigating the adverse effects of inappropriate medication use, thereby promoting better health outcomes, and enhancing the overall quality of life for older individuals [19, 20]. In response, we developed the APIMedOlder, a user-friendly web-based online platform that grants health professionals free access to PIM identification criteria, based in the EU(7)-PIM list [4, 21].

The APIMedOlder web application is integrated into a website containing information about the research team, associated scientific publications, and recognized distinctions and awards, available at apimedolder.com. The searches can be conducted using either the International Nonproprietary Name (INN) or the Anatomical Therapeutic

Chemical (ATC) code for a specific drug. If a drug is identified as a PIM, the user is provided with essential information, including the main reason, dose adjustment/special considerations of use and alternative drugs and/or therapies. Besides computers, the APIMedOlder web-based application it is also optimized for use on mobile phones and tablet devices. This platform was designed to serve as a practical and simple tool with a user-friendly interface, to enhance its applicability in clinical practice.

As we go deeper into the landscape of prescribing medications for older adults, it is crucial to understand preferences and trends in the use of tools like APIMedOlder. So, this study aims to describe what users of APIMedOlder have been searching for one year.

2 Methods

Data were retrospectively collected from searches conducted on the APIMedOlder web application between November 16, 2022, and November 16, 2023, encompassing one year, and providing a substantial dataset for analysis. Searches related to PIM or to other medications were both considered for a comprehensive examination of searches. Healthcare professional categories included physicians, pharmacists, pharmacy technicians, nurses, researchers, students, and others.

Descriptive statistics, such as frequencies and percentages were used to analyze the data. The outcomes included the distribution of searches across professional categories and the prevalence of searches for specific medications. Subgroup analyses were conducted to explore variations in search patterns among different healthcare professionals' categories.

3 Results

A total of 400 searches were analyzed over the twelve-month period. Of the total searches, 42.8% were identified as PIM. The most frequently searched drugs included omeprazole (4.5%), quetiapine (3.5%), furosemide (3.0%), alprazolam (2.8%), and paracetamol (2.5%). Of these, omeprazole and alprazolam are classified as PIMs. The detailed description of all drug searches can be found in Appendix 1. The distribution of searches across healthcare professionals' categories included pharmacists (39.0%), physicians (26.5%), students (23.5%), pharmacy technicians (4.8%), nurses (3.5%), researchers (1.5%), and other health professionals (1.3%).

Regarding searches by professional category, community pharmacists constituted the largest subgroup (44.2%) of searches made by pharmacists, followed by regulatory affairs (16.7%), pharmacovigilance (11.5%), and hospital pharmacists (9.0%). Searches made by physicians were mostly from general practitioners (50.9%), pediatricians (9.4%), and immunoallergologists (8.5%). Students pursuing a nursing degree accounted for 53.2% of student searches, followed by pharmacy students (26.6%). In 94.7% of the searches, pharmacy technicians did not specify their professional specialty, being the remaining from the education sector. Regarding nurses, most of the searches were from geriatric (57.1%), and emergency (35.7%) specialties. In 66.7% of the searches, researchers did not specify their specialty, being the remaining from

pharmacoepidemiology area. The distribution of searches made by other healthcare professionals involved oral hygienists (40.0%), regulatory affairs (20.0%) and secretarial services (20.0%). The detailed description of searches by specialty according to each professional category can be found in Appendix 2.

The most searched drugs by pharmacists were omeprazole (7.1%), furosemide (5.8%), paracetamol (5.1%), lorazepam (4.5%), and pantoprazole (3.8%). Oxycodone (6.6%), tramadol (6.6%), omeprazole (4.7%), rosuvastatin (3.8%), and opicapone (3.8%) were the most searched drugs by physicians. Regarding students, the most searched drugs were quetiapine (6.4%), lactulose (4.3%), donepezil (4.3%), metformin (3.2%), and alprazolam (3.2%). Amiodarone (10.5%), tamsulosin (10.5%), finasteride (10.5%), and haloperidol (10.5%) were the most searched drugs by pharmacy technicians. Regarding nurses, quetiapine (21.4%), and carbocisteine (21.4%) were the most searched ones. Researchers mostly searched about clonazepam (16.7%), bromazepam (16.7%), zolpidem (16.7%), and escitalopram (16.7%). The searches made by other healthcare professionals mostly focused on omeprazole (20.0%), amoxicillin (20.0%), paracetamol (20.0%), and potassium clorazepate (20.0%).

4 Discussion

This study provides valuable data into the utilization patterns of the APIMedOlder web application and preferences in medication searches conducted by various healthcare professionals over a twelve-month period. Notably, a substantial proportion of the searches (42.8%) were associated with PIMs, emphasizing the APIMedOlder online web application potential and importance of addressing concerns related to medication safety and appropriateness.

The specific drugs most frequently searched were omeprazole, quetiapine, furosemide, alprazolam, and paracetamol, indicating a heightened awareness of potential risks associated with these drugs in older populations. Of particular concern were omeprazole and alprazolam, identified as PIM, suggesting a need for targeted interventions and educational efforts surrounding the appropriate use of these medications.

Pharmacists were the most active group, constituting 39.0% of the searches, with community pharmacists leading. Community pharmacists are considered accessible healthcare providers, having regular and direct interactions with patients [22], therefore, increasing their awareness of older patient's medication, and possible making them more alert to issues related to PIMs, as part of their daily practice [23]. In fact, one study found that the proficient engagement of community pharmacists with patients regarding medication adherence and the appropriate use of medicines resulted in improved health outcomes for patients [24]. Physicians and students also actively engaged in medication searches, with general practitioners, and nursing students emerging as prominent subgroups within these categories. As the main prescribers of medication in primary care, general practitioners are often seeking for additional support and updated information on drug efficacy, dosages, and potential interactions to ensure optimal patient care [25]. Regarding nursing students and other healthcare-related students, develop essential skills in researching and understanding medications are part of their educational curriculum,

also preparing them for future clinical practice. One study found that nursing students exhibited a heightened awareness and interest in leveraging technology-enhanced information sources, such as medication management programs or applications, to integrate their knowledge into practice [26]. Other health professionals accounted for a smaller proportion of searches, reflecting a lesser but diverse user engagement.

The drugs of interest varied across professional groups. For pharmacists, omeprazole, furosemide, and paracetamol were frequently searched. These are widely dispensed drugs across Portuguese community pharmacies [27]. So, pharmacists, being at the forefront of dispensing, may frequently encounter these drugs and, consequently, seek for updated information on their uses, dosages, interactions, and potential side effects. Besides, according to the EU(7)-PIM List, omeprazole, as well as other proton pump inhibitors, are considered PIM if taken for a period longer than 8 weeks [4, 21]. Conversely, physicians showed interest in opioids such as oxycodone and tramadol. Opioids carry a risk of adverse effects, including respiratory depression, constipation, and dependence, especially in older adults [28]. Due to its higher propensity for the occurrence of adverse effects in older adults, such as confusion, vertigo and nausea, tramadol is considered a PIM, whether in sustained or non-sustained release [4, 21]. Therefore, physicians need to stay vigilant about these potential side effects in this population. Students' searches reflected their educational focus, with quetiapine, lactulose, and donepezil among the top drugs, maybe for better understand their therapeutic uses, mechanisms of action, and indications.

Actual data were collected from actual searches made on the APIMedOlder web application. This provides insights into the practical use of the tool by healthcare professionals. The inclusion of a diverse range of healthcare professionals enhances the generalizability of findings across different sectors of the healthcare system. Besides, identifying specific drugs of interest by each professional category could guide further educational interventions in specific settings. Regarding limitations, this study did not evaluate the impact of APIMedOlder on actual prescribing behavior. While the searches made indicate the interest of healthcare professionals, the study does not evaluate whether the tool influences clinical decision-making or improves patient outcomes. APIMedOlder web application is not yet widely publicized among healthcare professionals. So, increasing awareness of the tool's existence and features is crucial for maximizing its impact. Collaborative efforts with professional organizations, educational institutions, and healthcare systems could facilitate broader adoption and utilization of this tool.

5 Conclusions

APIMedOlder shows promise as a valuable resource for health professionals. Although this web-based application is not yet widely publicized among health professionals, nearly half of the searches were related to PIM. This finding highlights the application's capability to enhance medication safety in older adults by aiding in the identification and reduction of inappropriate prescriptions. Collaborative efforts between healthcare professionals could enhance knowledge sharing and promote a holistic approach to medication safety. Future research should explore the reasons behind the identified patterns

and assess the impact of interventions on improving medication-related knowledge and practices within healthcare professionals.

Appendix 1

See Table 1.

Table 1 Description of all drug searches (n = 400)

INN	ATC code	PIM*	n	%
Omeprazole	A02BC01	Yes	18	4.5
Quetiapine	N05AH04	–	14	3.5
Furosemide	C03CA01	–	12	3.0
Alprazolam	N05BA12	Yes	11	2.8
Paracetamol	N02BE01	–	10	2.5
Pantoprazole	A02BC02	Yes	9	2.3
Lorazepam	N05BA06	Yes	9	2.3
Tramadol	N02AX02	Yes	8	2.0
Oxycodone	N02AA05	–	7	1.8
Opicapone	N04BX04	–	6	1.5
Escitalopram	N06AB10	–	6	1.5
Donepezil	N06DA02	–	6	1.5
Pioglitazone	A10BG03	Yes	5	1.3
Rosuvastatin	C10AA07	–	5	1.3
Sildenafil	G04BE03	–	5	1.3
Amoxicilin	J01CA04	–	5	1.3
Diazepam	N05BA01	Yes	5	1.3
Zolpidem	N05CF02	Yes	5	1.3
Lactulose	A06AD11	–	4	1.0
Metformin	A10BA02	–	4	1.0
Gliclazide	A10BB09	–	4	1.0
Acetylsalicylic acid	N02BA01	Yes	4	1.0
Olanzapine	N05AH03	Yes	4	1.0
Domperidone	A03FA03	Yes	3	0.8
Loperamide	A07DA03	Yes	3	0.8
Glibenclamide	A10BB01	Yes	3	0.8
Semaglutide	A10BJ06	–	3	0.8
Amiodarone	C01BD01	Yes	3	0.8

(continued)

Table 1 (continued)

INN	ATC code	PIM*	n	%
Salmeterol	R03AC12	–	2	0.5
Mometasone	R03BA07	–	2	0.5
Omalizumab	R03DX05	–	2	0.5
Magnesium hydroxide	A02AA04	Yes	1	0.3
Magaldrate	A02AD02	Yes	1	0.3
Esomeprazole	A02BC05	Yes	1	0.3
Liquid paraffin	A06AA01	Yes	1	0.3
Bisacodyl	A06AB02	Yes	1	0.3
Racecadotril	A07XA04	Yes	1	0.3
Glipizide	A10BB07	Yes	1	0.3
Glimepiride	A10BB12	Yes	1	0.3
Metformin and ertugliflozin	A10BD23	–	1	0.3
Sitagliptin	A10BH01	Yes	1	0.3
Dapagliflozin	A10BK01	–	1	0.3
Calcium carbonate	A12AA04	–	1	0.3
Calcium. combinations with vitamin D and/or other drugs	A12AX	–	1	0.3
Warfarin	B01AA03	–	1	0.3
Clopidogrel	B01AC04	–	1	0.3
Ticlopidine	B01AC05	Yes	1	0.3
Rivaroxaban	B01AF01	Yes	1	0.3
Ferrous sulfate	B03AA07	Yes	1	0.3
Digoxin	C01AA05	Yes	1	0.3
Pentoxifylline	C04AD03	Yes	1	0.3
Timolol	C07AA06	–	1	0.3
Nebivolol	C07AB12	–	1	0.3
Nifedipine	C08CA05	Yes	1	0.3
Captopril	C09AA01	–	1	0.3
Perindopril	C09AA04	–	1	0.3
Losartan	C09CA01	–	1	0.3
Simvastatin	C10AA01	–	1	0.3
Pitavastatin	C10AA08	–	1	0.3
Tibolone	G03CX01	Yes	1	0.3
Prednisolone	H02AB06	–	1	0.3
Calcitonin (salmon synthetic)	H05BA01	–	1	0.3
Flucloxacillin	J01CF05	–	1	0.3
Norfloxacin	J01MA06	–	1	0.3
Moxifloxacin	J01MA14	–	1	0.3
Nitrofurantoin	J01XE01	Yes	1	0.3
Itraconazole	J02AC02	–	1	0.3

(continued)

Table 1 (continued)

INN	ATC code	PIM*	n	%
Hepatitis B. purified antigen	J07BC01	–	1	0.3
Natalizumab	L04AA23	–	1	0.3
Diclofenac	M01AB05	Yes	1	0.3
Meloxicam	M01AC06	Yes	1	0.3
Allopurinol	M04AA01	–	1	0.3
Tapentadol	N02AX06	–	1	0.3
Metamizole sodium	N02BB02	–	1	0.3
Zolmitriptan	N02CC03	Yes	1	0.3
Phenobarbital	N03AA02	Yes	1	0.3
Clonazepam	N03AE01	Yes	1	0.3
Eslicarbazepine	N03AF04	–	1	0.3
Bromocriptine	N04BC01	Yes	1	0.3
Chlorpromazine	N05AA01	Yes	1	0.3
Droperidol	N05AD08	Yes	1	0.3
Ziprasidone	N05AE04	Yes	1	0.3
Zuclopenthixol	N05AF05	Yes	1	0.3
Pimozide	N05AG02	Yes	1	0.3
Lithium	N05AN01	Yes	1	0.3
Bromazepam	N05BA08	Yes	1	0.3
Ethyl loflazepate	N05BA18	Yes	1	0.3
Hydroxyzine	N05BB01	Yes	1	0.3
Midazolam	N05CD08	Yes	1	0.3
Amitriptyline	N06AA09	Yes	1	0.3
Fluvoxamine	N06AB08	Yes	1	0.3
Mianserin	N06AX03	–	1	0.3
Duloxetine	N06AX21	–	1	0.3
Indacaterol	R03AC18	–	1	0.3
Fluticasone	R03BA05	–	1	0.3
Glycopyrronium bromide	R03BB06	–	1	0.3
Aminoalkyl ethers	R06AA	–	1	0.3
Brimonidine	S01EA05	–	1	0.3
Not identified	–	–	57	14.3

ATC: Anatomical Therapeutic Chemical; INN: International Nonproprietary Name; PIM: Potentially Inappropriate Medication.

* According to the Portuguese version of the EU(7)-PIM list.

Appendix 2

See Table 2.

Table 2 Description of searches by specialty according to each professional category

Professional category	Specialty	n	%
Physicians	General practice	54	50.9
	Pediatrics	10	9.4
	Immunoallergology	9	8.5
	Internal medicine	5	4.7
	Clinical pharmacology	5	4.7
	Public health	4	3.8
	Oncology	3	2.8
	Cardiology	2	1.9
	Geriatrics	1	0.9
	Intensive care medicine	1	0.9
	Not identified	12	11.3
	Total	106	100
Pharmacists	Community pharmacy	69	44.2
	Regulatory affairs	26	16.7
	Pharmacovigilance	18	11.5
	Hospital pharmacy	14	9.0
	Pharmaceutical technology	5	3.2
	Associativism	1	0.6
	Clinical pharmacology	1	0.6
	Not identified	22	14.1
	Total	156	100
Pharmacy Technicians	Education	1	5.3
	Not identified	18	94.7
	Total	19	100
Nurses	Geriatrics	8	57.1
	Emergency	5	35.7
	Not identified	1	7.1
	Total	14	100
Researchers	Pharmacoepidemiology	2	33.3
	Not identified	4	66.7

(continued)

Table 2 (*continued*)

Professional category	Specialty	n	%
Students	Total	6	100
	Nursing	50	53.2
	Pharmacy	25	26.6
	Medicine	3	3.2
	General practice	2	2.1
	Regulatory affairs	1	1.1
	Not identified	13	13.8
	Total	94	100
Other healthcare professionals	Oral hygienist	2	40.0
	Regulatory affairs	1	20.0
	Clinical secretary	1	20.0
	Not identified	1	20.0
	Total	5	100

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CHAPTER 8

Understanding potentially inappropriate medication: A focus
group study with general practitioners

VIII. Understanding potentially inappropriate medication: A focus group study with general practitioners

RESUMEN

La polifarmacia y el uso de medicamentos potencialmente inapropiados (PIM) representan desafíos significativos para los adultos mayores, a menudo causando resultados adversos en la salud. Aunque las herramientas de salud digital ofrecen soluciones prometedoras para mejorar la gestión de la medicación en esta población, su integración en la atención primaria sigue siendo lenta. Este estudio tiene como objetivo explorar las perspectivas de los médicos de familia portugueses sobre la polifarmacia, los PIM y la adopción de herramientas digitales para la adecuación de la medicación en adultos mayores. Se realizaron cinco grupos focales cualitativos con 37 médicos de familia que trabajaban en centros de atención primaria del norte de Portugal. Las sesiones fueron grabadas y se llevó a cabo un análisis temático. Emergieron cinco temas principales: factores asociados a la polifarmacia, desafíos en la deprescripción, problemas relacionados con los PIM, estrategias para gestionar la polifarmacia y barreras y facilitadores en la adopción de herramientas digitales para la adecuación de la medicación. Se identificaron ocho barreras y nueve facilitadores. Este estudio resalta la complejidad de la gestión de la medicación en adultos mayores y destaca el potencial de las herramientas digitales para optimizar el uso de los medicamentos. Son necesarias intervenciones personalizadas y esfuerzos colaborativos entre todos los actores del sistema de salud para mejorar la gestión de la medicación y los resultados en la salud de los adultos mayores.

Palabras clave: estudio con grupos focales; médicos de familia; adultos mayores; polifarmacia; medicamentos potencialmente inapropiados; herramientas digitales de salud.



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Understanding potentially inappropriate medication: A focus group study with general practitioners

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ABSTRACT

Introduction: Polypharmacy and Potentially Inappropriate Medication (PIM) pose significant challenges for older adults, frequently leading to adverse health outcomes. While digital health tools offer promise solutions to improve medication management for this population, their integration into primary care settings remains slow. This study aims to explore the perspectives of Portuguese general practitioners (GPs) regarding polypharmacy, PIM, and the adoption of digital health-related tools for medication appropriateness in older adults. **Methods:** Five qualitative focus group sessions were conducted with 37 GPs working in Portuguese primary healthcare facilities of the north. The sessions were recorded, and a thematic analysis was performed. **Results:** The following five themes emerged: factors associated with polypharmacy, challenges in deprescribing, problems related to PIM, strategies to handle polypharmacy, and barriers and facilitators adopting digital health-related tools for medication appropriateness. Eight barriers and nine facilitators were identified. **Conclusion:** This study underscores the complexity of medication management in older adults and highlights the potential of digital health tools to optimize medication use. Tailored interventions and collaborative efforts among all healthcare stakeholders are essential to enhance medication management and improve health outcomes in older adults.

1. Introduction

Polypharmacy, defined as the use of five or more medication daily [1], is common among older adults with a systematic review presenting worldwide prevalence values ranging from 2.6 % to 86.6 % [2]. This wide range of prevalence can be attributed to differences in study populations, healthcare settings, methodological approaches, and operational definitions of polypharmacy across several countries [2]. Linked to negative health outcomes like adverse drug reactions, drug interactions, and medication non-adherence [3,4], polypharmacy becomes increasingly significant [5], requiring attention from healthcare professionals to optimize medication use, through several interventions

[6].

Potentially Inappropriate Medication (PIM) refers to drugs with higher risks than benefits for older people [7,8]. A systematic review and meta-analysis conducted in 2023 concluded that, overall, the pooled prevalence of PIM use among older patients in outpatient services was 36.7 % [9], based on data from 94 studies covering nearly 371.2 million older participants from 17 countries. The prevalence varied by region, with Africa having the highest at 47.0 %, followed by South America (46.9 %), Asia (37.2 %), Europe (35.0 %), North America (29.0 %), and Oceania (23.6 %) [9]. PIM can lead to poor clinical outcomes and prolonged hospitalizations [10,11], greater healthcare services use and, therefore, may represent higher costs [8,12]. These concerns have been

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the reason behind the development of criteria for PIM identification, such as the Beers criteria [13], Screening Tool of Older Persons' Prescriptions (STOPP) criteria [14], the EU(7)-PIM list [15], among others [7].

Healthcare providers often seek tools and strategies for supporting drug use appropriateness [6,16,17], with digital health-related tools offering promising solutions by providing healthcare professionals with valuable information and resources [18–20]. Deprescribing, the supervised withdrawal of unnecessary or potentially harmful medication [21], represents another solution to optimize medication regimens in older patients [22,23]. Studies focused on polypharmacy refer to deprescribing as possibly associated with the reduction of adverse drug reactions, improved quality of life, and medication adherence [24].

Focus group studies offer the advantage of providing rich, qualitative data through in-depth discussions, allowing for a deeper understanding of participant attitudes and behaviors, and promoting interaction among participants with spontaneity when compared to surveys or group interviews [25,26]. They enable real-time feedback and dynamic interactions, where researchers can probe further into interesting areas as they arise, thus uncovering factors and insights that might remain hidden in more structured survey formats [26,27].

This study aimed to explore the perspectives of general practitioners (GPs) in Portuguese primary healthcare on polypharmacy, PIM, and the adoption of digital health-related tools for medication appropriateness in older adults. The findings shed light on the complexities of managing medications in this population and provide insights into the feasibility and acceptability of digital health interventions in primary care. By identifying barriers and facilitators to the adoption of digital tools, we aim to inform the development of interventions that support evidence-based prescribing practices and enhance patient safety in older adults.

2. Materials and Methods

Ethical Approval.

This study obtained ethical approval of the Regional Health Administration (Administração Regional de Saúde – ARS) of North of Portugal (reference CE/2023/70).

2.1. Study design

This is an explorative, qualitative focus group study about polypharmacy, PIM in older adults, and digital tools for clinical decision support on medication appropriateness for this population.

2.2. Study population

Primary healthcare facility directors were contacted by email with an invitation for all GPs to participate in the focus group meetings. Participation was voluntary, without any incentives, and all GPs signed an informed consent form before participation.

2.3. Setting

The sessions took place at 5 public primary healthcare facilities belonging to the ARS of the North and serving a total of 14,100 registered older adults (≥ 65 years) [28]. The Portuguese healthcare system is tax-funded under a National Health Service (Serviço Nacional de Saúde, SNS) which provides universal coverage for all residents in the country.

2.4. Focus group sessions

Sessions were held from November 2023 to April 2024. They were audio-recorded and led by a female Ph.D. student moderator (DAR) following a guide developed by experts in pharmacology and epidemiology (Supplementary material 1). At the beginning of each session,

participants were reminded of the study's aims and informed about the recording. Sessions, conducted in private rooms at the participants' workplaces, lasted approximately 30 to 60 min and included only the moderator and the GPs. Questions continued until information saturation was achieved.

2.5. Analysis

All the sessions were transcribed and coded by a researcher (DAR). Each session was codified with the acronym 'FG' followed by an alphanumeric character. Participants in each session were also codified with the corresponding session acronym, followed by the acronym 'GP' and an alphanumeric character (e.g., FG1GP1). After a month, the transcription was reviewed. Each transcript was read multiple times and analyzed thematically using Taguette, a free and open-source computer-assisted qualitative data analysis software [29], with tags assigned to quotes reflecting shared themes across all transcripts. This study followed the COREQ – Consolidated Criteria for Reporting Qualitative Research (Supplementary material 2) [30].

3. Results

Overall, 5 FG were conducted with a total of 37 GPs enrolled. The sociodemographic characteristics of the participants can be found in Table 1. The thematic analysis revealed five major themes: factors associated with polypharmacy, challenges in deprescribing, problems related to PIM, strategies to handle polypharmacy, and barriers and facilitators adopting digital health-related tools for medication appropriateness.

3.1. Factors associated with polypharmacy

According to GPs, multiple health conditions lead to the prescription of multiple medications (Table 2). Increased access to complementary diagnostic and therapeutic means also raises prescription rates.

"The easy access we have nowadays to complementary diagnostic and therapeutic means, therefore, leads to more medical diagnoses." FG2GP5.

Increased life expectancy leads to new medical conditions requiring treatment, meaning more medication for the patient. Complaints from older adults with multimorbidity also contribute to multiple prescriptions. Lack of coordination among healthcare providers across various levels (primary care, hospitals, and private services) implies multiple prescribers leading to overlapping prescriptions, unawareness of the patient's total medication regimen, and medication duplication.

"There are patients who visit many doctors, and we're not aware that they are taking other medication." FG1GP8

GPs also mention medical inertia, where existing medications are maintained without reevaluating their necessity or efficacy.

"There might also be some inertia in rethinking therapeutic goals." FG1GP8

Sociocultural factors like pharmaceutical marketing, influence from others in the community, and easy access to medication without prescriptions contribute to polypharmacy. Many older adults also lack support and live in social isolation.

Table 1
Sociodemographic characteristics of the study participants.

	Female	Male	Total
n (%)	26 (30.27 %)	11 (29.73 %)	37 (100 %)
Mean age (min, max)	39.04 (24–69)	38.64 (25–65)	38.92 (24–69)
Mean years of experience (min, max)	12.00 (0–45)	12.91 (0–41)	12.27 (0–45)

Table 2
Major themes from focus groups related with polypharmacy and deprescribing.

Major themes	Subthemes	Coding concepts
Factors associated with polypharmacy	Complexity in health care Internal and external barriers Practical limitations	Multiple pathologies Multiple prescribers GP inertia Sociocultural factors Consultation time Resistance
Challenges in deprescribing	GP-related Patient-related Practical limitations	Updated medical knowledge Communication with the patient Security and confidence Sensitivity Resistance Perception of disinvestment in healthcare Obtaining medication without a prescription Complexity of the clinical situation Multiple prescribers Consultation time Technical difficulties Several levels of healthcare Number of patients per doctor Patient literacy/education Specific guidelines for GP
Strategies for handling polypharmacy	Coordination and collaboration Health literacy Support tools Clinical practice	Prescription alerts Criteria for deprescribing Medication review Deprescription follow-up

"In addition to non-prescribed drugs, there's also the sale in pharmacies, television, marketing..." FG2GP2

"... they often do it because the neighbour does it." FG2GP2

Lack of time during consultations is cited as a challenge to properly manage medication in older adults, preventing adequate medication review.

"... the time allocated for a complex patient, in all their magnitude, is the same time allocated for a hypertensive patient with no comorbidities, or for a healthy adult." FG4GP3

Fear of adverse effects from deprescribing and patient resistance were also mentioned as barriers to reducing polypharmacy.

"...sometimes there is also resistance from the patient regarding deprescribing. We try, and often the patient doesn't want to stop taking certain medication..." FG5GP4

3.2. Challenges in deprescribing

Some GPs admitted they may not be aware of the latest guidelines or changes in medication indications, and therefore, the need to deprescribe. Some older patients resist discontinuing certain medication, especially if taken for a long time. However, acceptance improves when deprescribing is well explained.

"... it's very difficult to take away the medication they've been taking for 20 years." FG4GP1

Multiple prescribers and complex clinical situations, like multiple comorbidities and drug interactions, also make deprescribing challenging.

"One of the things is also the type of patient's conditions, because one thing is to withdraw a medication for cholesterol, and another is to withdraw a benzodiazepine." FG2GP3

Some patients may see deprescribing as a sign they no longer deserve healthcare, and the perception of disinvestment in health among older

adults concerns GPs regarding the deprescribing process.

"...they may often feel it's a disinvestment in their health. It's as if we're giving up on giving them more years of life or improving their quality of life." FG2GP8

Lack of time during consultations is a significant obstacle to the proper deprescribing of medication since it often does not allow for adequate medication review.

"When our time is almost up, and the consultation is about to end, we can't always do the review." FG2GP1

GPs mentioned technical difficulties like internet failures and slow digital systems.

"We don't have a reliable internet. It's always slow and with errors." FG3GP2

"The computers are very outdated." FG2GP9

They highlighted the difficulty in explaining to patients why certain medication needs to be stopped. There was an observation that some patients try to obtain medication without a prescription. Some GPs admitted lacking confidence and security in deprescribing and recognized a possible lack of sensitivity, highlighting the need for a more balanced approach between prescribing and deprescribing.

"I think a lot about deprescribing, but honestly, I have a lot of difficulty. (...) I also think I lack confidence." FG5GP2

3.3. Problems associated with potentially inappropriate medication

GPs acknowledged awareness of PIM and mentioned Beers and START/STOPP criteria as tools to identify PIM in older adults. However, while acknowledging their utility, many GPs admitted they don't use these criteria regularly, citing complexity or lack of time during the consultation.

"...they are not very easy to apply. It is difficult and requires a lot of work and time during the consultation." FG5GP7

GPs mentioned benzodiazepines as the drug class causing the most concern in older patients, as they are particularly difficult to discontinue due to dependence and resistance. They also expressed concern about prolonged use of antidepressants, especially tricyclic antidepressants. Nonsteroidal anti-inflammatory drugs (NSAIDs) and anticholinergics were identified as problematic drug classes due to the risk of adverse effects and drug interactions. Other drugs of concern included statins, aspirin, proton pump inhibitors (IBPs), anticoagulants, antihypertensives, antidiabetics, and multivitamins, which are sold without prescription and can cause interactions.

"The biggest difficulty lies with benzodiazepines..." FG1GP1

"Anticholinergics are also not highly recommended, and there are many (older adults) taking anticholinergics." FG3GP3

GPs noted that older adults often attempt to obtain drugs at the pharmacy without a medical prescription, such as anti-inflammatories, aspirin, benzodiazepines, and antibiotics.

"There is starting to be some difficulty in the pharmacy in providing all medication, but many of them are still obtained very easily." FG2GP9

3.4. Strategies for handling polypharmacy

For improving polypharmacy in older adults, GPs emphasize the need for coordination across healthcare levels, including a shared access base for chronic medication and collaboration with pharmacies to support deprescribing.

"I believe the management of the therapeutic regimen cannot solely rely on the physician. (...) it must involve other professionals as well, such as nursing and pharmacy...." FG5GP2

Increasing health literacy was cited as a strategy, including educating patients on medications risks and benefits, involving them in the decision-making process, and requiring more training and guidelines for physicians on deprescribing.

"When polypharmacy originates from them, I think it's largely up to us to educate them." FG3GP4

They suggest implementing alerts in the prescription system to identify similar medication already prescribed. Reducing or discontinuing unnecessary medication, especially for bedridden older patients, should be considered. GPs call for more frequent medication reviews and close monitoring after deprescribing.

"If they were followed more periodically, withdrawal would be much easier." FG3GP7

GPs also expressed the need to reduce the number of patients per physician to allow for more individualized care.

"They should reduce the number of patients per doctor." FG4GP1

3.5. Barriers and facilitators to the adoption of digital health-related tools for medication appropriateness

GPs identified eight barriers and nine facilitators regarding the adoption of digital health-related tools for medication appropriateness (Figs. 1 and 2).

A frequently cited barrier was the lack of integration with existing prescription systems, which GPs said is necessary for practical daily use.

"It couldn't be a standalone application; it had to be integrated." FG4GP1

GPs also worried about increased bureaucracy and complexity in the prescription process with new digital tools.

"If it brings more bureaucracy, if it delays the process, it doesn't help either. In other words, it has to be a useful platform that doesn't cause constraints." FG1GP8

Using digital tools may limit the time available during consultations for medication review and deprescribing.

"That doesn't take much time. Not delaying the consultation time." FG2GP6

GPs frequently mentioned poor internet and outdated technology as

barriers to using digital tools efficiently. They noted that digital tools depend on central authorization, making individual willingness insufficient. Alert fatigue was also mentioned, as GPs feel discouraged from using a tool that requires "too many clicks" (FG1GP1). Lastly, GPs also feel uncomfortable using technology devices in front of patients, fearing it makes their decisions seem less credible.

"... I don't feel comfortable in front of a patient (...) and have to spend 10 min looking things up on the computer..." FG3GP1

Concerning facilitators, GPs emphasized the need for integration with the existing prescription system.

"If it were available in the software programs we already use, it would be more practical." FG2GP2

GPs expressed interest in easy-to-use, accessible, and intuitive tools that provide information quickly and succinctly. They also prefer personalized alerts specific to each patient, without excessive workflow interruptions. Ideal tools would alert about drug interactions, renal function adjustments, and include risk calculators.

"The drug-drug interaction, I think, is important. Adjustment according to glomerular filtration rate, which we often don't have. And then risk calculators." FG5GP3

From the GPs' perspective, effective digital tools could help them focus on patients, reduce cognitive load, and minimize time spent on administrative tasks, thus optimizing the useful consultation time with the patient.

"If we had the assistance of digital tools, we could focus more on the patient." FG3GP7

Free access to digital tools was also mentioned as a facilitator for more frequent use. Reducing prescribing errors and improving patient safety were seen as key motivations for using these tools.

"It can increase patient safety and prescription safety. I think that's the goal." FG1GP8

4. Discussion

The findings from this study highlight the complex challenges faced by GPs in managing polypharmacy and PIM in older adults, as well as their perceptions of digital health-related tools as potential solutions. Several factors contributing to polypharmacy, strategies for handling it, and challenges in deprescribing were identified. Concerning PIM, GPs revealed awareness, however, they do not frequently use the criteria for PIM identification in clinical practice. During the focus group sessions,

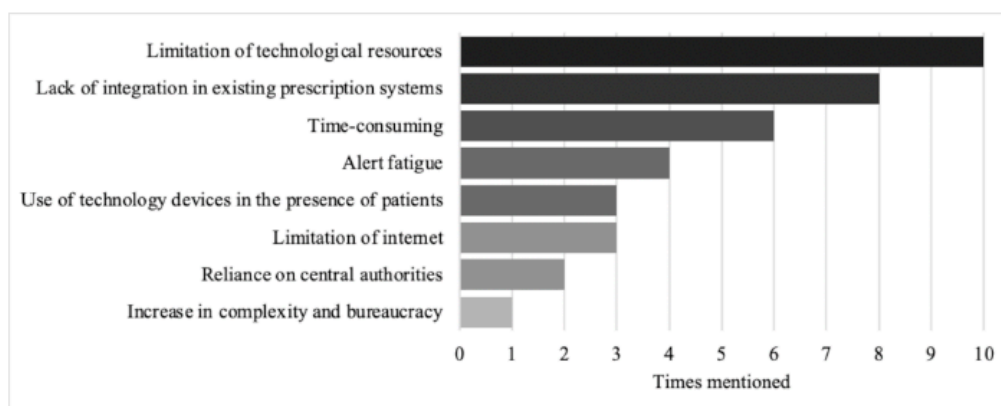


Fig. 1. Barriers to the adoption of digital health-related tools for medication appropriateness.

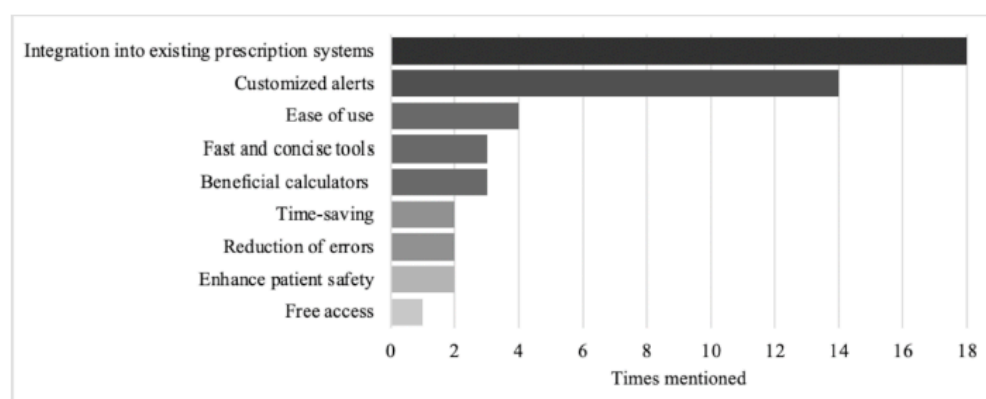


Fig. 2. Facilitators to the adoption of digital health-related tools for medication appropriateness.

key obstacles and facilitators were identified by GPs. Table 3 provides a structured overview of these obstacles and facilitators, along with our proposed solutions, which may be useful in clinical practice for healthcare professionals and policymakers. Eight barriers and nine facilitators were identified regarding adopting digital health-related tools for medication appropriateness.

Key factors contributing to polypharmacy include multiple health conditions, access to several healthcare services, multiple prescribers and lack of coordination among providers. These findings are consistent with existing research, which highlights the complexity of medication management in older adults and emphasizes the need for comprehensive approaches to polypharmacy [17,31]. A study conducted in Australia also identified multimorbidity as a primary driver of polypharmacy, stressing the importance of integrated care models to mitigate risks associated with excessive medication use [32]. Another focus group study with Portuguese healthcare professionals confirmed that multiple comorbidities make polypharmacy a persistent issue among older adults [33]. Managing multiple health issues often requires prescribing multiple medications, which increases the risk of adverse drug reactions and medication interactions [34]. Addressing multimorbidity through integrated care models that emphasize comprehensive medication reviews and patient-centered care planning is essential for optimizing medication use [35]. Interventions targeting polypharmacy have been associated with reductions in potentially inappropriate prescriptions and improved medication adherence [36].

GPs discussed several strategies for handling polypharmacy, including improved coordination among healthcare levels, patient education, and medication review. Medication reviews can enhance outcomes by reducing inappropriate prescribing and drug-related problems [37]. However, effective medication optimization requires more than just reviews; coordination among multidisciplinary teams is crucial [38]. In Denmark, a study on medication communication between older adults and healthcare providers emphasized the role of shared decision-making in managing polypharmacy [39]. Additionally, the prevalence of polypharmacy in older adults is linked to education levels, highlighting the need to improve patient literacy [40]. A focus group study with Portuguese older adults found that they often referred to medication by pill color or purpose rather than by name or precautions, indicating a lack of knowledge about their prescriptions [41]. A narrative review of existing literature conducted in primary care settings showed that health literacy among older adults was a significant factor influencing medication adherence and safe medication use [31].

Deprescribing challenges were highlighted by GPs, including patient resistance, time constraints during consultations, and technical difficulties. These issues are consistent with a recent review highlighting deprescribing as a complex process affected by similar barriers,

including lack of time and patient resistance [42]. Research from Germany also highlighted the challenges faced by healthcare professionals in applying deprescribing guidelines and the need for structured, patient-centered deprescribing interventions [43]. Interventions aimed at deprescribing may reduce mortality and the use of PIM among community-dwelling older adults [44]. Effective deprescribing requires consideration of the patient's functional status, living conditions, and care plans [45]. Therefore, this study supports the need for tailored deprescribing approaches that address patient preferences and clinical complexities [46,47]. At the policy level, integrating deprescribing guidelines into clinical protocols and incentivizing structured medication reviews may encourage more proactive deprescribing practices [48,49]. Government and professional organizations should collaborate to establish deprescribing task forces, ensuring that evidence-based medication optimization strategies are widely implemented across healthcare settings. Additionally, incorporating deprescribing education into undergraduate and postgraduate medical curricula, alongside continuous professional development programs, could strengthen GPs' confidence and skills in medication optimization [50]. Educational workshops and case-based learning sessions should be provided regularly to update clinicians on deprescribing guidelines and strategies to overcome patient resistance. Training healthcare professionals in doctor-patient communication skills can also enhance trust and persuasion, improving patient adherence and reducing potential distrust [51]. Moreover, establishing multidisciplinary teams could facilitate more comprehensive medication assessments and deprescribing initiatives [52]. Investment in digital infrastructures is also crucial to overcoming technical difficulties still present in primary healthcare, by ensuring reliable internet access, enhancing clinical software performance, and supporting the integration of digital health tools [53]. This supports data-driven decision-making, strengthens integrated care models, and improves accessibility, ultimately fostering more efficient and patient-centered healthcare delivery [54].

GPs expressed concern about commonly prescribed drug classes such as benzodiazepines, antidepressants, and NSAIDs. Benzodiazepine use in older adults often exceeds evidence-based recommendations [55]. Barriers to reducing sedative-hypnotic prescriptions include patient and prescriber inertia, skills and awareness issues, and health system constraints [56]. Reluctance to deprescribing antidepressants is often due to fears of withdrawal symptoms, relapse, and the complexities of managing multiple comorbidities [57]. A study found that the prescribing practices of NSAIDs are not aligned with clinical guidelines for safe use in older individuals [58]. Prescriptions should be tailored to individual needs and preferences [59]. Effective strategies to minimize high-risk medication include enhancing health literacy among patients, families, and care teams and achieving mutual agreements [45].

Table 3
Obstacles, facilitators and proposed solutions for optimizing medication use in older adults.

Problems discussed by GPs	Obstacles to resolution identified by GPs	Facilitators to resolution identified by GPs	Proposed solutions
Polypharmacy	Multiple pathologies and multiple prescribers	Coordination across levels of healthcare	Integrated care models focusing on comprehensive medication reviews Strengthening interprofessional collaboration Patient-centered care planning
	GP inertia	Specific guidelines for GPs	Integrate deprescribing guidelines into clinical protocols Implementation of evidence-based prescribing guidelines
	Pharmaceutical marketing and community influence	Patient education	Enhancing patient awareness campaigns providing educational materials Training healthcare professionals in doctor-patient communication skills
	Limited consultation time	Reduce the number of patients per GP	Establishing multidisciplinary teams to support medication management
	Patient resistance	Deprescription follow-up	Structured, patient-centered deprescribing interventions Shared decision-making models Training healthcare professionals in doctor-patient communication skills
PIM	Lack of consistent use of PIM criteria	Awareness of the importance of medication optimization for patient safety	Incorporating PIM criteria and deprescribing into undergraduate and postgraduate medical education, along with continuous professional development Educational workshops and case-based learning sessions
Deprescribing	Inappropriate medications frequently prescribed and difficult to discontinue due to dependence and resistance	Implement alerts in the prescription system Regular medication reviews	Promoting better use of PIM criteria and guidelines Tailoring prescriptions to individual needs and preferences
	Lack of updated medical knowledge	Continuing medical education	Integrate deprescribing guidelines into clinical protocols Implementation of

Table 3 (continued)

Problems discussed by GPs	Obstacles to resolution identified by GPs	Facilitators to resolution identified by GPs	Proposed solutions
	Sensitivity towards deprescribing	Increased GPs confidence and security	evidence-based prescribing guidelines Incorporating PIM criteria and deprescribing into undergraduate and postgraduate medical education, along with continuous professional development Educational workshops and case-based learning sessions
	Patient resistance	Patient education	Enhancing patient awareness campaigns providing educational materials Training healthcare professionals in doctor-patient communication skills
	Perception of disinvestment in healthcare	Stronger GP-patient communication	Framing deprescribing as a patient-centered approach Promoting shared decision-making strategies
	Obtaining medication without a prescription Complexity of the clinical situation and multiple prescribers Limited consultation time	Better pharmacy regulations Improved coordination among prescribers Reduce the number of patients per GP	Strengthening pharmacy policies on medication dispensing Coordination among multidisciplinary teams
	Technical difficulties (internet failures and slow digital systems)	Improved technology infrastructure and system optimization	Establishing multidisciplinary teams to support medication management Investment in digital infrastructure, ensuring reliable internet access and upgrading clinical software for better performance

Developing patient-centered deprescribing conversations, shared decision-making models, and educational materials tailored to older adults can improve acceptance [60]. Moreover, strengthening pharmacy regulations and policies on medication dispensing is crucial to prevent the acquisition of medication without a prescription, ensuring safer and more controlled access to pharmaceuticals, and promoting better public health outcomes [61].

Despite their awareness of PIM criteria such as the Beers and STOPP criteria, GPs admitted they rarely use them in practice. Although studies aimed at assessing physicians' knowledge concerning PIM criteria are limited, some conducted in other countries have also revealed a weak awareness [62–65], underlining the need for more education and training on these tools, perhaps by integrating this topic as part of undergraduate and postgraduate medical education, as suggested before [66].

The study also explored GPs' views on digital health tools for medication appropriateness. In recent years, several digital health solutions have been developed to support medication optimization, including clinical decision support systems (CDSS) integrated into electronic health records (EHRs), deprescribing algorithms, and artificial intelligence-driven tools [67,68]. GPs acknowledged the potential benefits of these tools, such as enhanced decision-making and patient safety. Implementing electronic medication optimization systems could improve safety by identifying patients at risk of adverse drug events in primary care settings [69]. Artificial intelligence (AI)-based tools also have proven effective in reducing medication errors compared to standard practices, playing a crucial role in patient safety [70]. Examples include MedAware, which uses AI to detect prescription errors by analyzing patterns in EHRs [71], and PINCER, a pharmacist-led intervention that identifies patients at risk of medication-related harm through computerized prescribing safety indicators [72,73]. MedSafer focuses on deprescribing by reviewing patient medications and providing evidence-based recommendations to manage polypharmacy [74,75]. Key facilitators for adoption identified in this study included ease of use, personalized alerts, and free access to the tools. However, optimizing the time available during consultations with older patients remains essential. Healthcare professionals are hesitant to adopt tools that increase their workload, preferring to focus on direct patient care [76,77]. Digital health solutions can also support personalized care for older adults, enhancing their overall well-being [78].

Despite the recognized benefits, the adoption of digital health tools remains slow, with GPs identifying several barriers, including poor integration into existing systems, increased bureaucracy, and alert fatigue. These findings align with a recent systematic review, which highlighted similar challenges, such as alert fatigue, time constraints, and limited internet and technological resources in primary care [79]. Integration with current prescription systems requires constant updates, often hindered by internet failures and outdated equipment. Addressing these barriers necessitates robust governance frameworks, investment in infrastructure to support seamless integration and usability, adherence to interoperability standards, and collaboration between healthcare and information technology teams [80]. Strategies to reduce the alert burden include establishing robust governance frameworks to oversee alert systems, regularly reviewing alert rules for clinical relevance, and implementing metrics to assess effectiveness [81]. It might be beneficial to prioritize alerts based on the potential risk to the patient, ensuring that high-risk alerts receive immediate attention while minimizing the overload on physicians. Improving clinicians' knowledge and usage of alert-management features, allowing them to customize alert thresholds, snooze non-urgent alerts, or suppress repeat notifications can help minimize alert fatigue, improve workflow efficiency, and ensure that critical alerts receive appropriate attention [82]. Therefore, continuous training and support for healthcare professionals are essential. Digital tools must be user-friendly and intuitive, ensuring that they are accessible to GPs with varying levels of technological expertise. The simplicity of the interface plays a key role in their successful adoption [83]. Institutional changes are also crucial for successful tool implementation, requiring effective coordination among health system stakeholders [84]. Engaging healthcare professionals in both the development and implementation phases of digital health tools is essential to ensure their usability and acceptance in routine practice [85]. Continuous monitoring and evaluation of the impact of these tools are necessary to ensure their effectiveness and identify areas for improvement. Regular feedback can guide adjustments and enhance tool usability in clinical settings. A United States study identified six key policy priorities for implementing digital health innovations: defining system-level innovation, establishing a clear mission, clarifying roles, standardizing processes, emphasizing change management, and aligning funding structures [86].

This study has several strengths. It facilitated critical reflection, offering GPs a platform to share their ideas and experiences, and

generating valuable insights. The sample, composed of GPs from various primary healthcare facilities in Northern Portugal, ensured diversity in practice settings. The methodological rigor employed enhances the reliability and validity of the findings. Thematic analysis of focus group data provided an in-depth understanding of factors influencing polypharmacy, medication management strategies, and barriers and facilitators to adopt digital health tools. Identifying common themes and patterns across the data led to comprehensive insights.

This study has some limitations. Shyer participants may have hesitated to share their views, potentially conforming to group trends and offering similar responses. GPs with a stronger interest or more experience in polypharmacy and digital health tools might have been more inclined to participate potentially leading to selection bias. As a result, the characteristics of the participating GPs, particularly their familiarity and enthusiasm for digital health tools, could influence the findings. Furthermore, the findings reflect the experiences of GPs in Portuguese primary healthcare settings and may not fully apply to other healthcare contexts or countries. Social desirability bias may also have influenced responses, as participants might have provided answers that they believed were more acceptable or aligned with the study's expectations. Recall bias may have also played a role, especially regarding participants' recollections of past practices with medication guidelines or digital tools. Nonetheless, no new information emerged in the final focus groups, indicating data saturation.

Recent studies continue to debate the adequacy of saturation as a method for determining sample sizes in qualitative research, particularly in focus group studies [87,88]. However, saturation remains a widely accepted concept, with methodological advancements refining its application for more credible qualitative outcomes [89]. A systematic review suggests that between 4 and 8 focus groups are necessary to achieve saturation, especially when the study population is homogeneous [90]. Another study found that code saturation was reached after 4 focus groups, identifying 94 % of all codes and 96 % of high-prevalence codes, indicating stability in the codebook [91]. Thus, the five focus groups conducted in this study provide sufficient data to meet the research aims.

This article provides valuable insights into the challenges GPs face with polypharmacy and PIM in older adults, as well as strategies and perceptions related to digital health tools. These insights can guide the development of targeted interventions to improve clinical practice, fostering a safer and more effective approach to medication management in older adults.

5. Conclusion

This study provides valuable insights into polypharmacy, PIM, and the adoption of digital tools for medication appropriateness in older adults from the perspective of Portuguese GPs. The findings emphasize the need for tailored interventions such as user-friendly digital tools and educational programs, to optimize medication use and improve patient outcomes. Promoting multidisciplinary collaboration among healthcare professionals, researchers, policymakers, and patients is essential. Future research should focus on developing and implementing targeted interventions leveraging the potential of digital health technologies to enhance medication optimization in primary care settings.

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CRediT authorship contribution statement

Daniela A. Rodrigues: Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Maria Teresa Herdeiro: Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. Ramona Mateos-Campos: Writing – review & editing, Validation, Supervision, Project administration. Adolfo Figueiras: Writing – review & editing, Validation. Fátima Roque: Writing – review & editing, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijmedinf.2025.105899>.

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SUPPLEMENTARY MATERIAL

Supplementary material 1

FOCUS GROUP GUIDE

FOCUS GROUP PARTICIPANT PRESENTATION

1. Can you please tell me your age and years of experience?

ATTITUDES AND PERCEPTIONS REGARDING POLYPHARMACY AND POTENTIALLY INAPPROPRIATE MEDICATIONS IN OLDER ADULTS

1. What are the main factors contributing to polypharmacy in older adults?
 - a. Is this a concern during prescribing?
2. What do you believe could be done to improve polypharmacy in older adults?
3. What is your perception regarding potentially inappropriate medications in the older population?
 - a. Is this a concern during prescribing?
4. Do you usually use sources of information when prescribing medications for older adults?
 - a. If yes, which ones?
5. What is your perception regarding the criteria described in the literature for identifying potentially inappropriate medications in older adults?
 - a. Do you usually use them?
 - b. If yes, which ones?

6. What are the medications/groups of medications that concern you the most when prescribing for older adults?
 - a. Why?

BARRIERS RELATED TO PRESCRIBING/DEPRESCRIBING MEDICATIONS IN THE ELDERLY

1. What are the main barriers to prescribing/deprescribing medications for older adults?
2. What is your perception regarding the older adult's reaction when deprescribing medications occurs?
 - a. Do they accept it, get upset, or express concern about the reasons?
 - b. Do they attempt to obtain the medication without a prescription from the pharmacy?

BARRIERS AND/OR FACILITATORS TO THE ADOPTION OF DIGITAL HEALTH TOOLS RELATED TO MEDICATION APPROPRIATENESS

1. What is your experience with digital tools related to medication appropriateness?
 - a. Do you usually use them?
 - b. If yes, what type of tools?
2. What are the main factors contributing to the adoption/use of digital tools related to medication appropriateness?
3. In your perception, what are the difficulties encountered in adopting/using these tools in your daily clinical practice?
4. Do you believe that using digital tools related to medication appropriateness influences your ability to provide effective care to older patients?

5. Do you have the necessary resources available to learn how to use these tools efficiently?
6. In your opinion, how should an "ideal" prescription support tool be designed, and what information should it contain?

Supplementary material 2

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
<i>Personal Characteristics</i>			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	3
Credentials	2	What were the researcher's credentials? <i>E.g., PhD, MD</i>	3
Occupation	3	What was their occupation at the time of the study?	3
Gender	4	Was the researcher male or female?	3
Experience and training	5	What experience or training did the researcher have?	-
<i>Relationship with participants</i>			
Relationship established	6	Was a relationship established prior to study commencement?	-
Participant knowledge of the interviewer	7	What did the participants know about the researcher? <i>e.g., personal goals, reasons for doing the research</i>	-
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? <i>e.g., Bias, assumptions, reasons, and interests in the research topic</i>	-
Domain 2: study design			
<i>Theoretical framework</i>			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? <i>e.g., grounded theory, discourse</i>	2,3

		<i>analysis, ethnography, phenomenology, content analysis</i>	
Participant selection			
Sampling	10	How were participants selected? <i>e.g., purposive, convenience, consecutive, snowball</i>	2
Method of approach	11	How were participants approached? <i>e.g., face-to-face, telephone, mail, email</i>	2
Sample size	12	How many participants were in the study?	3
Non-participation	13	How many people refused to participate or dropped out? Reasons?	-
Setting			
Setting of data collection	14	Where was the data collected? <i>e.g., home, clinic, workplace</i>	3
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	3
Description of sample	16	What are the important characteristics of the sample? <i>e.g., demographic data, date</i>	3
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	3
Repeat interviews	18	Were repeat interviews carried out? If yes, how many?	2,3
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	3
Field notes	20	Were field notes made during and/or after the interview or focus group?	-
Duration	21	What was the duration of the interviews or focus group?	3
Data saturation	22	Was data saturation discussed?	3
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	-
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	3
Description of the coding tree	25	Did authors provide a description of the coding tree?	2,3
Derivation of themes	26	Were themes identified in advance or derived from the data?	3
Software	27	What software, if applicable, was used to manage the data?	3
Participant checking	28	Did participants provide feedback on the findings?	-
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? <i>e.g., participant number</i>	4-10
Data and findings consistent	30	Was there consistency between the data presented and the findings?	3-13
Clarity of major themes	31	Were major themes clearly presented in the findings?	4-10
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	4-13

CHAPTER 9

Reducing Potentially Inappropriate Prescriptions Through a Multifaceted Intervention: a Nonrandomized Cluster-Control Based Intervention

IX. Reducing Potentially Inappropriate Prescriptions Through a Multifaceted Intervention: a Nonrandomized Cluster-Control Based Intervention

RESUMEN

Este estudio tuvo como objetivo evaluar el impacto de una intervención multifacética que incorpora la herramienta APIMedOlder en la reducción de la prescripción de medicamentos potencialmente inapropiados (PIM) en adultos mayores. Se realizó un estudio controlado por conglomerados en atención primaria de la región central de Portugal. Médicos de familia participaron en una intervención educativa que incluyó formación sobre el uso de la herramienta APIMedOlder. Se recopilaron datos sobre la prescripción de PIM antes, durante y después de la intervención, medidos en Dosis Diarias Definidas por 1000 habitantes por día (DID). Se analizaron las diferencias en las tendencias de prescripción de PIM entre los grupos a lo largo del tiempo. La intervención incluyó 44 sesiones, alcanzando aproximadamente al 58% de los médicos de familia objetivo. Al inicio, el grupo intervención presentó una DID de PIM menor (336,71) en comparación con el grupo control (365,38). Tras la intervención, el grupo control mostró un aumento marcado en la prescripción de PIM, especialmente a los uno y tres meses, mientras que el grupo intervención mantuvo valores de DID estables o reducidos. El efecto se redujo a los seis meses. La intervención educativa multifacética sugirió un beneficio moderado y a corto plazo en contener el aumento de la prescripción de PIM en adultos mayores en atención primaria. No obstante, los efectos sostenidos a largo plazo parecen limitados, lo que resalta la necesidad de soporte continuo y estrategias de refuerzo para mantener mejoras en las prácticas de prescripción.

Palabras clave: medicamentos potencialmente inapropiados; APIMedOlder; herramienta digital; adultos mayores; atención primaria; intervención multifacética.

Reducing Potentially Inappropriate Prescriptions Through a Multifaceted Intervention: a Nonrandomized Cluster-Control Based Intervention

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ABSTRACT

Background: The use of Potentially Inappropriate Medication (PIM) in older adults remains prevalent, often leading to adverse outcomes. Despite existing guidelines, high rates of PIM use persist, indicating the need for additional strategies. APIMedOlder, a digital tool based on the EU(7)-PIM list adapted for Portugal, was developed to support healthcare professionals in identifying and addressing PIM use. **Aim:** To evaluate the impact of a multifaceted intervention incorporating the APIMedOlder tool on reducing PIM prescriptions in older adults. **Methods:** A nonrandomized controlled cluster study was conducted in primary healthcare of central region in Portugal. General practitioners (GPs) participated in an educational intervention that included

training on the APIMedOlder tool. Data on PIM prescriptions were collected before, during and after the intervention, measured in Defined Daily Doses per 1000 inhabitants per day (DID). Differences in PIM prescribing trends were analyzed over time. **Results:** The intervention involved 44 sessions, reaching approximately 58% of targeted GPs. At baseline, the intervention group had lower PIM DID (336.71) compared to control (365.38). Post-intervention, the control group showed a marked increase in PIM prescriptions, particularly at one and three months, while the intervention group maintained stable or reduced DID values. The effect diminished by six months. **Conclusion:** The multifaceted educational intervention suggested a moderate, short-term benefit in containing the rise of PIM prescriptions in older adults in primary care. However, sustained effects over the long term appear limited, underscoring the need for ongoing support and reinforcement strategies to maintain improvements in prescribing practices.

Keywords

Potentially Inappropriate Medication; APIMedOlder; Digital Tool; Older Adults; Primary Care; Multifaceted Intervention.

INTRODUCTION

The use of Potentially Inappropriate Medication (PIM) in older adults remains a significant public health problem, often leading to adverse drug reactions (ADRs), increased healthcare utilization, and poorer clinical outcome [1,2]. The global pooled prevalence of PIM use among older patients in outpatient services was 36.7%, with Europe showing a prevalence of 35.0% [3]. In Portugal, the prevalence among older adults taking at least one PIM in primary healthcare settings ranged from 50.1% to 63.8% [4]. Despite several guidelines and recommendations aimed at optimizing prescribing practices [5], the persistence of PIM use among older adults suggests that additional interventions are necessary to support healthcare professionals in improving medication appropriateness.

Digital tools have emerged as valuable resources to enhance clinical decision-making, operational efficiency, and diagnostic accuracy [6]. In this context, the APIMedOlder web application (<https://apimedolder.com>) was developed to assist healthcare professionals in searching and identifying PIM, based on the Portuguese adaptation of the EU(7)-PIM list [7,8]. However, although digital tools are increasingly integrated into healthcare settings, their implementation and enhancement still present challenges [9]. The effective integration of such tools into clinical practice requires not only technological accessibility but also targeted educational interventions that enhance healthcare professionals' knowledge, confidence, and willingness to use them [10]. Therefore, this study aims to evaluate the impact of a multifaceted intervention incorporating the

APIMedOlder tool on reducing the prescription of PIM in older adults. The findings of this study would provide insights into the effectiveness of digital decision-support tools combined with an educational intervention in primary care settings. Furthermore, they would contribute to the ongoing discussion on how to optimize medication use in older adults and improve patient safety through structured interventions targeting prescribing behaviors.

METHODS

Study population and setting

In Portugal, general practitioners (GPs) are at the forefront of primary healthcare, being responsible for prescribing medications in primary care settings, playing a crucial role in medication management for older adults [11]. Given their central role in prescribing, GPs were the target of this intervention to ensure a direct impact on prescribing behaviors and medication safety. The study was conducted within the area of Portugal's Regional Health Administration of the Centre (Administração Regional de Saúde do Centro, ARSC), which serves a population of approximately 506200 older adults (aged 65 years and older). This region includes 186 Primary Healthcare Centers. The study population comprised all GPs working within the Public National Health System in this area (~1017).

Study Design

The study employed a nonrandomized controlled cluster design to minimize contamination between the intervention and control groups. Given the organizational structure of primary care services within the ARSC, which includes 8 Local Health Units (Unidades Locais de Saúde, ULS), the clusters were defined at the ULS level rather than the individual GP level. Of the 8 clusters, 4 were assigned to the intervention group, continuing a previous project that involved an educational intervention targeting older patients registered at these ULS. The project, named MedElderly (SAICT-POL/23585/2016), was funded by the FCT and received approval from the ARSC in 2017. The remaining 4 were allocated to the control group.

APIMedOlder web application

The APIMedOlder web application [12], developed in 2022, is a digital tool designed to support healthcare professionals in identifying PIM in older adults, based on the Portuguese adaptation of the EU(7)-PIM list [7]. The search for the PIM can be conducted using either the International

Nonproprietary Name (INN) or the Anatomical Therapeutic Chemical (ATC) code of a given drug. If a medication is identified as a PIM, the system provides the rationale behind its classification, recommendations for dose adjustments or special considerations, and suggested alternative medications and/or therapies. The platform is also optimized for use on mobile phones and tablets, ensuring accessibility in various clinical settings. A usability study of the APIMedOlder web application has already been conducted to assess its practicality and user experience among healthcare professionals [13]. The results were very positive, indicating high usability and suggesting that APIMedOlder is a user-friendly tool [13].

Ethical considerations

This study obtained ethics approval from ARSC (proc. 37/22). The educational sessions were exclusively designed for health professionals, specifically GPs, and did not involve any patients. The GPs were invited to participate in the study and agreed to take part in the intervention sessions.

Intervention

The intervention group consisted of 4 clusters, which included 83 Primary Healthcare Centers comprising approximately 484 GPs according to data from the public-access platform developed by the Shared Services of the Ministry of Health (Serviços Partilhados do Ministério da Saúde) [14], and serving an older population of approximately 239800 individuals. The educational intervention was implemented using a combination of active and passive approaches. The active component was structured to be delivered through multiple sessions with GPs using an outreach visit format, structured to be both informative and interactive. Each session was divided into two main sections. The first one focused on polypharmacy and the use of PIM in older adults. It addressed the risks associated with PIM use, and the key challenges faced by prescribers when managing complex medication regimens in older patients. The second one was dedicated to presenting the APIMedOlder web application. This section included an interactive presentation of the application, focusing on its functionalities, such as identifying PIM, suggesting safer alternatives, and providing tailored recommendations based on the Portuguese version of the EU(7)-PIM list [7]. Participants were encouraged to explore the application in real time, and questions were addressed, and practical demonstrations were provided. Participants were granted continued access to the APIMedOlder application to enable exploration and integration into their routine practice. The passive component involved the distribution of educational materials, including posters and flyers with concise instructions for navigating the application.

From an operational point of view, the following steps were followed to carry out the intervention: an email invitation was sent to the clinical director of each ULS in the intervention group, inviting all GPs to take part in the initiative. The clinical directors played a key role in organizing the outreach visits, which were scheduled during weekly staff meetings to ensure the highest possible attendance of GPs. The presentation lasted approximately one hour and began with a presentation of data highlighting key information about PIM. This was followed by the screening of illustrative videos demonstrating the functionality of the APIMedOlder tool. The videos provided step-by-step guidance on how to use the tool to access comprehensive information about PIM, including identifying them, understanding their risks, and exploring safer therapeutic alternatives. The intervention took place between June 1, 2022, and February 29, 2024.

Control group

The control group, which did not receive the intervention, consisted of 4 clusters, including 103 Primary Healthcare Centers comprising approximately 533 GPs, according to data from the public-access platform developed by the Shared Services of the Ministry of Health [14], serving an older population of approximately 266400 individuals.

Follow-up

The follow-up period lasted six months, beginning on March 1, 2024, and ending on August 31, 2024. This period was divided into three distinct timeframes for analysis: the first month following the intervention, from March 1 to March 31, 2024; the first three months, from March 1 to May 31, 2024; and the entire six-month follow-up period, from March 1 to August 31, 2024. This segmentation allowed for a detailed evaluation of the intervention's impact over short-, medium-, and long-term intervals. A 13-month baseline period prior to the intervention, from May 1, 2021 to May 31, 2022, was used to assess the dependent variables and establish pre-intervention comparability between the control and intervention groups.

Data Source

To quantify PIM use, we utilized published prescription data from each ULS, measured in Defined Daily Doses (DDD) for each PIM in accordance with the ATC classification, sourced from the official System of Information and Monitoring of the Portuguese National Health System. This public-access platform was developed by the Shared Services of the Ministry of Health [15], and provide aggregated data, anonymized information, with no reference to identifiable individuals. The database consolidates and centralizes data from the clinical and

administrative activities of primary healthcare units, enabling the characterization and monitoring of all functional units within the Portuguese National Health System. It was accessed between February 27 and November 14, 2024, and the data extracted included active substance, age group (≥ 65 years), DDD and ULS for each period.

Study Medication

Due to the limitations of the available database, not all criteria from the EU(7)-PIM list could be applied. Of the 184 PIM identified in the Portuguese version of the EU(7)-PIM list and available in the APIMedOlder tool, a total of 143 PIM were analyzed in this study, comprising 140 active substances and 3 drug classes: aluminum-containing antacids (A02AB, A02AD), estrogens (G03C), and selective serotonin 5-HT₁ agonists (N02CC). The remaining 41 PIM were excluded for the following reasons: their classification as PIM depended on dose and/or treatment duration, or therapeutic regimen (n=20); had lost their marketing holder in Portugal (n=10) [16]; they were no longer marketed in Portugal (n=7) [16]; or there was no DDD information available (n=4) (Supplementary Table S1).

Statistical analysis

The data were expressed as the number of DDD per 1000 inhabitants per day (DID), considering the demographic data of older population in each cluster in 2021, 2022, and 2023 (Supplementary Table S2). For the calculation of DID, the average demographic values from 2021 and 2022, and 2022 and 2023 were used to ensure consistency across the study periods. Additionally, for the data collected in 2024, the demographic values from 2023 were applied, as the 2024 data was not yet available at the time of analysis. The DID Difference between Groups represents the difference in the DID values between the intervention group and the control group over the study period. It was calculated by subtracting the DID for the control group from the DID for the intervention group. The Temporal Difference measures the variation in the difference between the intervention and control groups over time relative to the baseline. It is calculated as the DID Difference between Groups at each time point minus the DID Difference between Groups at the baseline. This approach allows for an assessment of how the effect of the intervention evolves over time, compared to the initial period before the intervention. The Absolute DID Difference quantifies the magnitude of the difference in DID change between the groups, regardless of direction. It was calculated as the absolute value of the difference between the change in DID in the intervention group and the change in DID in the control group over the 6-month follow-up period compared to baseline.

RESULTS

Intervention

A total of 44 interventions were conducted, comprising 18 active and 26 passive interventions, involving the participation of 57.85% of the GPs in the intervention group (~280 GPs), as shown in the study flowchart (Figure 1).

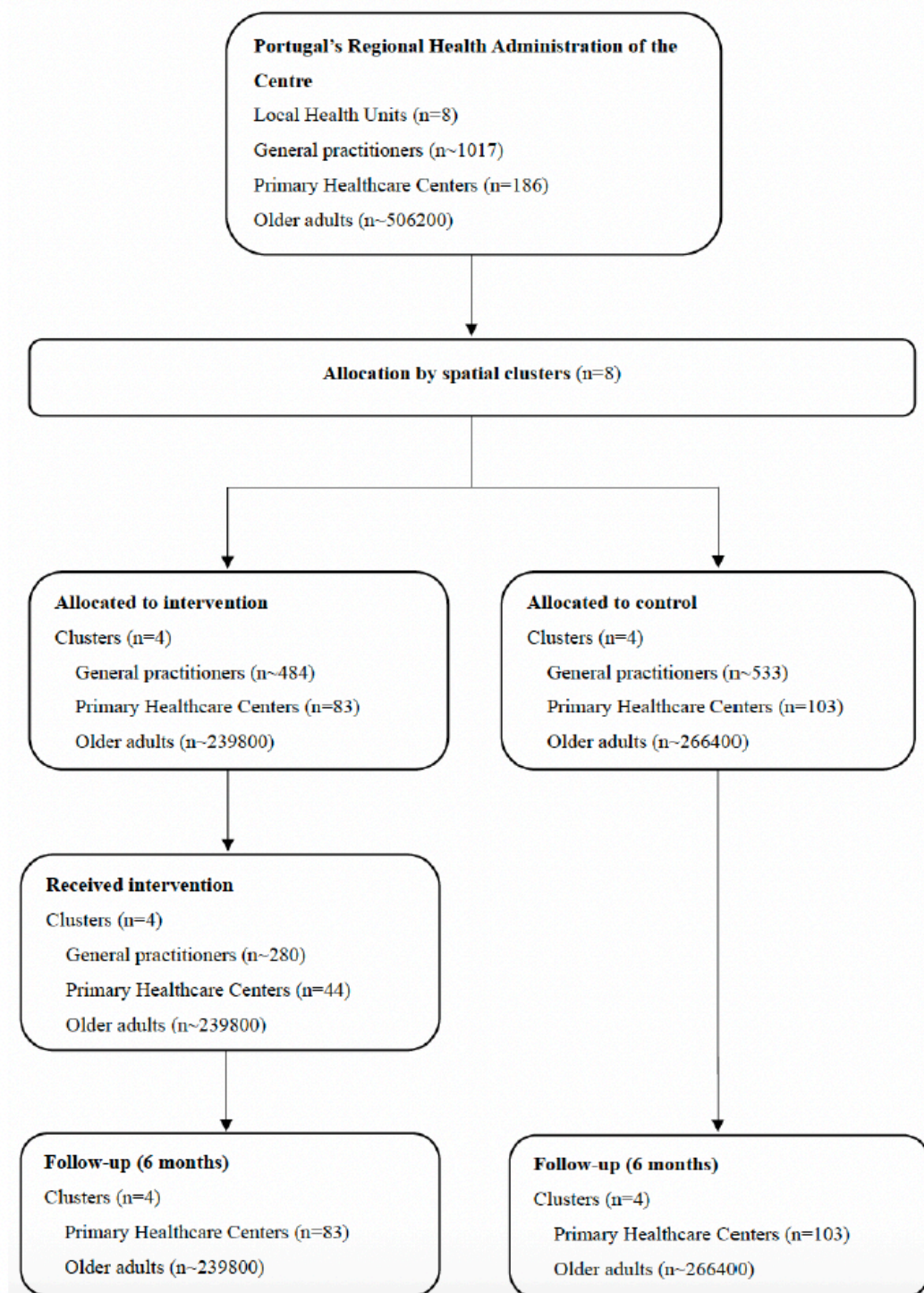


Figure 1: Study flowchart.

Overall Trends Between Intervention and Control Groups

The analysis of DID revealed differences between the intervention and control groups over time (Table 1). At baseline, the DID for the intervention group was 336.71, compared to 365.38 for the control group, resulting in a DID Difference between Groups of -28.68. This initial difference indicates that, prior to the intervention, the intervention group already had lower DID values. During the intervention, the DID in the intervention group decreased to 335.62, while the control group decreased to 334.88, leading to a DID Difference between Groups of 0.74. This corresponds to a Temporal Difference of 29.42 relative to the baseline. In the first month after the intervention, the DID for the intervention group was 336.50, while the control group showed an increase to 422.07, yielding a DID Difference between Groups of -85.57 and a Temporal Difference of -56.89. After 3 months, the intervention group's DID rose to 368.07, whereas the control group increased further to 447.64. This reduced the DID Difference between Groups to -79.57, with a Temporal Difference of -50.89. After 6 months, the DID for the intervention group had further increased to 398.70, while the control group decreased to 428.75. This resulted in a smaller DID Difference between Groups of -30.05, with the Temporal Difference nearly returning to baseline levels at -1.37.

Table 1. Evolution of DID over time in intervention and control groups.

Timepoint	Control Group	Intervention Group	DID Difference between Groups (Intervention – Control)	Temporal Difference vs. Baseline
Baseline	365.38	336.71	-28.68	-
During intervention	334.88	335.62	0.74	29.42
1 Month Post-Intervention	422.07	336.50	-85.57	-56.89
3 Months Post-Intervention	447.64	368.07	-79.57	-50.89
6 Months Post-Intervention	428.75	398.70	-30.05	-1.37

DID: Defined Daily Dose per 1000 inhabitants per day.

PIM-Specific Analysis

The disaggregated analysis by active substance reveals varied patterns in the use of specific PIM over time. To explore the potential impact of the intervention on individual medication, PIM showing a reduction in DID in the intervention group, but not in the control group, over the 6-month follow-up period compared to baseline were identified (Table 2). Notably, fluoxetine showed a reduction of 0.67 DID, and diltiazem presented a decrease of 1.36 DID in the

intervention group, representing the largest absolute differences between the intervention and control groups.

Table 2. Potentially Inappropriate Medication with a reduction in DID in the intervention group and no reduction in the control group over 6 months follow-up period compared to baseline.

PIM (INN)	ATC Code	DID Difference* (Control Group)	DID Difference* (Intervention Group)	Absolute DID Difference
Famotidine	A02BA03	0.00	-0.00	0.00
Sodium picosulfate	A06AB08	0.03	-0.04	0.08
Amiodarone	C01BD01	0.76	-0.03	0.79
Vinburnine	C04AX17	0.06	-0.12	0.18
Diltiazem	C08DB01	0.54	-1.36	1.90
Estrogens	G03C	0.17	-0.03	0.20
Flavoxate	G04BD02	0.03	-0.03	0.06
Oxybutynin	G04BD04	0.05	-0.06	0.11
Indometacin	M01AB01	0.02	-0.10	0.12
Colchicine	M04AC01	0.11	-0.04	0.16
Topiramate	N03AX11	0.04	-0.02	0.06
Trihexyphenidyl	N04AA01	0.05	-0.09	0.14
Pramipexole	N04BC05	0.04	-0.04	0.07
Chlorpromazine	N05AA01	0.00	-0.02	0.02
Levomepromazine	N05AA02	0.03	-0.01	0.04
Zuclopenthixol	N05AF05	0.01	-0.00	0.01
Estazolam	N05CD04	0.08	-0.21	0.29
Temazepam	N05CD07	0.02	-0.00	0.02
Midazolam	N05CD08	0.09	-0.04	0.14
Fluoxetine	N06AB03	1.64	-0.67	2.31
Triprolidine	R06AX07	0.19	-0.04	0.23

* Note: The DID Difference represents the change in DID between the 6-month follow-up and baseline (i.e., DID at 6 months minus DID at baseline). A negative value indicates a reduction in the prescription of PIM, while a positive value indicates an increase.

ATC: Anatomical Therapeutic Chemical classification; DID: Defined Daily Dose per 1000 inhabitants per day; INN: International Nonproprietary Name; PIM: Potentially Inappropriate Medication.

Otherwise, no relevant changes were observed over time in the use of certain PIM, both in the control and intervention groups (Supplementary Table S3). The DID Difference values remained close to zero or stable across all time points, and the absolute difference between groups at 6 months was negligible. Examples include aluminium-containing antacids – combinations, with a

DID difference of 0.00 (in both groups); liquid paraffin, with a DID difference of 0.00 (also in both groups); and ciamemazine, with a DID difference of -0.05 (in both groups), all of them with an absolute difference of 0.00.

Some PIMs showed divergent trends between groups, with DID values increasing or remaining stable in the intervention group while decreasing in the control group over the 6-month follow-up period compared to baseline (Table 3). Pioglitazone exhibited the largest absolute DID difference, with a reduction in the control group (-0.10) and a slight increase in the intervention group (+0.01), resulting in an absolute DID difference of 0.11. Other examples include tizanidine, a muscle relaxant, ziprasidone and pimozide, two antipsychotics.

Table 3. Potentially Inappropriate Medication with stable or increased DID in the intervention group and a reduction in the control group over 6 months follow-up period compared to baseline.

PIM (INN)	ATC Code	DID Difference* (Control Group)	DID Difference* (Intervention Group)	Absolute DID Difference
Pioglitazone	A10BG03	-0,10	0,01	0,11
Tizanidine	M03BX02	-0,02	0,00	0,02
Ziprasidone	N05AE04	-0,01	0,00	0,00
Pimozide	N05AG02	-0,02	0,00	0,02

* Note: The DID Difference represents the change in DID between the 6-month follow-up and baseline (i.e., DID at 6 months minus DID at baseline). A negative value indicates a reduction in the prescription of PIM, while a positive value indicates an increase.

ATC: Anatomical Therapeutic Chemical classification; DID: Defined Daily Dose per 1000 inhabitants per day; INN: International Nonproprietary Name; PIM: Potentially Inappropriate Medication.

DISCUSSION

The overall results suggest a moderate and time-dependent effect of the intervention. Although the intervention group exhibited lower baseline DID values, a clear difference between the control and intervention groups emerged during the follow-up period. Specifically, a marked increase in PIM prescribing was observed in the control group, particularly one month after the intervention, whereas the increase was significantly attenuated in the intervention group. This pattern suggests a relative benefit of the intervention in containing the upward trend of PIM prescriptions, particularly in the short term. After three months, the effect was slightly smaller than in the first month, which may suggest that GPs were using the tool less or were still slowly adjusting their prescribing habits. At six months, the difference between the two groups decreased considerably, suggesting that the impact may have diminished over time, and the effect of the intervention was not sustained in the long term. These findings align with existing research, which shows that most

deprescribing interventions tend to produce short-term improvements in medication appropriateness, but often fail to sustain their impact or translate into long-term clinical outcomes [17–19].

Fluoxetine and diltiazem showed the biggest DID decrease in the intervention group compared to the control group. These changes suggest that the intervention may have contributed to decreased prescribing of these PIM, highlighting its potential to influence prescribing behaviour and promote safer medication practices in older adults. According to the EU(7)-PIM list, fluoxetine is considered a PIM for older adults because it can cause central nervous system side effects such as nausea, insomnia, dizziness, and confusion, as well as increase the risk of hyponatremia [8]. Diltiazem is also classified as a PIM because it may worsen constipation and carries a risk of bradycardia [8]. The risks associated with these PIM could be more easily understood by GPs during the intervention, prompting earlier and more consistent changes in prescribing practices. Besides, these drugs, in many cases, can be reduced or discontinued safely, with a lower incidence of discontinuation-emergent withdrawal symptoms [20,21]. This may have encouraged prescribers to stop these medication.

The absence of change, or even an increase, for other PIM highlights that the intervention's impact may vary by therapeutic class or prescribing habits. Furthermore, it underscores the multifactorial challenges of deprescribing in older adults, as previously identified by GPs, such as clinical inertia, time constraints, fragmented care, patient resistance, and uncertainty or limited confidence in deprescribing decisions [22]. These cases highlight the importance of continuous monitoring and the need to better understand context-specific barriers to deprescribing certain medications, even in the presence of targeted interventions.

Multiple barriers may have limited sustained engagement with the APIMedOlder tool, including the need for training, time constraints, unfamiliarity with technology, reluctance to change, and lack of trust [23–25]. Organizational challenges like poor internet connectivity, and lack of system integration [23–25] may also have contributed to reduced adoption of the tool over time.

Another factor that may have limited the effectiveness of the intervention is the involvement of multiple prescribers in the care of older adults. As highlighted by the United States Deprescribing Research Network, the presence of multiple prescribers can compromise the safe management of medications by disrupting the timely exchange of clinical information and reducing continuity of care [26]. Older adults are often followed by different healthcare providers over time. This fragmentation of care can lead to inconsistent prescribing practices and hinder the continuity of medication review processes [26].

A major strength of this study is the use of real-world, prescribing data, allowing for an evaluation of the intervention's impact across an entire regional healthcare system. The combination of active and passive educational components, supported by a user-friendly web application, is another strength, enhancing both engagement and practicality. However, there are also limitations to acknowledge. First, some PIM were excluded from analysis potentially underestimating PIM use. This exclusion was partly due to limitations in the publicly available prescribing data, which are not fully complete. The restricted nature of these data limits the ability to assess the intervention's impact across the full range of PIM. Broader access to more complete prescribing datasets for researchers would be important to support more robust evaluations and produce stronger evidence to inform clinical practice. Second, the impact of the intervention may not last over time, as the DID difference almost returned to baseline after six months. This finding suggests that ongoing support and reinforcement may be necessary to maintain changes in prescribing behavior. Additionally, although using clusters helped reduce contamination, it's still possible that some informal sharing of information between groups occurred.

The APIMedOlder app helped identify PIM in real time and encouraged the use of safer alternatives, supporting clinical decisions. However, the short-lasting effects suggest that a single intervention may not be enough. Future strategies should include ongoing training as part of professional development, along with regular feedback, digital prompts, or reminders to keep the changes going. Also, because the results varied depending on the type of medication, it's important to use more focused approaches, especially for the most common or high-risk PIM, and to target areas where complex or unclear clinical situations make change more difficult.

CONCLUSION

This study suggests that a multifaceted educational intervention incorporating the APIMedOlder digital tool contributed to a moderate reduction in the prescription of PIM among older adults in primary care, especially in the short term. The intervention appeared to attenuate the increasing trend of PIM prescriptions observed during follow-up, with possible decreases in certain medication. However, the diminishing effect over six months indicates challenges in sustaining changes in prescribing behaviour. These findings highlight the potential value of combining targeted educational strategies with digital decision-support tools to improve medication appropriateness in older patients. Further research with larger samples and longer follow-up is needed to confirm these observations and to identify ways to maintain the benefits of such interventions.

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Supplementary Material

Table S1: Excluded PIM with reasons (n=41).

ATC Code	Potentially inappropriate medication	Reason of exclusion
A02BA01	Cimetidine	(a) not currently being marketed in Portugal
A02BA02	Ranitidine	(b) lost their marketing holder in Portugal
A02BC	Proton pump inhibitors	(c) duration of treatment-dependent
A03AB06	Otilonium bromide	(d) without a defined daily dose
A03FA03	Domperidone	(e) dose-dependent
A06AB02	Bisacodyl	(c) duration of treatment-dependent
A06AB06	Senna glycosides	(d) without a defined daily dose
A06AX05	Prucalopride	(a) not currently being marketed in Portugal
A07DA03	Loperamide	(c) duration of treatment-dependent
A10BB07	Glipizide	(b) lost their marketing holder in Portugal
B03AA	Iron bivalent, oral preparations	(e) dose-dependent
C01BD07	Dronedarone	(a) not currently being marketed in Portugal
C02AC02	Guanfacine	(a) not currently being marketed in Portugal
C03DA01	Spironolactone	(e) dose-dependent
C04AX21	Naftidrofuryl	(b) lost their marketing holder in Portugal
C05CA05	Hidrosmin	(d) without a defined daily dose
C05CA54	Troxerutin-vincamine	(d) without a defined daily dose
G04CA03	Terazosin	(a) not currently being marketed in Portugal
J01XE01	Nitrofurantoin	(c) duration of treatment-dependent
M01AC05	Lomoxicam	(b) lost their marketing holder in Portugal
M01AE01	Ibuprofen	(f) duration of treatment and dose-dependent
M01AE02	Naproxen	(f) duration of treatment and dose-dependent
M01AG01	Mefenamic acid	(b) lost their marketing holder in Portugal
M01AX01	Nabumetone	(a) not currently being marketed in Portugal
M05BX03	Strontium ranelate	(b) lost their marketing holder in Portugal
N02BA01	Acetylsalicylic acid	(e) dose-dependent
N04BC03	Dihydroergocryptine mesylate	(b) lost their marketing holder in Portugal
N05AD01	Haloperidol	(e) dose-dependent
N05AH03	Olanzapine	(e) dose-dependent
N05AX08	Risperidone	(c) duration of treatment-dependent
N05BA02	Chlordiazepoxide	(b) lost their marketing holder in Portugal
N05BA04	Oxazepam	(e) dose-dependent
N05BA06	Lorazepam	(e) dose-dependent
N05BA11	Prazepam	(b) lost their marketing holder in Portugal

N05CD09	Brotizolam	(e) dose-dependent
N05CD11	Loprazolam	(e) dose-dependent
N05CF02	Zolpidem	(e) dose-dependent
N06BX02	Pyritinol	(a) not currently being marketed in Portugal
R05DA04	Codeine	(c) duration of treatment-dependent
R06AD07	Mequitazine	(b) lost their marketing holder in Portugal
no ATC	Insulin, sliding scale	(g) therapeutic scheme-dependent

ATC: Anatomical Therapeutic Chemical classification.

Table S2: Demographic data of older population.

Group/ULS/Year	2021	2022	2023
Intervention Group			
ULS Aveiro	88065	90180	92583
ULS Cova da Beira	24677	24875	25185
ULS Guarda	47254	47292	47606
ULS Viseu	72627	73345	74471
Total	232623	235692	239845
Control Group			
ULS Baixo Mondego	29167	29465	29962
ULS Castelo Branco	31842	31912	32034
ULS Coimbra	103927	105002	106773
ULS Leiria	93641	95386	97633
Total	258577	261765	266402

ULS: Local Health Unit (Unidade Local de Saúde).

Table S3: Potentially Inappropriate Medication with no relevant change in DID in either the intervention or control group over the 6-month follow-up period.

PIM (INN)	ATC Code	DID Difference* (Control Group)	DID Difference* (Intervention Group)	Absolute DID Difference
Aluminium compounds; Combinations and complexes of aluminium, calcium and magnesium compounds	A02AB; A02AD	0,00	0,00	0,00
Trimebutine	A03AA05	0,00	0,00	0,00
Pinaverium	A03AX04	0,00	0,00	0,00
Liquid paraffin	A06AA01	0,00	0,00	0,00
Racecadotril	A07XA04	0,02	0,02	0,00

Urapidil	C02CA06	0,00	0,00	0,00
Labetalol	C07AG01	0,00	0,00	0,00
Acemetacin	M01AB11	0,75	0,75	0,00
Ketoprofen	M01AE03	-0,05	-0,05	0,01
Bromocriptine	N04BC01	0,00	0,00	0,00
Cyamemazine	N05AA06	-0,05	-0,05	0,00
Droperidol	N05AD08	0,00	0,00	0,00
Flupentixol	N05AF01	-0,01	-0,01	0,01
Imipramine	N06AA02	-0,01	-0,01	0,00
Reboxetine	N06AX18	0,00	0,00	0,00
Diphenhydramine	R06AA02	0,00	0,00	0,00
Clemastine	R06AA04	0,00	0,00	0,00
Dexchlorpheniramine	R06AB02	0,00	0,00	0,00
Promethazine	R06AD02	-0,03	-0,03	0,00

* Note: The DID Difference represents the change in DID between the 6-month follow-up and baseline (i.e., DID at 6 months minus DID at baseline). A negative value indicates a reduction in the prescription of PIM, while a positive value indicates an increase.

ATC: Anatomical Therapeutic Chemical classification; DID: Defined Daily Dose per 1000 inhabitants per day; INN: International Nonproprietary Name; PIM: Potentially Inappropriate Medication.

CHAPTER 10

Discussion

X. DISCUSSION

This project aimed to reduce the prescription of Potentially Inappropriate Medication (PIM) in older adults (≥ 65 years old), particularly in a region of Portugal with a pronounced aging population, through an educational intervention concerning the APIMedOlder, a web application designed to support healthcare professionals. The analysis of the available prescribing data comparing the intervention and control groups, while accounting for baseline values, suggests that educational interventions combined with digital tools have the potential to improve medication prescribing, especially in the short term; however, sustaining these improvements over time remains challenging and depends on continued support, engagement, and structural conditions in primary care.

1. Systematic Analysis of Interventions to Reduce Potentially inappropriate Medication and Barriers and Facilitators to the Adoption of Digital Health Tools

The first review, focused on the effectiveness of interventions to reduce PIM, revealed that educational interventions were successfully implemented in 75% of cases where this strategy was adopted to reduce inappropriate medication prescriptions in older adults in primary care. However, when only controlled intervention studies were analyzed, the review did not find greater effectiveness of educational interventions compared to other strategies. Multifaceted approaches also emerged as viable solutions, with many of these interventions incorporating educational components. This underscores the critical role of education as a core element in strategies to reduce PIM, highlighting the value of combining educational approaches with other measures to address the complexity of prescribing practices in older adults. Educational interventions, when integrated into multidisciplinary approaches to medication review, play a key role in improving clinical decision-making and optimizing prescribing in older adults [1]. Such interventions can positively influence healthcare professionals' behaviors and enhance medication management, ultimately contributing to better patient outcomes [1]. In primary care setting, general practitioners (GPs) handle a heavy patient load and a diversity of cases [2], therefore practical and ongoing training on PIM prescribing is essential through approaches that are practical and integrated into their workflow.

The second review, which analyzed the barriers and facilitators for the adoption of digital health tools, provided crucial insights into how GPs perceive and utilize digital technologies. Despite the potential of these tools to improve medication appropriateness, several barriers were identified such as lack of time, resistance to change, and concerns about tool usability. Facilitators such as ease of use, real-time feedback, and integration into the workflow, are essential to overcoming these barriers. Therefore, by providing clinicians with real-time up-to-date clinical guidelines and drug information, these tools can

enhance their knowledge, skills, and ability to make better prescribing decisions, and reduce medication errors, ultimately ensuring safer and more efficient medication management for older adults.

Considering the findings of the two reviews, it became clear that combining educational interventions with digital tools, such as APIMedOlder, provide a powerful approach to reduce PIM in older patients. Evidence supports that multifaceted interventions targeting the reduction of PIM in older adults have shown promising outcomes, particularly when they integrate electronic decision support tools, patient-centered care priorities, and shared decision-making [3]. Educational interventions have been shown to improve healthcare professionals' knowledge, skills, and behaviours [4]. Digital tools, particularly clinical decision support systems (CDSS), can complement these interventions by reinforcing learning through real-time access to clinical guidelines and decision support, thereby sustaining improvements in prescribing practices and promoting safer medication management [5]. The implementation of such strategies in the primary care context requires careful consideration of the unique dynamics of this setting. Practical and ongoing training is essential to ensure healthcare professionals are confident in using tools like APIMedOlder. To overcome the barriers identified, such training can emphasize how digital tools can contribute to improved quality of care and patient safety.

2. Prescription of Potentially Inappropriate Medication in Older Adults in Portugal

The high prevalence of PIM identified among older adults in primary care in Portugal between April 2021 and August 2022, using three established criteria: the EU(7)-PIM list (63.8%), Beers 2019 criteria (66.8%), and Screening Tool of the Older Persons' Prescriptions (STOPP) version 2 criteria (50.1%) highlight the need for targeted interventions to address inappropriate prescribing. Moreover, the poor concordance (<0.834) observed between the three criteria underscores the complexity of PIM identification and the variability in prescribing practices. Such discrepancies reflect the differences in clinical priorities, population-specific considerations, and the contextual adaptation of these criteria. The high rates of PIM observed not only validate these concerns but also emphasize the pressing need for accessible, streamlined, and clinically relevant tools to support decision-making. In this context, the APIMedOlder tool plays a crucial role in addressing these challenges by integrating validated PIM criteria into a platform and offering a user-friendly interface, reducing the burden of manual medication review and enabling more consistent and evidence-based prescribing practices for older adults.

3. APIMedOlder Web Application Usability and Potentially Inappropriate Medication Search Trends

To further explore the practical application of the APIMedOlder tool, a usability study was conducted to evaluate its integration into the clinical workflow and its acceptability among healthcare

professionals. The findings revealed that the overall evaluation was positive, with a mean score of 87.17 (0-100) on the System Usability Scale (SUS), and APIMedOlder was perceived as intuitive and easy to use. These findings align with the facilitators identified in the systematic review on digital health tools, which emphasized ease of use, integration into the clinical workflow, and real-time support as key elements influencing adoption. Moreover, the positive usability outcomes suggest that APIMedOlder holds strong potential for effective implementation in real-world clinical practice.

The data of searches collected from the APIMedOlder web application provide important insights into how healthcare professionals interact with tools designed to improve medication safety and appropriateness. The high percentage (42.8%) of searches related to PIM further reinforces the relevance of APIMedOlder as a practical tool in clinical practice and reveals an increase of the awareness of the potential risks associated with these medication in older adults.

Aligning the results of both studies, the high usability scores of the APIMedOlder tool are reflected in the meaningful engagement patterns observed, particularly the substantial proportion of searches related to PIM. This connection suggests that healthcare professionals who find the tool intuitive and well-integrated into their clinical workflow are more likely to use it consistently, reinforcing safer prescribing practices. Together, these findings highlight the strong potential of APIMedOlder to effectively support clinical decision-making and improve medication safety for older adults.

4. Focus Group Insights

Building on the positive usability and engagement findings of the APIMedOlder tool, the qualitative study with Portuguese GPs provides valuable contextual insights into the real-world challenges of managing polypharmacy and PIM in older adults. The GPs identified multiple factors contributing to polypharmacy, including patient complexity and fragmented care, and emphasized the importance of improved coordination and continuous education as key strategies to address these issues. However, they also highlighted significant barriers to deprescribing, such as patient resistance and limited consultation time, which complicate efforts to optimize medication regimens. As the demands on healthcare systems increase due to population aging, it is essential to advocate for policies that prioritize investment in primary care infrastructure [6]. This need is particularly evident, as GPs frequently reported poor internet connectivity and outdated technology as significant barriers to digital tools effective use. Addressing these technical limitations is crucial to ensure that primary care settings are equipped to meet the challenges of aging populations and to support healthcare professionals in providing efficient, evidence-based care.

Importantly, despite recognizing established criteria for PIM identification, GPs reported low use of these tools in everyday practice, reflecting a gap between guideline availability and clinical implementation. This underscores the need for a practical, accessible tool like APIMedOlder to help GPs incorporate these criteria into their clinical decision-making processes and improve medication safety. The study also reaffirmed the underutilization of digital health tools, pointing to integration difficulties and usability concerns as major impediments to adoption. These findings align with the earlier systematic review identifying ease of use, workflow integration, and real-time support as essential facilitators for the successful implementation of digital interventions like APIMedOlder. The high prevalence of PIM previously observed is aligned with barriers reported by GPs, where limited time, low familiarity with explicit criteria, and difficulty integrating them into routine care were cited as key obstacles.

Together, these insights highlight that while digital tools have strong potential to support safer prescribing and reduce PIM, their effectiveness depends on addressing the multifaceted challenges faced by GPs in routine clinical settings. As demonstrated in other studies, tools designed to support PIM identification and decision-making have shown varying levels of adoption and usability depending on the extent of user training and the alignment with clinical workflows [7,8]. Tailored educational interventions combined with user-friendly, seamlessly integrated digital solutions appear crucial to overcome barriers and improve medication management outcomes in older adults.

5. Impact of the Intervention on Potentially Inappropriate Medication Prescriptions

The analysis of the intervention revealed distinct trends between the intervention and control groups, highlighting the complexity of changing prescribing behaviors. Although the intervention group already exhibited slightly lower Defined Daily Doses per 1000 inhabitants per day (DID) values at baseline (336.71 vs. 365.38), the pattern of change suggests some positive effects associated with the intervention, particularly in the short term. However, the effect appeared to diminish by six months, raising questions about the sustainability of impact and highlighting the potential need to reinforce interventions to maintain positive prescribing behaviors.

The integration of these results with the evidence from the systematic reviews reinforces that no single strategy is sufficient to address the complex issue of inappropriate prescribing in older adults. Instead, interventions must be multifaceted, context-sensitive, and sustained. The educational sessions may have contributed to increased engagement and awareness among GPs. However, challenges such as time constraints, workload, and digital infrastructure limitations, as previously identified by GPs in the qualitative study, could continue to influence the extent to which these interventions translate into

practice change. The findings also suggest that even when digital tools are usable and well-received, their adoption and impact in long-term can be limited.

Moreover, such results are consistent with the identified gap between knowledge and implementation. Despite recognizing the importance of avoiding PIM, being familiar with established identification criteria, and having access to resources such as APIMedOlder, many GPs continue to face barriers to deprescribing in practice. This reinforces the need to move beyond dissemination of knowledge alone, toward creating enabling environments where GPs are supported through time, training, infrastructure, and interprofessional collaboration.

It is also important to highlight specific subgroups of medications with significant clinical relevance in older adults. One such group comprises drugs with strong anticholinergic properties, which are well-documented for increasing the risk of cognitive decline, falls, and functional impairment in this population [9]. In a recent study conducted within the same timeframe and population context of this project, the use of potentially inappropriate anticholinergic medications was analyzed based on the 2023 Beers criteria, with results showing that 8.9% of older adults were exposed to at least one potentially inappropriate anticholinergic [10]. When assessing the impact of this multifaceted intervention, a reduction in the prescription of several of these medication (such as flavoxate, oxybutynin, trihexyphenidyl, chlorpromazine, and triprolidine) as observed in the intervention group, but not in the control group. These findings suggest that APIMedOlder may contribute not only to reducing general PIM prescription but also to addressing the use of high-risk subgroups such as anticholinergics. This reinforces the importance of integrating specific medication risk profiles into digital decision-support tools and designing educational content that draws attention to the risks associated with such drug classes.

6. Implications for Practice and Policy

APIMedOlder, designed to assist clinicians in identifying PIM in older adults, can play a key role in supporting clinical practice by enhancing healthcare professionals' knowledge and awareness about PIM and the criteria used to identify them, potentially leading to better clinical decision-making. The tool can enable GPs to evaluate prescriptions more efficiently based on specific guidelines, contributing to safer and more evidence-based prescribing practices. This approach aligns with the growing emphasis in Portugal and other countries on improving the quality of care, ensuring that healthcare professionals are well-equipped to make patient-centered and evidence-based decisions [11,12]. Therefore, policymakers should prioritize the inclusion of tools like APIMedOlder in national health strategies, ensuring they are accessible and compatible with existing healthcare infrastructure. The development and implementation of APIMedOlder also represent a significant opportunity to strengthen

collaboration between researchers, healthcare professionals, and policymakers. These collaborations facilitate the alignment of research priorities with real-world healthcare needs and policy objectives, ensuring that such tools are not only scientifically robust but also practical for everyday clinical use [13,14].

Studies have shown that reducing the use of PIM in older adults can lead to significant reductions in healthcare costs by minimizing Adverse Drug Reactions (ADRs), hospital admissions, and overall medication expenditures, ultimately optimizing healthcare resource utilization [15-17]. Therefore, in addition to improve clinical outcomes, integrating tools like APIMedOlder into clinical practice have the potential to reduce healthcare costs associated with medication-related problems.

To maximize its impact, integrating APIMedOlder into existing electronic prescribing systems would further streamline its use during consultations and facilitate real-time decision support. Moreover, its inclusion in continuing medical education programs could reinforce healthcare professionals' competence in medication review and deprescribing, supporting a culture of evidence-based and patient-centered prescribing.

Ensuring that tools like APIMedOlder are adaptable to different healthcare settings, languages, and cultural contexts can enhance their applicability at both national and international levels, serving as a model for other countries facing similar challenges.

7. Strengths and Limitations

A key strength of this study is the integration of educational interventions with the APIMedOlder tool, addressing both knowledge gaps and practical challenges in prescribing practices. This combined approach supports healthcare professionals in making informed, evidence-based decisions in a time-efficient manner. By merging theoretical knowledge with a digital decision-support system, the intervention facilitates the translation of guidelines into clinical practice.

The real-world applicability of APIMedOlder is another strength of the study. The tool's ability to identify PIM and provide alternatives in real-time addresses a pressing issue in primary care, improving medication safety and potentially reducing the risks of polypharmacy and PIM for older adults.

Moreover, this study draws upon qualitative insights from healthcare professionals to ensure that the intervention is tailored to the specific context and needs of end-users. The incorporation of this feedback during development and usability testing represents another strength, as the intervention becomes more aligned with real-life clinical needs, enhancing its relevance, acceptance, and user engagement.

Finally, it contributes to the growing field of implementation science by exploring not only the outcomes of the intervention, but also the barriers and facilitators to its adoption. This comprehensive perspective provides valuable insights into how to design, implement, and scale digital interventions that can sustainably improve prescribing quality in older populations.

The integration of APIMedOlder with other electronic prescribing systems or medical records already in use within healthcare facilities was not addressed in this project. This can be a limitation, as such integration could improve the efficiency of the prescribing process, reduce technical barriers, and facilitate the adoption of the tool by GPs. However, the integration was not pursued due to several practical constraints. Firstly, the process of linking APIMedOlder with existing systems involves complex bureaucratic procedures, as it requires approvals and alignment with institutional information technology policies. Additionally, such integration would have required substantial time and resources, including technical expertise to ensure compatibility and seamless functionality. Given the time limitations of the project and the focus on evaluating the usability and functionality of the tool itself, the decision was made to exclude this aspect from the scope of the study.

Another important limitation concerns the data available from the public database used in the study assessing the impact of the intervention. This dataset does not provide detailed clinical information such as medication dosage or treatment duration. Consequently, it was not possible to identify PIM that are dose- or duration-dependent as defined in the EU(7)-PIM list. This limitation may have led to an underestimation of the intervention's true effect on PIM prescribing and underscores the need for access to more precise clinical data in future studies. Due to this constraint, it was also not feasible to assess the appropriateness of certain medication classes that are highly consumed by older adults in Portugal, such as proton pump inhibitors (PPIs). According to the EU(7)-PIM criteria, PPIs are only considered potentially inappropriate when used for more than 8 weeks [18], a parameter that could not be evaluated using the available data. This is particularly relevant considering that in a retrospective study using prescription data from the period between April 2021 and August 2022, we found that nearly 79% of older adults on PPIs had been using them for a longer period than recommended, and nearly half (49.79%) were prescribed PPIs without a digestive system-related diagnosis [19].

Although the results seem to be positive in the short-term implementation of APIMedOlder in one region of Portugal, the generalization of the findings to other areas of the country or different healthcare systems may be limited by the variability in prescribing practices and primary care conditions.

Overall, the integration of educational strategies and user-friendly digital tools, such as APIMedOlder, emerges as a promising and scalable approach to enhance medication safety and appropriateness for

older adults in primary care settings. This project provides a model that can be replicated and adapted across healthcare systems aiming to optimize prescribing practices and promote healthy longevity.

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[19] Rodrigues DA, Herdeiro MT, Mateos-Campos R, Figueiras A, Roque F. Magnitude and Determinants of Long-term Use of Proton Pump Inhibitors Among Portuguese Older Adults in Primary Health Care. *Clin Ther* 2024 Feb;46(2):e54-e58. <https://doi.org/10.1016/j.clinthera.2023.11.011>. Epub 2023 Dec 6.

CHAPTER 11

Conclusions and Future Directions

XI. CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, the findings from this project highlight the value of combining educational interventions with digital tools to reduce Potentially Inappropriate Medication (PIM) in older adults. This integrated approach could enhance healthcare professionals' knowledge and support clinical decision-making through real-time, evidence-based assistance. However, addressing the challenges of implementation requires a holistic approach that considers systemic barriers, the practical needs of general practitioners (GPs), and the complexity of patient care in primary settings. By addressing these challenges, this work contributes to ongoing efforts to improve medication safety, optimize prescribing practices, and promote high-quality, patient-centered care for the aging population.

Keeping the interface simple and intuitive will be essential to ensure that the APIMedOlder is quick to learn and easy to integrate into the daily workflow of GPs. Although the results demonstrated a positive level of acceptance, continuous training could serve as a highly effective approach to further enhance user adoption and ensure sustained engagement with the tool. Maintaining a continuous cycle of evaluation and feedback with users will help identify usability issues that may arise over time and allow for quick adjustments to improve its effectiveness and acceptance.

Given the dynamic nature of the pharmaceutical market, it is crucial to ensure the periodic updating of APIMedOlder to reflect changes such as the introduction of new medications or the withdrawal of other ones. Regular updates would maintain the tool's relevance, accuracy, and trustworthiness. Establishing a structured update mechanism, informed by the latest clinical guidelines and market trends, will help keep the tool aligned with the evolving landscape of medication management.

Future research should investigate the feasibility of integrating APIMedOlder with healthcare systems to enhance its impact and use in clinical settings. Assessing how the tool can be embedded into existing workflows would be critical to ensuring its practical application and sustained use by GPs and other healthcare professionals.

Additionally, evaluating the long-term impact of the application on clinical decision-making and patient outcomes is essential to understanding its contribution to optimizing medication use in older populations. Expanding the implementation of APIMedOlder across different regions of Portugal could provide valuable insights into its scalability and adaptability within diverse primary care settings. This expansion would also allow for comparative analyses across various healthcare systems, offering a broader perspective on how digital tools can improve prescribing practices for aging populations.

Future research should also explore patient perceptions of digital tools, particularly regarding how these innovations might influence their acceptance of deprescribing processes and engagement in healthcare decisions. Understanding patient experiences could provide critical insights into optimizing the design and implementation of such technologies.

Moreover, emerging technologies such as artificial intelligence and machine learning present promising opportunities for enhancing digital tools like APIMedOlder. By enabling more personalized and precise recommendations, these innovations have the potential to improve medication management. Further investigation into interdisciplinary collaboration is also needed, focusing on how the combined expertise of physicians, pharmacists, nurses, and other healthcare professionals can maximize the impact of digital tools on clinical practice.

Future developments could also focus on the adaptation of the most widely used international criteria to the Portuguese context, based on local prescribing profiles and healthcare system characteristics. Given the overlap among different tools and the insights gained from this research, there is potential to create tailored criteria for specific settings or populations.

Overall, this project presents an innovative, evidence-based contribution to the field of geriatric pharmacotherapy by bridging research, clinical education, and digital health. The development and evaluation of APIMedOlder represent a meaningful step toward more structured and safer prescribing practices for older adults.

APPENDIX A

Presented communications related to the PhD project

A. Presented communications related to the PhD project

⇒ *Poster Presentation:*

Daniela A. Rodrigues, Ana I. Plácido, Ramona Mateos-Campos, Adolfo Figueiras, Maria Teresa Herdeiro, Fátima Roque. Teste de usabilidade da aplicação online APIMedOlder para pesquisa de Medicamentos Potencialmente Inapropriados. II Jornadas de Investigação Clínica, December 13, 2022, Clinical Academic Center of Beiras, Polytechnic Institute of Guarda, Guarda, Portugal.

Daniela A. Rodrigues, Ramona Mateos-Campos, Adolfo Figueiras, Maria Teresa Herdeiro, Fátima Roque. Usability testing of a web application for health professionals about potentially inappropriate medications in older adults: APIMedOlder. Congreso Internacional Multidisciplinar de Estudiantes de Doctorado, CIMED, March 22-24, 2023, University of La Laguna (ULL), Santa Cruz de Tenerife, Spain.

Daniela A. Rodrigues, Maria Roque, Ramona Mateos-Campos, Adolfo Figueiras, Maria Teresa Herdeiro, Fátima Roque. What are the barriers and facilitators that influence the adoption of digital health-related tools for medication appropriateness? European Drug Utilization Research Group (EuroDURG) Conference 2023, June 27-30, 2023, University of Bologna, Bologna, Italy.

Daniela A. Rodrigues, Adolfo Figueiras, Ramona Mateos-Campos, Maria Teresa Herdeiro, Fátima Roque. Comparação entre os critérios de Beers 2019, a versão 2 dos critérios STOPP e a lista EU(7)-PIM numa amostra de idosos em cuidados de saúde primários. Estrada Nacional 2 do Conhecimento do VI Encontro da Sociedade Portuguesa de Farmacêuticos dos Cuidados de Saúde, SPFCs “Vamos falar”, October 14-16, 2023, Ramada by Wyndham Hotel, Lisbon, Portugal.

Daniela A. Rodrigues, Adolfo Figueiras, Maria Teresa Herdeiro, Fátima Roque. Proton pump inhibitors inappropriate use among community-dwelling older adults in Portugal. 22nd Annual Meeting of the International Society of Pharmacovigilance (ISoP), November 6-9, 2023, Sanur Prime Plaza Hotel Bali, Bali, Indonesia.

Daniela A. Rodrigues, Maria Teresa Herdeiro, Ramona Mateos-Campos, Adolfo Figueiras, Fátima Roque. Potentially inappropriate anticholinergic drugs use: A Portuguese study with older outpatients. 9th European Congress of Pharmacology of the Federation of European Pharmacological Societies (EPHAR), 23-26 June 2024. Athens, Greece.

Daniela A. Rodrigues, Maria Teresa Herdeiro, Ramona Mateos-Campos, Adolfo Figueiras, Fátima Roque. Educational intervention and development of a tool to improve the use of Potentially Inappropriate Medication in older adults. Encontro Ciência 2024 – Science and Technology Summit in Portugal, 3-5 July 2024. Porto, Portugal.

⇒ *Oral Presentation:*

Daniela A. Rodrigues. Potentially Inappropriate Medications in Older Adults – Preliminary Results from the APIMedOlder Project. 2º Seminário de Inverno. March 16, 2022, Polytechnic Institute of Guarda, Guarda, Portugal.

Daniela A. Rodrigues. Prevenir o uso de medicamentos potencialmente inapropriados em idosos. Workshop – Uso racional de medicamentos: da prevenção à ação, April 8, 2022, University of Aveiro, Aveiro, Portugal.

Daniela A. Rodrigues. Prevenir o uso de medicamentos potencialmente inapropriados em idosos. Workshop – Uso Racional de Medicamentos: Barreiras Sociais e Institucionais, June 30, 2022, School of Health of the Polytechnic Institute of Guarda, Guarda, Portugal.

Daniela A. Rodrigues, Ramona Mateos-Campos, Adolfo Figueiras, Maria Teresa Herdeiro, Fátima Roque. Perfil de Consumo de Inibidores da Bomba de Protões na População Idosa. VII Jornadas de Educação e Investigação em Saúde, March 2, 2023, School of Health of the Polytechnic Institute of Guarda, Guarda, Portugal.

Daniela A. Rodrigues, Ana I. Plácido, Ramona Mateos-Campos, Adolfo Figueiras, Maria Teresa Herdeiro, Fátima Roque. APIMedOLder web application for potentially inappropriate medications identification – How it has been used and what has been searched? 3rd International Age.Comm Congress – Sustainability and Aging, November 16-18, 2023, School of Technology of the Polytechnic Institute of Castelo Branco, Castelo Branco, Portugal.

Daniela A. Rodrigues, Maria Teresa Herdeiro, Ramona Mateos-Campos, Adolfo Figueiras, Fátima Roque. Advancing Geriatric Pharmacotherapy: A Comprehensive Exploration from Operationalization of the EU(7)-PIM List to Impact of the APIMedOlder Digital Health Tool. 54th Meeting of the Portuguese Society of Pharmacology, 42nd Meeting of Clinical Pharmacology and 23rd Meeting of Toxicology, February 7-9, 2024, NOVA Medical School, Lisbon, Portugal.

Daniela A. Rodrigues, Maria Teresa Herdeiro, Ramona Mateos-Campos, Adolfo Figueiras and Fátima Roque. Educational intervention and development of a tool to improve the use of Potentially Inappropriate Medication in older adults. Lunch Seminar CICS-UBI, September 25, 2024, University of Covilhã, Covilhã, Portugal.

APPENDIX B

Event organization related to the PhD project

B. Event organization related to the PhD project

Co-organizer of the Workshop –Uso Racional de Medicamentos: Barreiras Sociais e Institucionais), June 30, 2022, School of Health of the Polytechnic Institute of Guarda, Guarda, Portugal.

Co-organizer of the Workshop –Uso racional de medicamentos: da prevenção à ação), April 8, 2022, University of Aveiro, Aveiro, Portugal.

APPENDIX C

Additional Thesis-Related Publications

C. Additional Thesis-Related Publications

Rodrigues DA, Herdeiro MT, Thürmann PA, Figueiras A, Coutinho P, Roque F. Operationalisation for Portugal of the EU(7)-PIM List for Identification of Potentially Inappropriate Medicines in Older Adults. *Acta Med Port.* 2021 Mar 1, 34(3):194-200. doi: 10.20344/amp.13618.

Rodrigues DA, Plácido AI, Tavares ABT, Azevedo D, Mateos-Campos R, Figueiras A, Herdeiro MT, Roque F. Potentially Inappropriate Medication Prescribing in Older Adults According to EU(7)-Potentially Inappropriate Medication List: A Nationwide Study in Portugal. *Curr Ther Res Clin Exp.* 2022 Jul 13, 97:100681. doi: 10.1016/j.curtheres.2022.100681.

Rodrigues DA, Herdeiro MT, Mateos-Campos R, Figueiras A, Roque F. Magnitude and Determinants of Long-term Use of Proton Pump Inhibitors Among Portuguese Older Adults in Primary Health Care. *Clin Ther.* 2024 Feb, 46(2):e54-e58. doi: 10.1016/j.clinthera.2023.11.011.

Rodrigues DA, Roque F, Herdeiro MT, Monteiro L. Translation and Adaptation of the STOPP/START Criteria Version 3 for Potentially Inappropriate Prescribing in Older People to European Portuguese: A Study Protocol. *Acta Med Port.* 2024 Dec 2, 37(12):847-852. doi: 10.20344/amp.21941.

Rodrigues DA, Herdeiro MT, Mateos-Campos R, Figueiras A, Roque F. Potentially inappropriate anticholinergic drug use among older adults in primary healthcare: prevalence and determinants. *Expert Opin Drug Saf.* 2025 Jul, 24(7):831-837. doi: 10.1080/14740338.2024.2385479.

APPENDIX D

Authorization from the Health Ethics Committee of the
Regional Health Administration (ARS) of the Centre for the
Implementation of the Educational Interventions (Proc.
37/2022)

D. Authorization from the Health Ethics Committee of the Regional Health Administration (ARS) of the Centre for the Implementation of the Educational Interventions (Proc. 37/2022)



COMISSÃO DE ÉTICA PARA A SAÚDE

PARECER FINAL: Favorável	DESPACHO: <i>Tomado conhecimento e deliberado homologar o Parecer Final da Comissão de Ética para a Saúde.</i> <i>26.05.2022</i>
------------------------------------	--

ASSUNTO:	Título do estudo: "Projeto APIMedOlder - Prevenir o uso de medicamentos potencialmente inapropriados em idosos através de um sistema de apoio à decisão clínica. Ensaio controlado por clusters em cuidados de saúde primários" (proc. 37/22) Autora principal: Maria de Fátima Roque dos Santos Marques Roque
-----------------	---

Conselho Diretivo
da A.R.S. do Centro, I.P.
[Signature]
Dr. Mário Ruivo
Vogal,

[Signature]
Dr. Fernando Craveiro

O objetivo principal deste estudo consiste na realização de uma intervenção educativa sobre a polimedicação no idoso e o uso de medicamentos potencialmente inapropriados (PIM), composta pela aplicação online APIMedOlder junto dos médicos pertencentes à ARS Centro.

A aplicação APIMedOlder foi desenvolvida no âmbito do projeto APIMedOlder e consiste numa aplicação disponível online com informação sobre os medicamentos classificados como potencialmente inapropriados segundo a lista EU(7)-PIM List adaptada para a realidade Portuguesa, publicada na Acta Médica.

Para a realização deste estudo serão contactados os Agrupamentos dos Centros de Saúde (ACeS) Cova da Beira, Baixo Vouga, Dão Lafões e ULS Guarda. Estes ACeS serão os clusters de intervenção, para dar continuidade a um projeto anterior que consistiu numa intervenção educativa dirigida a utentes idosos inscritos nestes ACeS, no âmbito do projeto MedElderly também financiado pela FCT e que recebeu parecer favorável da ARS Centro em 2017. As intervenções educativas serão previamente articuladas com os diretores clínicos dos centros de saúde. A intervenção educativa consistirá na apresentação de: (i) informações sobre PIM e o seu impacto nos resultados de saúde em doentes idosos; (ii) dados de prescrição de PIM em Portugal; (iii) fatores identificados como subjacentes à prescrição de PIM; e (iv) apresentação da aplicação online APIMedOlder, que inclui a versão portuguesa da lista EU(7)-PIM publicada na Acta Médica Portuguesa. A intervenção educativa incluirá também a disponibilização de material educativo, como cartazes, flyers, posters e vídeos. Antes de participarem no estudo, será entregue um consentimento informado a todos os participantes onde constará: (i) uma breve explicação do estudo e da intervenção, (ii) um pedido de autorização para participação no estudo. Após o término deste processo, os participantes terão total autonomia para utilizarem a aplicação online APIMedOlder. Posteriormente, será-lhes pedido que preencham um breve questionário de satisfação no final da aplicação online, o qual se encontra dividido em duas secções compostas por: a) duas breves questões de natureza sociodemográfica, de dados como sexo e idade; e b) dez questões de resposta fechada relacionadas com a plataforma online através da escala de Likert de acordo com um questionário (System Usability Scale - SUS) validado para a realidade nacional. Após a avaliação feita pelo grupo de médicos que aceite participar no estudo, os dados obtidos serão devidamente analisados e utilizados pela equipa de investigação para melhorar a aplicação.

O Relator e Presidente da CES da ARS do Centro

[Signature]

APPENDIX E

Authorization from the Ethics Committee of the Polytechnic
Institute of Guarda (IPG) for the Implementation of the
Usability Study of the APIMedOlder Web Application (No.
3/2022)

E. Authorization from the Ethics Committee of the Polytechnic Institute of Guarda (IPG) for the Implementation of the Usability Study of the APIMedOlder Web Application (No. 3/2022)



COMISSÃO DE ÉTICA DO INSTITUTO POLITÉCNICO DA GUARDA

EMIÇÃO DE PARECER

Parecer nº 3/2022

Assunto: Estudo piloto de usabilidade da aplicação online APIMedOlder

Parecer Final:

Parecer favorável

O estudo apresentado enquadra-se no âmbito do projeto APIMedOlder, no qual o IPG é o promotor.

Trata-se de um estudo piloto de usabilidade “Prevenir o uso de medicamento potencialmente inapropriados em idosos através de um sistema de apoio à decisão clínica. Ensaio controlado aleatório por clusters em cuidados de saúde primários”. Tem como principal objetivo avaliar a usabilidade da aplicação online dirigida a profissionais de saúde, recorrendo a uma amostra de médicos, farmacêuticos, técnicos de farmácia e enfermeiros.

Os investigadores apresentam o protocolo de trabalho a desenvolver, o consentimento informado para uso do contacto de e-mail dos potenciais participantes e o consentimento informado para participação no estudo piloto.

Esta Comissão de Ética deverá receber cópia do Relatório final.

A Vice-Presidente da Comissão de Ética:

APPENDIX F

Authorization from the Ethics Committee of the Regional
Health Administration (ARS) of the North for the
Implementation of the Focus Group Study (Ref: CE/2023/70)

F. Authorization from the Ethics Committee of the Regional Health Administration (ARS) of the North for the Implementation of the Focus Group Study (Ref: CE/2023/70)

 REPÚBLICA PORTUGUESA SAÚDE	 SNS SERVIÇO NACIONAL DE SAÚDE	 ARS NORTE Administração Regional de Saúde do Norte, I.P.
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☐	☐	☒	DATA: 2023-07-12
COMUNICAÇÃO	INFORMAÇÃO	PARECER	REFERÊNCIA: CE/2023/70

PARA	CONSELHO DIRETIVO
DE	COMISSÃO DE ÉTICA
ASSUNTO ..	PI 20230049 - ATITUDES E PERCEÇÕES DOS MÉDICOS DE MEDICINA GERAL E FAMILIAR EM RELAÇÃO À POLIMEDICAÇÃO E AO USO DE MEDICAMENTOS POTENCIALMENTE INAPROPRIADOS EM IDOSOS.

A - Apresentação do pedido em apreciação
A Comissão de Ética da Administração Regional de Saúde do Norte, I.P. recebeu o pedido de parecer sobre o projeto intitulado "**Atitudes e percepções dos médicos de Medicina Geral e Familiar em relação à polimedicação e ao uso de medicamentos potencialmente inapropriados em idosos.**", que pretende explorar as percepções e atitudes médicos de MGF pertencentes à Administração Regional de Saúde do Norte em relação à polimedicação, à utilização de medicamentos potencialmente inapropriados (PIM) em idosos, à desprescrição de medicamentos em idosos e às barreiras e/ou facilitadores na adoção de ferramentas digitais no apoio à decisão clínica sobre a adequação da medicação. O pedido de parecer é formulado pela equipa de investigação constituída por **Daniela Almeida Rodrigues** licenciada em Farmácia, com Mestrado em Ciências Aplicadas à Saúde pelo Instituto Politécnico da Guarda Escola Superior de Saúde, bolsista de investigação de doutoramento da FCT na Unidade para o Desenvolvimento do Interior (UDI) do Politécnico da Guarda (IPG) e pelas suas orientadoras, a Professora Doutora **Fátima Roque** Professora Adjunta da Escola Superior de Saúde do Politécnico da Guarda e a Professora Doutora **Maria Teresa Herdeiro**, Professora Auxiliar no Departamento de Ciências Médicas, da Universidade de Aveiro
O pedido de parecer foi instruído com os documentos obrigatórios para a sua submissão.

B - Identificação de questões com eventuais implicações éticas ou metodológicas
Trata-se de estudo qualitativo cujo objetivo principal é otimizar a aplicação online APIMedOlder de apoio à prescrição de medicamentos na população idosa através da realização de grupos focais com médicos de MGF pertencentes à Administração Regional de Saúde do Norte (ARS Norte) de forma explorar as suas percepções e atitudes em relação à polimedicação e à utilização de PIM em idosos; à desprescrição de medicamentos em idosos; às barreiras e/ou facilitadores na adoção de ferramentas digitais no apoio à decisão clínica sobre a adequação da medicação.
A população em estudo são os médicos dos cuidados de saúde primários e a amostra de conveniência será constituída pelos médicos de MGF da ARS Norte quem aceitem participar no estudo. Para a realização deste estudo, serão contactados por e-mail os Diretores Executivos Agrupamentos dos Centros de Saúde (ACeS) da ARS Norte, para apresentação do estudo e agendamento de sessões de grupos focais que serão previamente articuladas com os centros de saúde. Os grupos focais serão conduzidos por um moderador contando com a

EXARADO NA ATA Nº 2023_31
REUNIÃO DE 2023-07-13

DELIBERADO AUTORIZAR
2023-07-13

Carlos Nunes
Presidente do CD


Paula Duarte
Vogal do CD



Rua Santa Catarina, 1288 4000-447 Porto
Telefone: 220411000 E-mail: arsn@arsnorte.min-saude.pt Website: www.arsnorte.min-saude.pt

1/2

presença de entre 6 e 8 participantes. As sessões terão uma duração de cerca de 60 a 90 minutos dependendo das novas ideias que possam surgir em cada sessão. Relativamente ao número de grupos, estima-se que após 3 ou 4 sessões seja atingido o ponto de saturação no qual o moderador consegue antecipar o que o grupo irá discutir, sem aquisição de novos dados. O estudo irá seguir critérios padronizados e as sessões irão consistir em questões de resposta aberta seguindo um guião elaborado após uma revisão bibliográfica e revisto por especialistas em farmacologia e epidemiologia.

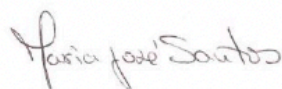
A participação no estudo é voluntária e não traz qualquer risco para os participantes e é possível desistir do estudo em qualquer momento, podendo cada participante exercer os seus direitos de acesso, retificação, eliminação, limitação e oposição, sempre que necessário. No início de cada sessão cada participante irá assinar o consentimento informado assegurando a segurança e confidencialidade de todos os dados facultados. Será também assegurada a destruição das gravações, assim que o projeto estiver terminado.

Após as sessões realizadas com os grupos de médicos que aceitem participar no estudo, os dados obtidos serão devidamente analisados e utilizados pela equipa de investigação para otimizar a aplicação online APIMedOlder de apoio à prescrição de medicamentos na população idosa. As gravações serão transcritas e os textos guardados em computador de acesso limitado apenas à investigadora do projeto.

C - Conclusão

Reconhecendo a relevância do estudo e considerando que o mesmo satisfaz os requisitos de confidencialidade dos direitos dos potenciais participantes, a Comissão de Ética da ARSN deliberou, nesta data, dar parecer favorável à realização do estudo. O investigador deve comunicar os resultados, assim que o estudo esteja concluído.

Porto, 11 de julho de 2023



Maria José Ferreira Santos
Presidente da Comissão de Ética

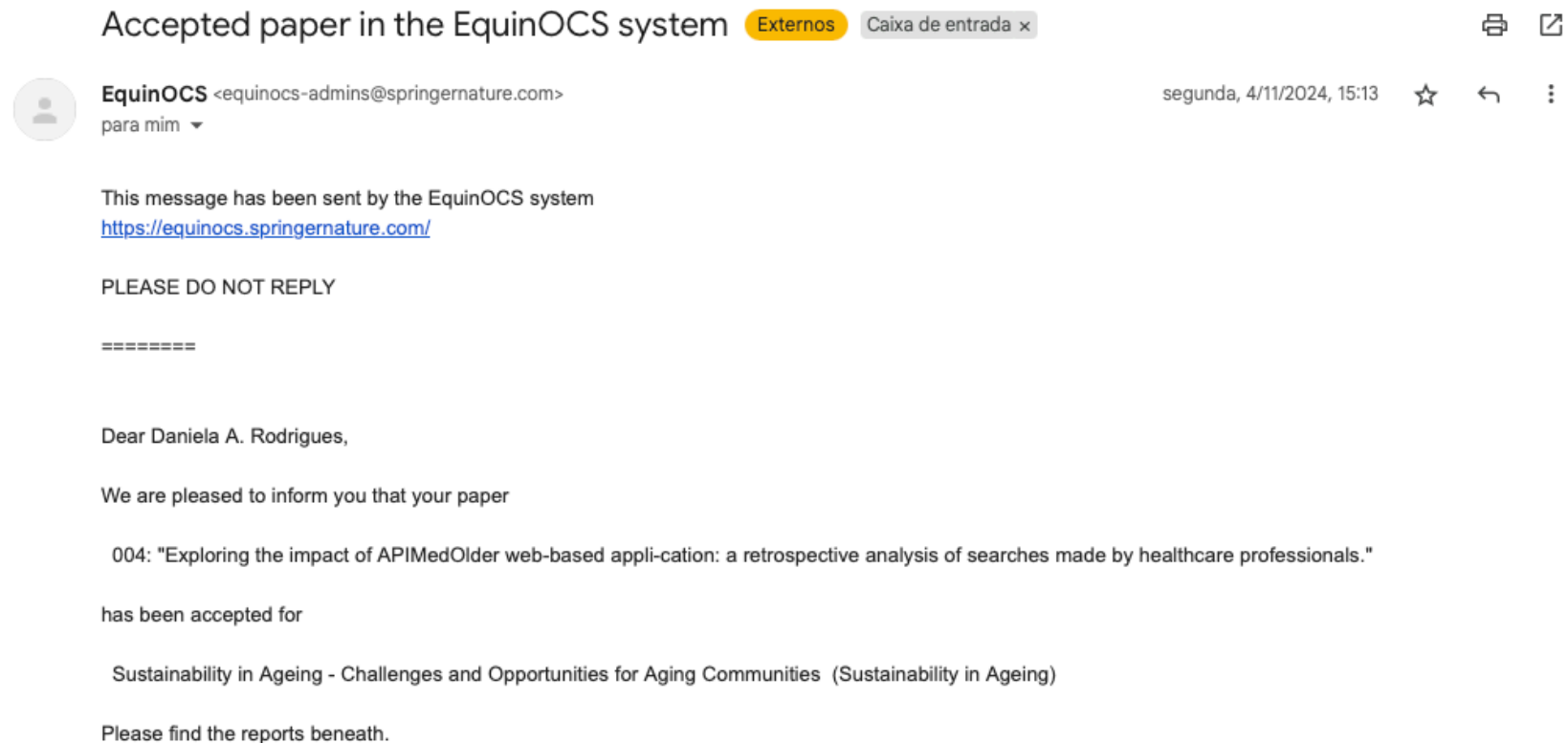


APPENDIX G

Email Confirming Acceptance for Publication – Book Chapter

“Exploring the Impact of APIMedOlder Web-Based
Application: A Retrospective Analysis of Searches Made by
Healthcare Professionals”

G. Email Confirming Acceptance for Publication – Book Chapter “Exploring the Impact of APIMedOlder Web-Based Application: A Retrospective Analysis of Searches Made by Healthcare Professionals”



APPENDIX H

Poster for the Dissemination of the Educational Intervention

H. Poster for the Dissemination of the Educational Intervention



API MedOlder

PRESCRIÇÃO APROPRIADA NO IDOSO

Prescrever com segurança!

APIMedOlder é uma ferramenta útil e prática disponível online que permite ao profissional de saúde ter acesso rápido à classificação de um medicamento como **Potencialmente Inapropriado*** no idoso.

Medicamento Potencialmente Inapropriado

Operacionalização para Portugal da Lista EU(7)-PIM para identificação de Medicamentos Potencialmente Inapropriados nos idosos

DESCOBRIR MAIS

www.apimedolder.com

*A classificação a cada medicamento é atribuída de acordo com a lista europeia EU(7)-PIM, adaptada para a realidade portuguesa.

Promovido por:

POLI TÉCNICO GUARDA

Financiado por:

universidade de aveiro

FCT
Fundação para a Ciência e a Tecnologia

COMPETE 2020

UNIÃO EUROPEIA
Fundo Europeu de Desenvolvimento Regional

APPENDIX I

Flyer for the Dissemination of the Educational Intervention

I. Flyer for the Dissemination of the Educational Intervention

VANTAGENS DE USAR A APLICAÇÃO

- Ferramenta útil de perfil simplificado
- Adaptada à realidade portuguesa
- Aumento da segurança e da eficácia dos medicamentos
- Diminuição de potenciais problemas relacionados com medicamentos

Prescreva com **SEGURANÇA**



Este trabalho foi desenvolvido no âmbito do projeto APIMedOlder (PTDC/MED-FAR/31598/2017), financiado pelo FEDER, através do COMPETE 2020—Programa Operacional Competitividade e Internacionalização (POCI-01-0145-FEDER-031598) e por fundos nacionais (OE), através da FCT/MCTES.

Promotores:   Financiadores:   

PRESCRIÇÃO APROPRIADA NO IDOSO



Sobre a aplicação **APIMedOlder...**

... encontra-se disponível online.

... permite ao profissional de saúde ter acesso rápido à classificação de um medicamento como **Potencialmente Inapropriado** no idoso.

... a classificação a cada medicamento é atribuída de acordo com a lista europeia **EU(7)-PIM**, adaptada para a **realidade portuguesa**¹.

... para além do **motivo** que justifica a designação de um determinado medicamento como potencialmente inadequado para o idoso, é também fornecida informação sobre **considerações especiais de uso e medicamentos/tratamentos alternativos**.

¹ Rodrigues DA, Herdeiro MT, Thürmann PA, Figueiras A, Coutinho P, Roque F. Operacionalização para Portugal da Lista EU(7)-PIM para Identificação de Medicamentos Potencialmente Inapropriados nos Idosos. Acta Med Port. 2021;34(3):194-200

Veja aqui como pode utilizar a aplicação!

1. Aceda a **www.apimedolder.com**
2. Assinale a opção correspondente à sua **profissão**
3. Introduza o nome da substância ativa (**DCI**) ou o **código ATC** do medicamento que pretende procurar
4. Clique em **Pesquisar**



APPENDIX J

Educational Material for the Intervention

J. Educational Material for the Intervention



1



2



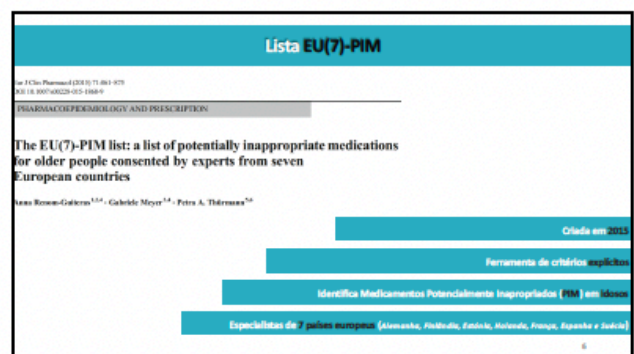
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4



5



6

Lista EU(7)-PIM operacionalizada para Portugal

Operacionalização para Portugal da Lista EU(7)-PIM para Identificação de Medicamentos Potencialmente Inapropriados nos Idosos

Operationalisation for Portugal of the EU(7)-PIM List for Identification of Potentially Inappropriate Medicines in Older Adults

David A. D'ERIGUES¹, Maria T. HERDEIRO¹, Paula A. THURMANN¹, Adolfo FIGUEIRAS², Paula COUTINHO¹, Fátima RODRIGUES^{1,3*}

Acta Med Port 2021; 34(2):189-200 • <https://doi.org/10.21948/AMP.2000>

Operacionalização em 2020

Lista de 184 PIM publicada em 2021

Website e aplicação online criados em 2022

7



8



9

Porque não desenvolver uma intervenção em Portugal?

Elevada percentagem de idosos em Portugal (23,4%)

Região entre 4ª e segunda mais envelhecida de Portugal (E=205,8)

Prevê-se que até 2030 esta tendência para o envelhecimento venha a duplicar

Como reduzir a prescrição de medicamentos potencialmente inapropriados em Portugal?

Realização de sessões educativas com médicos de Medicina Geral e Familiar

Apresentação da aplicação APIMedOlder

10

APLICAÇÃO APIMEDOLDER

Agora é mais fácil prescrever com segurança!

Através da nova aplicação disponível online → APIMedOlder

Medicamento Potencialmente Inapropriado

Perfil simplificado

Aplicável na prática clínica

Resumo dos

Exercício de segurança e eficácia terapêutica

Distribuição de pontos: problemas relacionados com medicamentos

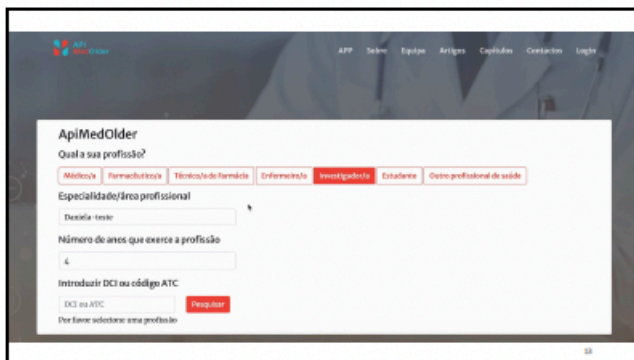
11

Medicamentos Potencialmente Inapropriados

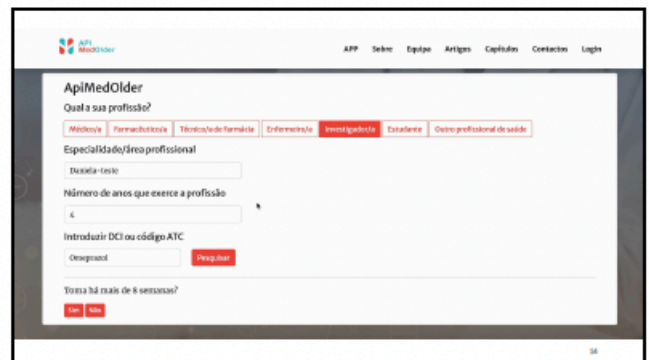
Operacionalização para Portugal da Lista EU(7)-PIM para Identificação de Medicamentos Potencialmente Inapropriados nos Idosos

PREQUER MATE

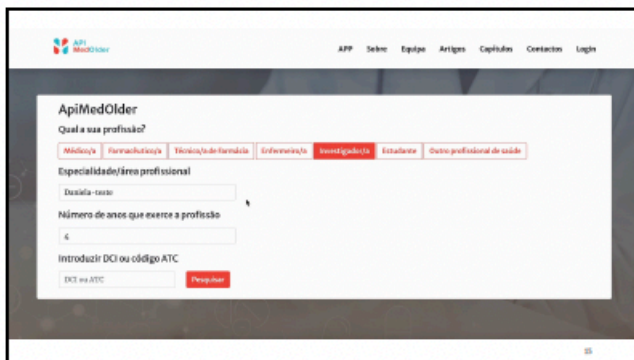
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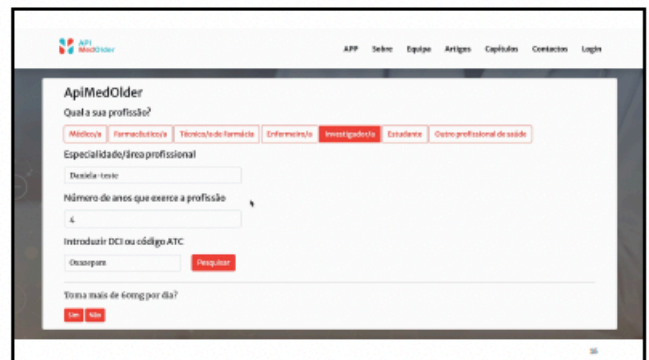
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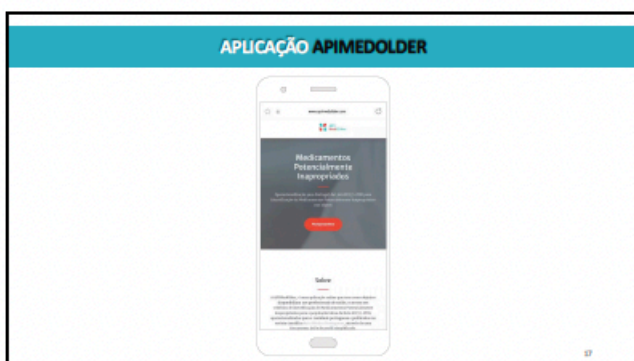
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15



16



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18