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Strategies to improve the quality of prescription in older adults

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STRATEGIES TO IMPROVE THE QUALITY OF PRESCRIPTION IN OLDER ADULTS

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LIST OF PUBLICATIONS

CORE PAPERS

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Reducing Potentially Inappropriate Prescriptions for Older Patients Using Computerized Decision Support Tools: Systematic Review.

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Monteiro L, Monteiro-Soares M, Mendonça LV, Ribeiro-Vaz I, Martins C, Teixeira A

Translation and adaptation of the STOPP-START screening tool to Portuguese for detecting inappropriate prescriptions in older people: a protocol.

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Monteiro, L.; Monteiro-Soares, M.; Matos, C.; Ribeiro-Vaz, I.; Teixeira, A.; Martins, C.

Inappropriate Prescriptions in Older People—Translation and Adaptation to Portuguese of the STOPP/START Screening Tool.

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ADDITIONAL PAPER

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LIST OF ABBREVIATIONS AND ACRONYSMS USED

ADR	Adverse Drug Reaction
AGS	American Geriatrics Society
EMBASE	Excerpta Medica Database
EHRs	Electronic Health Records
EU	European Union
FORTA	Fit For The Aged
GP	General Practitioner
LESS CHRON	Criteria List of Evidence-baSed depreScribing for CHRONic patients
PIMs	Potentially Inappropriate Medications
PIP	Potentially Inappropriate Prescription
PPOs	Potential Prescribing Omissions
OR	Odds Ratio
RCT	Randomized controlled trial
SD	Standard Deviation
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older Persons' Prescriptions

Abstract

Background

Older adults are more vulnerable to polypharmacy and inappropriate prescribing, which encompasses the prescription of potentially inappropriate medications and potential prescribing omissions. Both situations may increase older adults' multimorbidity and mortality. Therefore, it is important improve the quality of prescriptions in older adults.

The objectives of the two studies in the present thesis were 1) to assess whether computerized decision support tools can potentially lead to a reduction in inappropriate prescriptions or potentially inappropriate medications in older adult patients and affect health outcomes, and 2) to translate and validate the Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) screening tool to enable its use by Portuguese general practitioners/family physicians.

Methods

In the first study, a systematic review was conducted by searching the literature in the MEDLINE, CENTRAL, EMBASE, and Web of Science databases for published interventional studies with the aim of assessing the impact of computerized decision support tools on potentially inappropriate medications and potentially inappropriate prescriptions in people aged 65 years and older.

The second study was conducted in four phases. The first phase (phase I) was the translation and adaptation of the STOPP/START screening tool into Portuguese followed by patient data collection (phase II). Phase III consisted of an intra-rater reliability and agreement study, and phase IV consisted of an inter-rater reliability and agreement study.

Results

In the first study a total of 3756 articles were identified, and 16 were included in the study. More than half (n = 10) of the studies were randomized control trials (RCTs), one was a crossover study, and five were pre-post intervention studies. A total of 266562 participants were included, and of those, 233144 participants in RCTs were included and assessed. Interventional design studies had several

different features. Computerized decision support tools were found to lead to a consistent reduction in the number of potentially inappropriate prescriptions started and mean number of potentially inappropriate prescriptions per patient. Computerized decision support tools also seemed to increase potentially inappropriate prescription discontinuation and drug appropriateness. However, in several studies, statistical significance was not achieved. A meta-analysis was not possible due to significant heterogeneity among the chosen systems and the definitions of outcomes.

In the second study, a dataset containing the information of 334 patients was analyzed by one general practitioner (GP)twice within a 2-week interval while another dataset containing the information of 205 patients was independently analyzed by three GPs. Intra-rater reliability assessment led to a Kappa coefficient (k) of 0.70 [95% confidence interval (CI) 0.65–0.74] and 0.60 (95% CI 0.52–0.68) for the STOPP and START criteria, respectively, and were considered to be substantial and moderate values, respectively. The results of the inter-rater reliability rating were almost perfect for all combinations of raters ($k > 0.93$).

Discussion

Managing polypharmacy in older adults poses a challenge for patients, families, prescribers, and healthcare systems. Our findings indicate that computerized decision support tools may reduce potentially inappropriate prescriptions and potentially inappropriate medications. Our thesis also resulted in the first adaptation of the STOPP/START criteria into Portuguese language. It provides clinicians with a screening tool for detecting potentially inappropriate prescribing in patients older than 65 years old that is easy and reliable to use.

Conclusions

This thesis suggests the use of two main evidence-based strategies to improve the quality of prescription in older adults: computerized decision support tools and the Portuguese version STOPP/START. These conclusions have an impact on patients' safety and quality of prescription. Medical education has now more evidence tools and policymakers are able to design health strategy with resources that are more effective. Managing prescription of older adults is a big challenge that requires more

findings. Therefore, future research should focus on randomized controlled trials assessing the impact of computerized decision support tools on health outcomes both in primary and secondary care.

RESUMO

INTRODUÇÃO

Os cidadãos idosos são mais vulneráveis à polifarmácia e à prescrição potencialmente inadequada, que abrange a prescrição de medicamentos potencialmente inapropriados e possíveis omissões na prescrição. Ambas as situações podem aumentar a multimorbilidade e a mortalidade dos idosos. Portanto, é importante melhorar a qualidade das prescrições em idosos.

Os objetivos dos dois estudos da presente tese foram 1) avaliar se ferramentas informatizadas de apoio à decisão podem potencialmente levar a uma redução de prescrições inapropriadas ou medicamentos potencialmente inapropriados em pacientes idosos e afetar os resultados de saúde, e 2) traduzir e validar a Ferramenta de avaliação da prescrição de idosos / Ferramenta de avaliação para alertar para tratamento correto (STOPP/START) para permitir a sua utilização por médicos em Portugal.

MÉTODOS

No primeiro estudo, foi realizada uma revisão sistemática pesquisando a literatura nos bancos de dados MEDLINE, CENTRAL, EMBASE e Web of Science para estudos intervencionais publicados com o objetivo de avaliar o impacto de ferramentas computadorizadas de apoio à decisão sobre medicamentos potencialmente inapropriados e medicamentos potencialmente inapropriados prescrições em pessoas com 65 anos ou mais.

O segundo estudo foi conduzido em quatro fases. A primeira fase (fase I) foi a tradução e adaptação do instrumento de triagem STOPP/START para português seguida da recolha de dados dos doentes (fase II). A fase III consistiu num estudo de confiabilidade e concordância intraavaliadores, e a fase IV consistiu em um estudo de confiabilidade e concordância entre avaliadores.

RESULTADOS

No primeiro estudo foram identificados um total de 3.756 artigos, dos quais 16 foram incluídos no estudo. Mais da metade (n = 10) dos estudos eram ensaios clínicos randomizados (RCTs), um era um *crossover study* e cinco eram pré-pós-intervenção. Um total de 266.562 participantes foram incluídos e, desses, 233.144 participantes em RCTs foram incluídos e analisados. Verificou-se que as ferramentas de apoio à decisão permitem uma redução consistente no número de prescrições potencialmente inapropriadas iniciadas e no número médio de prescrições potencialmente inapropriadas por paciente. Ferramentas computadorizadas de apoio à decisão também parecem aumentar a desprescrição de

medicamentos potencialmente inapropriadas e a adequação da prescrição. No entanto, em vários estudos, a significância estatística não foi alcançada. Não foi possível realizar uma meta-análise devido à significativa heterogeneidade.

No segundo estudo, um conjunto de dados contendo as informações de 334 pacientes foi analisado por um medico em duas ocasiões com um intervalo de 2 semanas, enquanto outro conjunto de dados contendo as informações de 205 pacientes foram analisadas independentemente por três médicos de família. A avaliação da confiabilidade intraavaliador levou a um coeficiente Kappa (k) de 0,70 [intervalo de confiança (IC) de 95% 0,65–0,74] e 0,60 (IC 95% 0,52–0,68) para os critérios STOPP e START, respetivamente, e foram considerados como sendo valores substanciais e moderados, respetivamente. Os resultados da avaliação da confiabilidade entre avaliadores foram quase perfeitos para todas as combinações de avaliadores (k > 0,93).

Discussão

Gerir a polifarmácia em idosos representa um desafio para doentes, familiares, médicos e sistemas de saúde. Os nossos resultados indicam que as ferramentas computadorizadas de apoio à decisão podem reduzir as prescrições potencialmente inapropriadas e os medicamentos potencialmente inapropriados. A nossa tese também resultou na primeira adaptação dos critérios STOPP/START para a língua portuguesa. Ele fornece aos médicos uma ferramenta de apoio para detetar prescrições potencialmente inadequadas e sugerir prescrições adequadas em doentes com mais de 65 anos.

Conclusão

Esta tese sugere a utilização de duas estratégias principais baseadas em evidência científica para melhorar a qualidade da prescrição em idosos: ferramentas computadorizadas de apoio à decisão e a versão portuguesa do STOPP/START. Estas conclusões têm impacto na segurança dos pacientes e na qualidade da prescrição. A educação médica tem agora mais ferramentas baseadas na prova científica e os decisores de política e planeamento em saúde podem desenhar estratégias de saúde com recursos mais eficazes. Gerir a prescrição de idosos é um grande desafio que requer mais investigação. Portanto, as linhas de investigação no future devem incluir ensaios clínicos randomizados avaliando o impacto das

ferramentas computadorizadas de apoio à decisão nos resultados de saúde tanto nos cuidados de saúde primários como nos secundários.

Preface and Acknowledgements

My personal journey that leaded me to this thesis started long before I decided to become a doctor. The choices I made, as so often occurs, were the result of both the environment and free will. As José Ortega y Gasset brilliant wrote "'I am I and my circumstance".

It will be exhausting to name all the persons and events that define "circumstance". Nevertheless, I realize that my family, teachers, and many personal encounters contribute to this path.

The passion for books and writing also played an important role. Many writers contribute by telling me stories that are both comforting and restless.

The idea for this thesis started to unravel when I was a medical student. In the primary care setting, I realized that many older adults took too many medications, and it was a struggle to manage polypharmacy for patients and family doctors.

Therefore, a question started to stimulate my thoughts: how can we improve the quality of prescriptions?

That question led me to apply to the Doctoral Program in Medicine.

The completion of this long endeavor was only possible due to the supervision of Prof. Carlos Martins, as advisor and Prof. Matilde Monteiro-Soares and Prof. Andreia Teixeira, as co-advisors.

Their patience, good advice, and rigorous scientific review were crucial to the conclusion of this project.

I am grateful to my father, mother, and sister for their encouragement and support.

I would like to dedicate this thesis to my treasured daughter Clara and my son Francisco, and to the love of my life, Cristina.

Thanks to her I realize that the most important part of life is to enjoy the journey and not just focus on the destination.

Thank you!

"It is better to light a candle than curse the darkness"

Proverb

CHAPTER 1.

INTRODUCTION

1.1. Definition and Characteristics of Older Adults

It is not an easy task to define older adults. However, a "classic" definition that considers the age of 65 or more as a landmark for the elderly has been established[1].

The worldwide population aged 65 and over is growing faster than all other age groups. According to official data from the United Nations Department of Economic and Social Affairs[2] by 2050, one in six people in the world will be over age 65 (16%). In 2019 that value was only one in 11 in 2019 (9%). In Organization for Economic Co-operation and Development countries, the number of older adults is increasing[3] as is their life expectancy[4].

In Portugal, the life expectancy at birth has increased from 67.1 years in 1970 to 80.7 years in 2020[5]. The old-age dependency ratio, that is the ratio between the number of elderly persons at an age when they are generally economically inactive (aged 65 and over) and the number of persons at working age, increased from 12.7% in 1961 to 36.9% in 2022[6].

In fact, by the middle of the 21st century one in four persons living in Europe and Northern America could be aged 65 or over. In 2018, for the first time in history, persons aged 65 or above outnumbered children under five years of age globally. The number of people aged 80 years or over is projected to triple from 143 million in 2019 to 426 million in 2050[2].

In developed countries the leading cause of deaths among older adults has changed from infection to heart disease, cancer, and stroke[7].

Regarding older adults it also important to manage the geriatric syndrome. Geriatric syndrome stands for common older adult health conditions, such as cognitive impairment, delirium, incontinence, falls, gait disorders, sleep disorders, sensory deficits, and fatigue.

The evidence proves a strong association between geriatric syndromes and dependency as reflected in activities of daily living[8].

Because the above conditions require a broader approach, a comprehensive geriatric assessment that is defined as a multidisciplinary approach in order to make diagnosis and treatment plan is therefore

recommended[9]. The goal is for older adults to have a good quality of life and not just increase their life expectancies[10].

Several core components to the comprehensive geriatric assessment, such as functional status, fall risk, social support, cognition, mood, and polypharmacy.

The functional status determines the ability of an elderly individual to perform activities of daily life. The daily living activities include self-care tasks (such as bathing), the ability to maintain the house (home repair, for example), and advanced tasks, such as using a cellphone.

Some validated tools to measure the functional status such as the 'Clinical Frailty Scale'[11], the Katz index[12] and the Lawton instrumental activities of daily living scale are available[13].

1.2. Polypharmacy

Despite the importance of polypharmacy, the existing literature does not provide a single and precise definition for this term. In fact, a systematic review found 138 definitions[14] and the World Health Organization (WHO) has a general definition that broadly states that it is 'the administration of many drugs at the same time or the administration of an excessive number of drugs'[15].

Focusing on the use of multiple medications by a patient, 5–10 medications is usually accepted as the cutoff[14,16]. The literature does not fully agree with the exact minimum number of medications[14, 17]. Nevertheless, we considered the use of 2 to 4 drugs as minor polypharmacy and of 5 or more drugs as major polypharmacy, using the definition recommended by Nagaraju[18].

The elderly are more likely to be treated with multiple medications[19]. The increased number of medications is a problem for every patient, but in older adults this amount increases the risk for adverse drug events, drug–drug interactions, and for prescription of potentially inappropriate medications. In fact, clinicians should suspect potentially inappropriate medication risks in older outpatients taking five or more medications daily[20].

Self-medication is also common in older adults, and some factors, such as long-standing illness and physical pain, can increase the possibility of self-medication[21].

The risk of non-adherence when an older patient has multiple medications is always present. A systematic review found some evidence that suggests that polypharmacy is associated with non-adherence and higher rates of hospitalization[22].

Older adults medicated with multiple medications are also more vulnerable to adverse drug reactions. This situation is often considered a new medical condition or a new pathology. Therefore, the clinician adds a new drug to treat that condition; however, this new medication was not necessary. This process is defined as a prescribing cascade[23]. Some examples of this process occur when antipsychotics cause extrapyramidal signs and symptoms, and the clinician subsequently adds antiparkinsonian therapy or when a cholinesterase inhibitor causes urinary incontinence that prompts the prescriber to add another drug to treat incontinence[23, 24].

Polypharmacy also causes an increasing economic burden on the healthcare systems[25, 26].

1.3. Prevention and ethics

Preventive medicine is a key role of any healthcare system. It is important to define the different types of prevention. The primary prevention is an action taken to prevent disease before it arises in people who feel well, and the goal is to decrease the incidence of the disease. The secondary prevention is an action to detect disease at an early stage in people who feel well with the goal of reducing morbidity and mortality. Tertiary prevention is the action to reduce the symptoms and complications of the disease in people who feel sick[27].

The caution regarding the act of prescribing a drug is related to the principle of non-maleficence. In fact, one of the main ethical principles is "*Primum non nocere*" translated as "*First, do no harm*"[28].

Therefore, when taking care of older adults, prescribers should protect them from

medical interventions that are likely to cause more harm than good. The goal of quaternary prevention is to reduce overmedicalization (overdiagnosis and overtreatment) and iatrogenic harm[27].

1.4. Multimorbility

Caring for older adults is particularly challenging[29] because older adults are more likely to have more than one chronic disease[30–32].

Multimorbidity, defined as the co-existence of two or more long-term conditions in an individual[33], can occur in any age, but it is more prevalent in older patients.

In patients who are over 65 years old, multimorbidity can be as high as 95%[31]. In recent studies, it was estimated that in Portugal it was higher than 90%, and cardiometabolic and mental disorders were the most common chronic health problems[30].

Patients who have multiple chronic conditions have poor health outcomes[34], namely decreased quality of life[35], psychological distress[35] and higher mortality[34, 36]. These problems also pose a challenge to the healthcare systems because of high healthcare utilization[37], particularly primary care utilization[38], more hospital admissions[39] and increased costs[32].

Therefore, adults aged with at least 65 years are more likely to be prescribed multiple drugs[40-42] and may be more susceptible to inappropriate medication use[20, 43, 44].

It is a challenge for healthcare professionals to manage multimorbidity. The guidelines focus only on one disease, and to apply all of them is not realistic[45]. Future guidelines must be patient-centered rather than disease-focused and integrate several chronic diseases.

1.5. Prescribing for older adults and pharmokinetics

Prescribing a medication is not an easy process. The first step is to decide if the appropriate care plan of treatment should include a drug. During this process, several questions arise. For example, which is the best drug? What is the appropriate dose? What is the expected time for the therapeutic effect to be noted? How can we monitor potential adverse drug effects?

The prescriber should make the decision based on the best available evidence and patients' own values. However, an information gap regarding older adults exists. Clinical drug trials, even regarding

medications useful for the elderly, often exclude these patients[46]. The common extrapolations may lead to mistakes such as higher drug dosage.

We should bear in mind the age-related changes in pharmacokinetics and pharmacodynamics in elderly people[47]. For example, with aging there is a natural decrease in renal function even without renal disease. With renal aging, an acceleration in the rate of decline in creatinine clearance occurs[48]. Renal aging explains why the same dose of lithium is at a higher plasma concentration in an older patient when compared with younger patient.

Older adults have an increase in body fat and total body water in addition to a lean body mass decrease. Therefore, hydrophilic drugs have a smaller apparent volume of distribution and lipophilic drugs have an increased distribution[49].

Also, with aging, we know that a different physiological effect of certain drugs, such as an increased sensitivity to benzodiazepines, occurs[50, 51].

Evidence is available that much of the older people's responses to medication is also due to the age-related changes in hepatic function[52].

The decline in the liver's capability to inactivate toxins may contribute to a pro-inflammatory state. Inflammation causes a down-regulation in drug metabolism. Therefore, medication prescribed to frail elderly people may undergo reduced systemic clearance, leading to further functional decline thus increasing the already frail status[52]. This decreasing hepatic function may lead to adverse drug reactions[53].

Other important morbidity in older patients is accidents due to falls. They are associated with the use of benzodiazepines, neuroleptics, antidepressants, and antihypertensives[54].

Multiple medications prescribed to frail elderly adults may also contribute to delirium. *Clostridium difficile* overgrowth is due to overuse of antibiotics and results in prolonged hospital stays, which therefore increases morbidity and mortality[53].

1.5.1. Herbal and dietary supplements

Ginseng, St. John's wort, and ginkgo biloba extract are defined as herbal or dietary supplements and are often used by older adults in as high as 63%[55].

In one study, in an ambulatory setting, almost three-quarters (74.2%) of the cohort combined the use of at least one prescription drug and one dietary supplement with 32.5% using three or more prescription drugs and three or more supplements[56].

The often online and TV marketing presents these products as 'natural' and free from risk, but the truth is that herbal medicines may interact with prescribed drugs and lead to adverse events. A retrospective review identified a total of 142 potential interactions observed over a 6-year period[57]. For example, ginkgo biloba extract taken with warfarin can increase the risk of bleeding.

1.5.2. Medication Review

Ginseng, St. John's wort, and ginkgo biloba extract are defined as herbal or dietary supplements and are often used by older adults in as high as 63%[55].

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1.5.3. Deprescription

Deprescription can be defined as "the process of withdrawal of inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes"[61].

To be successful, this process should include shared decision-making. It must be evidence-based and consist of a team that includes all of the members in the prescribing and administration of medications and supported by improved healthcare informatics[62].

Various authors suggest a stepwise protocol approach to deprescribing ranging from 4[63] to 10 steps[64]. Scott et al. also suggested the following 5-step protocol[65]:

(1) determine all drugs the patient is currently taking and the reasons for each one,

(2) consider overall risk of drug-induced harm in individual patients when determining the required intensity of deprescribing intervention,

(3) assess each drug in regard to its current or future benefit potential when compared with current or future harm or burden potential,

(4) prioritize drugs for discontinuation that have the lowest benefit/harm ratio and lowest likelihood of adverse withdrawal reactions or disease rebound syndromes, and

(5) implement a discontinuation regimen and monitor patients closely for improvement in outcomes or onset of adverse effects.

The process of deprescribing must be balanced and closely monitored because of the adverse effects caused by stopping medication, such as adverse drug withdrawal reactions, pharmacokinetic and pharmacodynamic changes, and return of the medical condition[66].

The doctor should also address patients' fears and beliefs due to the fact that patients may be against the idea of deprescribing[67].

1.5.4. Potentially inappropriate medications and potentially inappropriate prescriptions

Older adults are more likely to receive potentially inappropriate medication (PIMs) prescriptions[20, 43, 44, 68].

A PIM can be described as a medication that has potentially more risks than benefits with a safer alternative available[68].

Potentially inappropriate medication prescribing is very common. In a nationwide study in Portugal, it was found in 68.6% of the patients. The likelihood of having potentially inappropriate

medication increased significantly in females, those with a number of chronic health problems, larger number of pharmacological subclasses, and larger number of prescribers[69]. Another recent study also identified a difference in gender when mainly alprazolam and fluoxetine were prescribed to older women, whereas rivaroxaban was mostly prescribed to older men[70].

Potentially inappropriate prescription (PIP) is a broader concept than PIM and includes over prescribing, under prescribing, and mis-prescribing of medications, such as inappropriate dose or duration[71].

Appropriate medicating the elderly does not simply mean to reduce the number of medications. In fact, some conditions require the prescription drugs. In one study, 50% of the patients had not been prescribed some type of recommended therapy[72].

Some reasons for the underutilization of drugs that are not directly related to the prescriber should be discussed. One of the top reasons is cost-related noncompliance. Due to financial reasons, older adults may not take the appropriate drug[73]. Therefore, appropriate medications should be addressed by the clinician regardless of the total number of medications[74]. The prescriber should recognize the medication benefit in the older population. That process may not be easy, but there are some tools that can help and are addressed in the next chapter.

1.6. Potentially inappropriate prescription screening tools

There are various tools available in order to help physicians to identify PIMs and PIPs.

The Medication Appropriateness Index measures appropriate prescribing based on a 3-point rating scale of a 10-item list. For each criterion (indication, effectiveness, dosage, directions, drug–drug interactions, drug–disease interactions, medication duplication, and cost), the evaluator rates whether the medication is appropriate, marginally appropriate, or inappropriate[75].

The Garfinkel tool is another geriatric-palliative approach and methodology to combat the problem of polypharmacy[76].

The List of Evidence-baSed depreScribing for CHRONic patients (LESS-CHRON) criteria is a comprehensive and standardized methodology to identify clinical situations for deprescribing drugs. Each

criterion contains indication for which the drug is prescribed, clinical situation that offers an opportunity to deprescribe, clinical variable to be monitored, and the minimum time to follow up the patient after deprescribing[77].

The Drug Burden Index (DBI) measures the exposure of the patient to anticholinergic and sedative medications, total number of medications, and daily dosing (78). The higher the DBI is, the more likely functional decline[78] and falls[79] will occur.

The European Union (EU)-PIM list is a screening tool that was developed by experts[7, 80]. This tool identifies 282 chemical substances or drug classes from 34 therapeutic groups as PIMs for older people. Some PIMs are restricted to a certain dose or duration of use.

The PRISCUS (Latin for 'time-honoured') list[81] is a German tool that identifies 83 drugs in a total of 18 drug classes that were rated as potentially inappropriate for elderly patients.

The Fit fOR The Aged (FORTA) List[82, 83] is a drug classification that combines positive and negative labelling of drugs that are chronically prescribed to elderly patients. This list classifies four categories of: (1) clear benefit; (2) proven but limited efficacy or some safety concerns; (3) questionable efficacy or safety profile, consider alternative; and (4) clearly avoid and find alternative.

In the Beers criteria of the American Geriatrics Society (AGS) guidelines[84], medications are grouped into five categories: (1) those potentially inappropriate in most older adults, (2) those that should typically be avoided in older adults with certain conditions, (3) drugs to use with caution, (4) drug-drug interactions, and (5) drug dose adjustment based on kidney function.

1.6.1 The STOPP/START (Screening Tool of Older Persons' Prescriptions—STOPP; Screening Tool to Alert to Right Treatment—START) criteria

The STOPP/START was first published in 2008[85] and was updated in version 2 in 2014[86].

It is an European important tool that can be used both in secondary and in primary care.

The STOPP/START is not just focused on deprescribing. In fact, this tool helps identify both PIMs (STOPP criteria) and potential prescribing omissions (START criteria).

Some literature shows that STOPP version 2 criteria identified substantially more PIMs than the EU[7]-PIM list[80], PRISCUS[81, 87, 88], and FORTA[87, 88].

Compared to the Beers criteria, STOPP/START criteria identified more PIMs and were found to be significantly associated with detecting adverse events in acutely ill older people[89–94].

Therefore STOPP/START is important tool for medication appropriateness. That is, when patients receive the right medication, at the right time, at the right dose, and for the right reasons.

1.7. Digital health

Informatics has changed our society and that change includes health care that nowadays is becoming increasingly more digital.

Digital health is the convergence of digital technologies with health, healthcare, living, and society, aiming to deliver high quality care[95].

This discipline includes health analytics and data visualization, including wearables, and mobile health, electronic health records (EHR), and telemedicine[96, 97].

EHR are almost ubiquitous in hospitals and primary care units, and it includes patient electronic medical files, prescribing diagnostic and laboratory tests, prescribing medications, and electronic guidelines for medical support[98, 99].

EHR has been a challenge, but the solution is not to return to paper-based records but to invest in better software that is useful friendly and that complements the work of the healthcare professionals[98].

Providing patients with access to EHRs may improve quality of care and safety[100]. Although more research is needed in various domains one study showed that it was effective in reducing glycolated haemoglobin (HbA1c) levels, a major predictor of mortality in type 2 diabetes[101].

New EHR should be evaluated regarding new metrics, such as clinician burden from digital technologies, interoperability across the healthcare systems, and quality of multidisciplinary communication[102].

1.7.1. Computerized Decision Support Tools

Computerized decision support (CDS) tools can be defined as computer-based systems that provide passive and active referential information in addition to reminders, alerts, and guidelines[103].

CDS tools can also aid clinicians in making diagnostic and therapeutic decisions in patient care[104].

These tools can also play an important role in patient-centered outcomes related to shared decision making for seriously ill patients[105].

We already established that they may have a positive impact on healthcare, such as leading to a reduction in ordering of unnecessary tests[99]. But there is still lacking evidence regarding the role of CDS tools in the process of prescription and patient-oriented outcomes.

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CHAPTER 2.

RESEARCH QUESTIONS AND AIMS

Considering the evidence that rational and appropriate prescription of older adults is a challenge and improves the quality of life of the elderly, we wanted to answer two questions:

Research question 1: In older adults do Computerized Decision Support Tools reduce potentially inappropriate prescriptions or potentially inappropriate medications?

Research Question 2: In older adults do Computerized Decision Support Tools improve clinical outcomes?

We guided the first part of this work considering the patient, intervention, comparison, and outcome (PICO) model.

P: Older adults

I: CDS

C: Usual care/standard-of-care

O: PIPS or PIMS

Considering the relevance of the STOPP/START screening tool and the lack of Portuguese validated tools, we aimed to translated and validate a Portuguese version.

Therefore, the following studies were undertaken and published:

Paper 1 (additional paper)

Monteiro L, Maricoto T, Solha IS, Monteiro-Soares M, Martins C

COMPUTERISED DECISION TO REDUCE INAPPROPRIATE MEDICATION IN THE ELDERLY: A SYSTEMATIC REVIEW WITH METAANALYSIS PROTOCOL.

BMJ Open 2018;8: e018988. doi:10.1136/bmjopen-2017-018988

Journal Impact Factor: 3.007 Quartile 2 (86/172)

The following three papers are the core papers of this thesis:

Paper 2

Monteiro L, Maricoto T, Solha I, Ribeiro-Vaz I, Martins C, Monteiro-Soares M.

REDUCING POTENTIALLY INAPPROPRIATE PRESCRIPTIONS FOR OLDER PATIENTS USING COMPUTERIZED DECISION SUPPORT TOOLS: SYSTEMATIC REVIEW.

J Med Internet Res. 2019 Nov 14;21(11): e15385. doi: 10.2196/15385. PMID: 31724956; PMCID: PMC6883366

Journal Impact Factor of 7.08 Quartile 1 (10/109)

Paper 3

Monteiro L, Monteiro-Soares M, Mendonça LV, Ribeiro-Vaz I, Martins C, Teixeira A TRANSLATION AND ADAPTATION OF THE STOPP-START SCREENING TOOL TO PORTUGUESE FOR DETECTING INAPPROPRIATE PRESCRIPTIONS IN OLDER PEOPLE: A PROTOCOL.

BMJ Open 2021;11: e043746. doi:10.1136/bmjopen-2020-043746

Journal Impact Factor: 3.007 Quartile 2 (86/172)

Paper 4

Monteiro, L.; Monteiro-Soares, M.; Matos, C.; Ribeiro-Vaz, I.; Teixeira, A.; Martins, C. INAPPROPRIATE PRESCRIPTIONS IN OLDER PEOPLE–TRANSLATION AND ADAPTATION TO PORTUGUESE OF THE STOPP/START SCREENING TOOL.

Int. J. Environ. Res. Public Health 2022, 19, 6896. doi.org/10.3390/ijerph19116896

Journal Impact Factor: 4.614. Quartile 2 (100/279)

CHAPTER 3.

COMPUTERISED DECISION TO REDUCE INAPPROPRIATE MEDICATION IN THE ELDERLY: A SYSTEMATIC REVIEW WITH META-ANALYSIS PROTOCOL (ADDITIONAL PAPER)

ABSTRACT

INTRODUCTION

Life expectancy continues to increase in developed countries. Elderly people are more likely to consume more medications and become vulnerable to age-related changes in drugs' pharmacokinetics and pharmacodynamics. Recent studies have identified opportunities and barriers for deprescribing potentially inappropriate medications. It has already been demonstrated that computerised decision support systems can reduce physician orders for unnecessary tests. We will systematically review the available literature to understand if computerised decision support is effective in reducing the use of potentially inappropriate medications, thus having an impact on health outcomes.

METHODS AND ANALYSIS

A systematic review will be conducted using MEDLINE, CENTRAL, EMBASE and Web of Science databases, as well as the grey literature assessing the effectiveness of computer decision support interventions in deprescribing inappropriate medications, with an impact on health outcomes in the elderly. The search will be performed during January and February 2018. Two reviewers will conduct articles' screening, selection and data extraction, independently and blind to each other. Eligible sources will be selected after discussing non-conformities. All extracted data from the included articles will be assessed based on studies' participants, design and setting, methodological quality, bias and other potential sources of heterogeneity.

This review will be conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement of quality for reporting systematic reviews and meta-analyses.

ETHICS AND DISSEMINATION

As a systematic review, this research is exempt from ethical approval. We intended to publish the full article in related peer-reviewed journal and present it at international conferences.

INTRODUCTION

In developed countries, ageing population is increasing.[1]Caring for older adults is a challenge for healthcare providers, as they are more likely to have multimorbidities[2,3] and to consume more medication.[4]

Polypharmacy, defined as 'the use of multiple drugs administered to the same patient, most commonly seen in elderly patients,[5,6] although frequent has a negative impact on senior health[7,8]. There is an increased risk of drug interactions and prescriptions of potentially inappropriate medications,[4] changes in pharmacokinetics and pharmacodynamics and limited generalisation of clinical research results due to common exclusion of subjects aged more than 65 years old.[9] So, prescribing medication for elderly patients should be evidence based and particularly cautious.

In several cases it is urgent to deprescribe, this is to begin 'the process of withdrawal of inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes.[10]

Inappropriate medication prescription, meaning 'the practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist,[5,11] can be reduced by several interventions.[12] However, they are not widely known and therefore used. In one hand, general practitioners report interest in learning and using more mobile technologies to assist in clinical care[13]; on the other hand, they refer an insufficient emphasis on geriatric pharmacotherapy training.[14]

It has already been shown that computerised decision support systems can reduce physicians' orders of unnecessary tests[15]. This systematic review aims to determine if computerised decision support is effective in reducing potentially inappropriate medication prescription in the elder population.

Other studies have addressed strategies to improve care of elderly in what concerns inappropriate medication prescription[12,16]. In 2013, one synthesis study identified eight

randomised controlled trials (RCT), two cluster RCTs and two controlled before-and-after studies[9]. In 2015, another study included 12 RCTs.[13] Both studies reported high heterogeneity on the included studies. However, these studies have not focused on computerised decision support systems. In addition, we consider that since the last study search, more adequate studies have been published and that, for the first time, a meta-analysis will be possible to conduct.

Methods and analysis

Eligibility Criteria

In this systematic review, we will select (1) interventional studies, such as RCTs, non-randomised controlled studies and quasirandomised controlled studies; (2) those that include participants aged 65 years or more, to whom one or more regular medications were prescribed, and (3) assess the impact of computerised decision support systems in withdrawal of potentially inappropriate medication prescription. On the other hand, studies including only moribund, terminal or palliative participants will be excluded. Studies published or in press will be included independent of the language, year of publication and setting in which it was conducted (hospitals, nursing centres, communities, and so on). Potentially inap- propriate medications will be defined using the Beers criteria[17] and STOPP/START criteria.[18]

Information Sources

Our sources of information will include electronic data-bases (namely MEDLINE, CENTRAL, EMBASE, Web of Science), trial registries, different types of grey literature and contact with specialists in the field. If further data are needed, authors of the selected articles will be contacted. The search will be performed in January and February 2018. The search will have no language restrictions. In those cases that none of the research team members are able to translate the included study, we will first contact the authors to ascertain if the main data are available in other languages and seek to translate whenever necessary. A second search using all

identified keywords and proprietary names of computerised decision support systems will then be undertaken across all included databases.

Search Strategy

Our initial search syntax in CENTRAL will be: (1) MeSH descriptor: [Medical Informatics Applications] explode all trees; (2) Computer decision support; (3) MeSH descriptor: [Deprescriptions] explode all trees; (4) MeSH descriptor: [Inappropriate Prescribing] explode all trees; (5) no. 1 or 2; (6) no. 3 or 4; (7) no. 5 and no. 6.

For PubMed, the query will be "(Medical Informatics Applications [MeSH Terms] OR (medical AND infor- matics AND applications)) AND ((Deprescriptions [Mesh Terms] OR deprescription OR deprescribing OR Inappropriate Prescribing [Mesh Terms] OR (inappropriate AND prescribing*) OR (inappropriate AND prescription*) OR (over* AND prescribing*)) OR medication errors [MeSH Terms] OR (error* AND medication) OR (drug AND use AND error*) AND (decision support systems, clinical [MeSH Terms] OR 'clinical decision support systems' OR (clinical AND decision AND support*) OR decision making, computer-assisted [MeSH Terms] OR (computer AND assisted AND decision AND making) OR (medical AND computer AND assisted AND decision AND making) OR medical order entry systems [MeSH Terms] OR (medical AND order entry systems) OR (medications AND alert AND systems) OR 'computorized physician order entry systems' OR 'computorized provider order entry systems' OR 'computorized physician order entry' OR 'computorized provider order entry')."

For Web of Science the query will be "TS=('Medical Informatics Applications' OR (medical AND informatics AND applications)) AND TS=((Deprescriptions OR deprescription OR deprescribing OR 'Inappropriate Prescribing' OR (inappropriate AND prescribing*) OR (inappropriate AND prescription*) OR (over* AND prescribing*)) OR 'medication errors' OR (error* AND medication) OR (drug AND use AND error*) AND TS=('clinical decision support systems' OR (clinical AND decision AND support*) OR decision making, computer-assisted [MeSH Terms] OR (computer AND assisted AND decision AND making) OR (medical AND

computer AND assisted AND decision AND making) OR 'medical order entry systems' OR (medical AND order entry systems) OR (medications AND alert AND systems) OR 'computorized physician order entry systems' OR 'computorized provider order entry systems' OR 'computorized physician order entry' OR 'computorized provider order entry')."

Study Selection Process

The selection process procedure will be made by two reviewers following several steps.

First, they will independently review the title and abstract of each reference. Each one will be categorised into either relevant, unsure or irrelevant. If a reference is considered irrelevant by the two authors it will be eliminated.

In the next phase, the two authors will review the full text of the remaining references and each one will independently select which articles should be included.

The two authors will compare their selected articles and discuss any disagreement in each phase.

If the two reviewers cannot reach an agreement all the authors of the paper will make the final decision.

Data Extraction and Management

Once the articles to be included are selected, data will be extracted and entered into data sheets independently by two reviewers. These two sheets, including their differences, will be checked by a third reviewer.

The following information will be extracted from each article: (1) study characteristics, intervention type; type of study; country, setting, follow-up duration; (2) participants' number and age; and (3) clinical outcomes. The primary outcome to be considered is the effect of intervention on withdrawal of potentially inappropriate medications (discontinuation rate). The authors will give priority to the following outcomes, by order of importance: mortality, hospitalisation, any reported adverse drug withdrawal effects and quality of life measurements.

Any potential difference among reviewers will be discussed with the team, and if not resolved, the manuscript authors will be contacted. Also, if required data are missing from the article or are incomplete or unclear, inquiries will similarly be sent to the authors.

Risk of Bias

Two reviewers will assess, independently and blinded to each other, the risk of bias by applying the Cochrane Collaboration Risk of Bias tool to all the included studies.[19]

Data Synthesis

The final report will present the available data of the computer decision to support in reducing inappropriate medication prescription in older adults.

Each outcome will be combined and calculated using the statistical software RevMan V.5.1,[20] according to statistical guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions.[21]

If we are able to include a group of studies that are sufficiently comparable and reliable, we will conduct a meta-analysis. We consider that we should use a random effects model taking in consideration the previous systematic reviews' results. We expect to encounter a sufficient number of studies, reporting a sufficient number of events, but that are not completely comparable (concerning the intervention, context and population).

If heterogeneity is severe (I^2 superior to 40%–50%) and studies' results are strongly biased, we will not perform a meta-analysis; thus, a narrative, qualitative summary will be done instead.

Effect sizes and 95% CI will be expressed as ORs. When a study reports zero event in both arms, we will consider using zero-cell correction methods.

Subgroup analyses will be used to explore possible sources of heterogeneity based on the following: setting, type of software, medication and participants' clinical characteristics.

Regarding subgroups, we assume it will be relevant to include subgroups regarding the tool used by software to identify targets: STOPP/START criteria subgroup and the Beers criteria.

We will also conduct metaregression to evaluate whether the covariates have significant influence on heterogeneity.

Forest plots will be produced when three or more studies are included in a meta-analysis. Data in tables will be presented by therapeutic class based on the Anatomical Therapeutic Classification codes.

Studies rated as having a high risk of bias will be included in the narrative synthesis but not on our meta-analysis and discussed in detail.

A systematic narrative synthesis will be provided in the text and tables to summarise and explain the characteristics and findings of the studies; it will explore the relation- ship within and between studies, in line with guidance from the Centre for Reviews and Dissemination.

To determine whether publication bias is present, we will include funnel plot and statistical tests in the assessment, namely Begg's test and Egger's test.

We will also ascertain if each RCT had its protocol published before recruitment of patients was initiated.

The quality of evidence for all outcomes will be judged with the Grading of Recommendations Assessment, and the Development and Evaluation working group methodology.[22]

The final paper will be prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. [23,24]

ETHICS AND DISSEMINATION

As a systematic review, this research is exempt from ethical approval. We intend to publish the full article in a related peer-reviewed journal and present it in international conferences.

Discussion

Although electronic health records are common in clinical practice, there is a lack of evidence of computer decision support systems regarding health outcomes. Deprescribing potentially inappropriate medication in the elderly is particularly difficult, although computer support may be an important tool. This systematic review will help identify the success of computerised decision support to reduce inappropriate medication prescription. Therefore, this review will be relevant for patients, health professionals and policymakers. One potential limitation of this study will be if we find a limited number of studies with considerable differences regarding their characteristics and methodology. This may impair our conclusions and impede meta-analysis. In addition, depending on the data available and obtained results we may not be able to define which is the best decision support available.

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Chapter 4.

Reducing Potentially Inappropriate Prescriptions for Older Patients Using Computerized Decision Support Tools: Systematic Review

Abstract

Background

Older adults are more vulnerable to polypharmacy and prescriptions of potentially inappropriate medications. There are several ways to address polypharmacy to prevent its occurrence. We focused on computerized decision support tools.

Objective

The available literature was reviewed to understand whether computerized decision support tools reduce potentially inappropriate prescriptions or potentially inappropriate medications in older adult patients and affect health outcomes.

Methods

Our systematic review was conducted by searching the literature in the MEDLINE, CENTRAL, EMBASE, and Web of Science databases for interventional studies published through February 2018 to assess the impact of computerized decision support tools on potentially inappropriate medications and potentially inappropriate prescriptions in people aged 65 years and older.

Results

A total of 3756 articles were identified, and 16 were included. More than half (n=10) of the studies were randomized controlled trials, one was a crossover study, and five were pre-post intervention studies. A total of 266,562 participants were included; of those, 233,144 participants were included and assessed in randomized controlled trials. Intervention designs had several different features. Computerized decision support tools consistently reduced the number of potentially inappropriate prescriptions started and mean number of potentially inappropriate prescriptions per patient. Computerized decision support tools also increased potentially inappropriate prescriptions discontinuation and drug appropriateness.

However, in several studies, statistical significance was not achieved. A meta-analysis was not possible due to the significant heterogeneity among the systems used and the definitions of outcomes.

Conclusions

Computerized decision support tools may reduce potentially inappropriate prescriptions and potentially inappropriate medications. More randomized controlled trials assessing the impact of computerized decision support tools that could be used both in primary and secondary health care are needed to evaluate the use of medication targets defined by the Beers or STOPP (Screening Tool of Older People's Prescriptions) criteria, adverse drug reactions, quality of life measurements, patient satisfaction, and professional satisfaction with a reasonable follow-up, which could clarify the clinical usefulness of these tools.

Trial Registration

International Prospective Register of Systematic Reviews (PROSPERO) CRD42017067021; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017067021

(J Med Internet Res 2019;21(11):e15385) doi: 10.2196/15385

INTRODUCTION

The older adult population is increasing in developed countries[1], and people worldwide are living longer[2,3]. According to the World Health Organization, people aged 60 years and older in 2020 will outnumber children younger than 5 years. In 2050, the world's population aged 60 years and older is expected to total 2 billion[2].

The aging of populations increases the pressure on health care systems, which should be aligned with the needs of older populations[4]. Older patients are more likely to have more than one chronic condition, known as multimorbidity[5,6]. The prevalence of multimorbidity is more than 90% in older patients[5]. Having more than one chronic condition requires the use of several medications. Thus, older adults are more vulnerable to polypharmacy[7], meaning the use of multiple drugs administered to the same patient[8,9], in addition to prescriptions of potentially inappropriate medications (PIMs)[10-12]. A PIM can be described as a medication use that has potentially more risks than benefits with a safer alternative available[10].

Due to changes in pharmacokinetics and pharmacodynamics, older people are more prone to drug interactions and adverse drug reactions[14,15]. Adverse drug reactions are considered a public health problem in older patients and a cause of disability and mortality[15]. Deprescribing is defined as "the process of withdrawal of inappropriate medication, supervised by a health care professional, with the goal of managing polypharmacy and improving outcomes"[16].

There are several ways to address polypharmacy to prevent its occurrence[17-23]. This review focused on computerized decision support (CDS) tools. Bates et al[24] defined CDS systems as computer-based systems providing "passive and active referential information as well as reminders, alerts, and guidelines." Payne[25] added that CDS tools can be defined as "computer applications designed to aid clinicians in making diagnostic and therapeutic decisions in patient care." CDS tools may have a positive impact on health care, such as reducing physicians' orders of unnecessary tests[26].

Previous studies reviewed such strategies, such as multidisciplinary team medication reviews, pharmacist medication reviews, computerized clinical decision support systems, and multifaceted approaches and reported substantial heterogeneity in the included studies, but did not focus on CDS[19,21]. One systematic review that did focus on CDS systems included studies published only through 2012, and new studies have been published since then[27]. This systematic review aims to clarify wether CDS tools can help in reducing PIPs or PIMs to improve clinical outcomes in older adults.

Methods

Eligibility Criteria

The systematic review was conducted according to a protocol previously published[28] and registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD42017067021). We searched for interventional controlled studies (type of study) with participants aged 65 years or older (population) that assessed whether CDS tools (intervention) could diminish PIM (outcome). Moribund or terminal participants were excluded along with those requiring palliative care. No other restriction was applied.

Search Methods

We searched MEDLINE, CENTRAL, EMBASE, and Web of Science for studies published through February 2018 without language restrictions. Specific queries were used according to each database's requirements that were described in detail elsewhere[29]. Trial registries, different types of grey literature, and contact with specialists in the field were also performed. The reference lists of all included studies were searched to identify any potentially pertinent study that might not have been identified by previous methods. References were checked from previously published systematic reviews.

Selection Process

Articles were selected by applying the criteria to the title and abstract of each study. Studies that were selected at this stage were then assessed in their entirety. Each stage was conducted by two

researchers blindly and independently. Two reviewers (LM and TM) examined the titles and abstracts and did the full-text screening. When disagreement occurred, it was resolved through consensus.

Data Collection Process

For all the included studies, characterization of data and results were exported into a datasheet by one of the authors (LM) and confirmed by the other (MS).

Type of Data Collected

Studies were characterized according to setting, intervention, comparison definition, study duration, number of included participants overall and in each study group, the proportion of missing data, participants' mean age, the proportion of male individuals, and deprescribing target. Outcomes retrieved from each study were categorized as PIP- or PIM-related and by overall number of prescriptions, adverse drug reactions, and potential drug-drug interactions.

Analysis of Results and Assessment of Risk of Bias

Possible bias in randomized controlled trials (RCTs) was independently identified using the Cochrane Collaboration Risk of Bias tool[29] by two researchers (TM and LM). This assessment was confirmed by other authors (IV and MS). Risk of bias was determined with regard to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and other biases.

The included articles did not permit the performance of a meta-analysis because there were not a minimum of three studies using the same deprescribing target. Thus, only a narrative synthesis was performed. We have summarized the main features and results of all the included studies, discussed their limitations, and proposed future research avenues.

RESULTS

DESCRIPTION OF THE STUDIES

Using our search strategy, 3756 articles were identified through MEDLINE, Central, EMBASE, and Web of Science databases. One article was identified through contact with specialists. After duplicates were removed, 2819 articles remained. The titles and abstracts were screened, and 2767 studies were excluded. Of these, 52 articles were selected to assess eligibility and their full text was analyzed. Of these, 36 articles were excluded. Ultimately, we included 16 studies in our systematic review. No new article was found by searching in the included studies' reference lists, trial registries, or grey literature. The article selection process and reasons for exclusion are described in *Figure 1*.

The characteristics of the included studies are described in *Table 1*. More than half (10/16) of the included studies were RCTs, one was a crossover study, and five were pre-post intervention studies. Most studies were conducted in North America (Canada and United States; n=11)[30-40]. The remaining were conducted in Europe (n=5)[41-45].

Six studies were conducted exclusively in secondary health care institutions[35,37,38,40,44,45]. In two studies, only emergency department participants were included[33,39]. In total, six studies were performed exclusively in primary health care institutions[30-32, 41-43], one study took place in a health maintenance organization[34], and one study included participants from both secondary and primary health care institutions[36]. Six studies took place at teaching hospitals[36-38, 40, 44, 45].

Most commonly, the standard of care was the only comparator (n=11). The interventional design was always based on a CDS tool, which was usually included in the electronic medical record with several different features. In some cases (n=6), complex interventions were performed that included training and engagement sessions and/or leaflet provision.

The RCTs had an inclusion period ranging from 3 to 30 months (see *Table 2*). The crossover study included four on-off periods with a 6-week duration[33]. The pre-post intervention studies frequently compared different time periods.

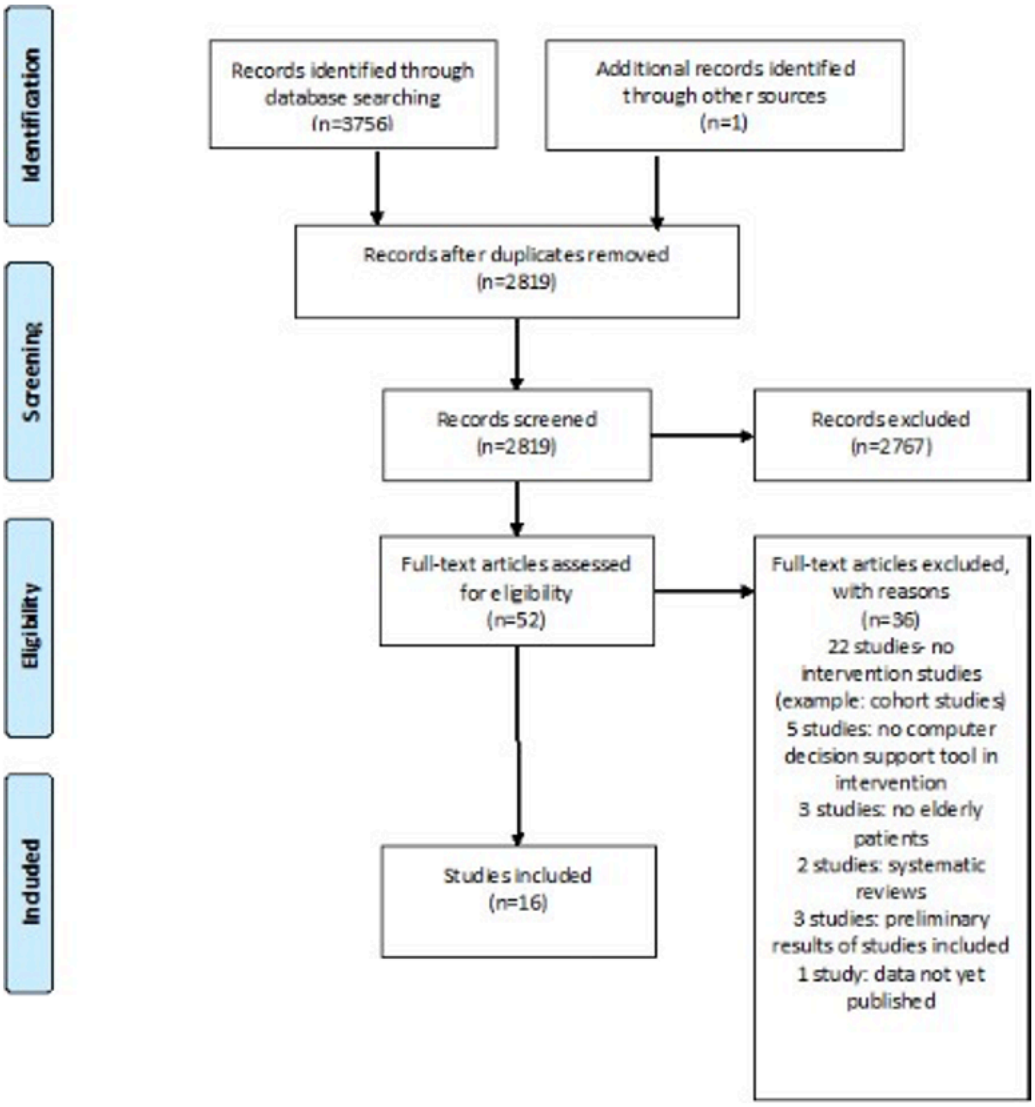

Figure 1 - Figure 1 from "Reducing potentially inappropriate prescriptions for older patients using computerized decision support tools: Systematic Review" Flow diagram on search and article inclusion, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

Table 1- *Table* 1 from "Reducing potentially inappropriate prescriptions for older patients using computerized decision support tools: Systematic Review"

Table 1 – Description of the included studies in the systematic review (N=16)

Author, year; (study); country	Setting	Comparator	Intervention	Desprescribing target
Randomized controlled trials				
Tamblyn et al[30], 2003; Canada	PHC[a]	Usual care[b]	Computerized decision support tool providing alert identified problem + presented possible consequences + provided alternative therapy	PIP[c] (159 clinically relevant PIPs in the elderly defined by expert consen- sus)
Price et al[31], 2017; Canada	PHC (8 GP[d])	Usual care	Clinical decision support tool showing alert with specific STOPP[e] guideline content in electronic medical reccord	PIPs (40 STOPP criteria)
Avery et al[41], 2012; (PINCER); UK	PHC (72 G)	Computer-generated simple feedback	PINCER; comparator + pharmacist- led information technology complex intervention	PIPs on NSAIDs[f], beta blockers, ACE[g] inhibitors, or loop diuretics
Erler et al[42], 2012; Ger- many	PHC (46 GP)	Usual Care	Interactive 1-hour workshop for physicians on detection and management of CKD[h] + provision of desk- top checklist of medications to be reduced or avoided + patient information leaflets + training in the use of software "DOSING"	Prescription exceeding recommended standard; daily dosage >30% or recommended; maximum daily dose in CKD patients
Clyne et al[43], 2015; (OPTI-SCRIPT); Ireland	PHC (21 GP)	Usual care+simple, patient-level PIP postal feedback	Comparator + academic detailing with pharmacist + medicine review with Web-based pharmaceutical treatment algorithms + leaflets	PIPs using 28 criteria from the study
Cossette et al[40], 2017; Canada	SHC[i] (teaching hospital)	Usual care	KT[j] strategy; distribution of educational materials + in-services by geriatricians + computerized alert systems pharmacist-physician	7 PIMs[k] based Beers and STOPP geriatric criteria and drugs with anti- cholinergic properties or acting on the central nervous system
Fried et al[32], 2017; (TRIM); USA	PHC (Veterans Affairs; medical center)	Usual care only and usual care with telephonic patient assessment	2 Web apps: (1) extracts information on medication and chronic conditions from the electronic health record, (2) interface for data chart review and telephonic patient assessment + a set of automated algorithms evaluating medication appropriateness + patient-specific medication management feedback report for the clinician	Medication appropriateness based on range of criteria, including feasibility in context of patient's cognition and social support, potential overtreatment of DM[l] or hypertension, "traditional" PIMs according to Beers and STOPP criteria, inappropriate renal dosing, and patient report of adverse medication effects.
O'Sullivan et al[44], 2016; Ireland	SHC (teaching hospital)	Usual medical and pharmaceutical care	Clinical decision support software supported structured pharmacist re- view of medication designed to optimize geriatric pharmaceutical care	Medicines associated with "nontrivial" adverse drug reactions (according to WHO)
Terrel et al[33], 2009; USA	ED[m] (teaching hospital)	Computerized; physician order entry without alerts	Computer-assisted decision support alert when PIM was being prescribed + rationale + recommend safer substitute therapies. If physician chose to continue, second menu displayed to query most important reason	9 high-use and high-impact PIMs[n]

Raebel et al[34], 2007; USA	HMO[o] (18 medical offices + 21 pharmacies)	Usual care	Medication alert generated from PIMS not allowing prescription la- bel to be printed until the pharmacist actively determined whether pre- scription should be dispensed; pharmacists should communicate notifications to prescribing clinicians	Newly prescribed PIMs based on the Beers, Zhan and Kaiser Performance Care Management Institute lists of medications to be avoided in older people[p]
Crossover studies				
Peterson et al[35], 2005; USA	SHC	Usual computerized order entry	Guided dosing of psychotropic medication integrated in Brigham Integrated Computer System	Benzodiazepines, opiates, and neuroleptics
Pre-post intervention studies				
Ruhland et al[36], 2017; USA	SHC + PHC; (1 teaching hospital + 2 community hospital + 31 clinics)	Usual care	Clinical decision support system creating an alert + rational and; alter- native medication through Epic (an integrated electronic medical record)	PIMs on glyburide
Mattison et al[37], 2010; USA	SHC (teaching hospital)	Usual care	Medication-specific warning system (advised alternative medication or dose reduction)	PIMs on medications not recommend- ed for use in older patients (not recommended medications) and those for which only a reduced dose was advised (dose-reduction medications)
Lester et al[38], 2015; USA	SHC (teaching hospital)	Computerized physician order entry without alerts	Computerized; physician order entry with pop-up alerts for selected PIPs containing links to articles relevant to the alert	PIPs on diphenhydramine, metoclopramide and antipsychotics
Ghibelli et al[45], 2013; (INTERcheck); Italy	SHC (teaching hospital)	Analysis without any interference	Computer-based application (INTERcheck that collects, stores and automatically; provides drug information to reduce or prevent PIPs)	PIMs from 2003 Beers Criteria; potential DDIs[q]; and Anticholinergic Cognitive Burden Scale
Stevens et al[39], 2017; (EQUiPPED); USA	ED (10 Veterans Affairs; medical centers)	Usual care	EQUiPPED interventions: education + informatics-based clinical decision support + individual provider feedback	PIMs from 2012 Beers Criteria category 1 (to avoid in all older adults)

[a]PHC: primary health care; [b]Each physician was given a computer, printer, health record software, and access to the internet.; [c]PIP: potentially inappropriate prescription.; [d]GP: general practice.
[e]STOPP: Screening Tool of Older People's Prescriptions.; [f]NSAID: nonsteroidal anti-inflammatory drug; [g]ACE: angiotensin-converting enzyme; [h]CKD: chronic kidney disease.; [i]SHC: secondary health care.; [j]KT: knowledge translation; [k]PIM: poter inappropriate medication; [l]DM: diabetes mellitus.; [m]ED: emergency department; [n]High-use and high-impact PIMs: promethazine, diphenhydramine, diazepam, propoxyphene with acetaminophen, hydroxyzine, amitriptyline, cyclobenzaprine, clon indomethacin; [o]HMO: health maintenance organization; [p]Examples of medications to be avoided in older people: amitriptyline, chlordiazepoxide, chlorpropamide, diazepam, doxepin, flurazepam, aspirin in combination with hydrocodone or oxycodone, keto oral meperidine, and piroxicam.; [q]DDI: drug-drug interaction.

Table 2 - Table 2 from "Reducing potentially inappropriate prescriptions for older patients using computerized decision support tools: Systematic Review"

Table 2 – Characterization of the included studies in the systematic review, including study type, study duration, sample size, and participant demographics

Study	Study duration (months); date range	Sample size, N	Participants, n	Age (years), mean (SD)	Gender (male), n (%)	Outcome missing data, n (%)
Randomized controlled trials						
Tamblyn et al[30]	13; (01/1997-02/1998)	12,560	C[a]: 6276; I[b]: 6284	C: 75 (6); I: 75 (6)	C: 2248 (36); I: 2439 (39)	N/R[c]
Price et al[31]	8; (02-10/2015)	81,905	C: 37,615; I: 44,290	N/R; all>65 years	N/R	N/R
Avery et al[41]	6 (and 12)	480,942	C: 37,659; I: 34,413	N/R	N/R	C: 22 (0,06); I: 28 (0,08) for outcome 3
Erler et al[42]	6	404	C: 206; I: 198	C: 80 (9); I: 81 (6)	C: 63 (31); I: 81 (41)	C: 9 (4); I: 0 (0)
Clyne et al[43]	6; (10/2012-09/2013)	196	C: 97; I: 99	C: 76 (5); I: 77 (5)	C: 50 (52); I: 55 (56)	C: 3 (3); I: 3 (3)
Cossette et al[40]	10 weeks; (09/2015-12/2015)	321	C: 133; I: 139	C: 81 (7); I: 82 (8)	C: 53 (41); I:48 (38)	C: 5 (4); I: 13 (9)
Fried et al[32]	3;(10/2014-01/2016)	156	C1: 36; C2: 39; I: 81	<70 years C: 25 (39); I: 27 (42)	C: 63 (99); I: 63 (99)	C1: 4 (11); C2:7 (18); I: 17 (21)
O'Sullivan et al[44]	13; (06/2011-07/2012)	737	C: 361; I: 376	C: 78b; (IQR 72-84); I: 77; (IQR 71-83)	C: 190 (51); I: 180 (50)	C: 17 (5); I: 17 (5)
Terrel et al[33]	30; (12/01/2005 – 07/07/2007)	5162	C: 2515; I: 2647	C: 74 (7); I: 74 (7)	C: 880 (35); I: 929 (35)	N/R
Raebel et al[34]	12; (18/05/2005-17/05/2006)	59,680	C: 29,840; I: 29,840	C: 74; (5-95 percentile 66-88); I: (5-95 percentile 66-88)	C: 12,843 (43); I: 12704 (43)	N/R
Crossover Studies						
Peterson et al[35]	4 × 6 week on-off pe- riods; (08/10/2001-16/05/2002)	3718	C: 1925; I: 1793	C: 75 (7); I: 75 (7)	C: 905 (47); I: 843 (47)	N/R
Pre-post Intervention Studies						
Ruhland et al[36]	3+3; (B[d]: 01/12/2014-28/02/2015); (A[e]: 01/03/2015-31/05/2015)	N/R	101 patients with activated alert	75	N/R	N/A[f]
Mattison et al[37]	6 + 41.5; (B: 1/06-29/11/2014; A: 17/03/2015-30/08/2008)	N/R	N/R	N/R; all >65 years	N/R	N/R
Lester et al[38]	12 + 24; (B: Q2 2010; A: Q2s 2011-2013)	29,465	B: 6604; A: 22,861	<75 years; B: 5279 (80); A: 15.633 (68)	N/R	N/R
Ghibelli et al[45]	2 + 2; (B: 04 to 05/2012; A: 06 to 07/2012)	134	B: 74; A: 60	B: 81; A: 81	B: 27 (36); A: 25 (42)	B: 0 (0); A: 0 (0)
Stevens et al[39]	>6 + >12	N/R	N/R	N/R; all >65 years	N/R	N/R

[a]C: comparator group; [b]I: intervention group; [c]N/R: not reported; [d]B: before; [e]A: after; [f]N/A: not applicable

A total of 233,144 participants were included and assessed in RCTs (mean sample size: 21,199; range 196-72,072 participants). The crossover study included 3718 individuals. The pre-post intervention studies included more than 29,700 participants. However, some studies did not report a raw number of participants included in each study period. There was no information regarding whether missing data influenced the outcome assessment in eight studies (50%).

According to our inclusion criteria, all individuals were older than 65 years of age. The mean age in the selected studies was approximately 75 years. Females were often more prevalent, especially in larger studies.

The deprescribing target varied among the studies, and several papers used more than one criterion[30,32-34,40,45]. PIM was defined in some papers using internationally recognized criteria, such as the Beers Criteria (n=5)[32,34,39,40,45], the Screening Tool of Older People's Prescriptions (STOPP) criteria (n=3)[31,32,40], and the Anticholinergic Cognitive Burden Scale (n=1)[45]. In other studies (n=4), some group medications were specifically the target, such as benzodiazepines, opiates, and neuroleptics[35]; glyburide[36]; nonsteroidal anti-inflammatory drugs (NSAIDs), beta blockers, angiotensin-converting enzyme (ACE) inhibitors, or loop diuretics[41]; and diphenhydramine, metoclopramide, and antipsychotics[38].

Results of the Studies

The main results of the included studies are described in *Tables 3* and *4*. Several definitions and units were used to measure the impact of CDS tools on changes in PIP and PIM drugs (overall or concerning specific drugs). Studies assessed the following PIP- or PIM-related outcomes: number of PIMs started per 1000 visits[30], number of PIMs discontinued per 1000 visits[30], proportion of discontinued PIMs[30], percentage of PIMs[43], mean number of PIMs, risk of receiving a prescription for a drug exceeding the recommended maximum dose[42], risk of receiving a prescription for a drug exceeding the recommended standard doses[42], proportion of reconciliation errors corrected[32], proportion of recommendations implemented[32,33], proportion of patients with at least one PIM, and/or proportion of all prescribed medications that were PIM[33].

Table 3 - Table 3 from "Reducing potentially inappropriate prescriptions for older patients using computerized decision support tools: Systematic Review"

Table 3 – Results of the included studies including changes in potentially inappropriate prescriptions or medications (N=16)

Study	PIP[a] – or PIM[b] – related outcomes Changes in PIP or PIM drugs	Changes in specific PIP or PIM drugs
Randomized controlled trials		
Tamblyn et al[30]	Number of PIP started per 1000 visits C[c]: 52.2 vs I[d]: 43.8, RR[e] 0.82 (CI[f] 95% 0.69 –0.98); PIP discontinuation C: 44.5% vs I: 47.5%, RR: 1.14 (95% CI 0.98-1.33); number of PIP discontinued per 1000 visits C: 67,4 vs I: 71,4, RR 1.06 (95% CI 0.89-1.26)	Number of PIP started per 1000 visits: drug-disease contraindication C: 18.4 vs I: 16.6, RR 0.89 (CI 95% 0.72-1.10); drug-age contraindication C: 13.7 vs I: 10.7, RR 0.77 (CI 95% 0.59-1.00); excessive duration therapy C: 17.1 vs I: 13.3, RR 0.78 (CI 95% 0.61-0.99); therapeutic duplication C: 6.8 vs I: 6.1, RR 0.87 (CI 95% 0.69-1.11); number of PIP discontinued per 1000 visits: drug- disease contraindication C: 57.9 vs I: 62.6, RR 1.08 (CI 95% 0.85-1.36); drug age contraindication C: 42.9 vs I: 40.7, RR 0.94 (CI 95% 0.79-1.13); excessive duration therapy C: 32.6 vs I: 32.3, RR 1.00 (CI 95% 0.77-1.29); therapeutic duplication C: 334.0 vs I: 317.1, RR 0.94 (CI 95% 0.59-1.51)
Price et al[31]	Change in PIP C: 0.1% vs I: 0.1%, *P*=.80	
Avery et al[41]	_ g	At 6 months: history of peptic ulcer prescribed an NSAID[h] without a PPI/history of peptic ulcer without PPI[i] AOR[j] 0.58 (95% CI 0.38-0.89); asthma prescribed a ß blocker/asthma AOR 0.73 (95% CI 0.58-0.91); aged ≥ 75 years long-term ACE[k] inhibitors or loop diuretics without urea and electrolyte monitoring in the previous 15 months aged ≥ 75 years receiving long-term ACE inhibitors or diuretics AOR 0.51 (95 % CI 0.34-0.78); secondary outcomes AOR varied from 0.39-0.96; at 12 months: history of peptic ulcer prescribed an NJSAID without PPI/history of peptic ulcer without PPI AOR 0.91 (95% CI 0.59-1.39); asthma prescribed a ß blocker/asthma AOR 0.78 (95% CI 0.63-0.97); aged ≥75 years receiving long-term ACE inhibitors or loop diuretics without urea and electrolyte monitoring in the previous 15 months aged ≥75 years receiving long-term ACE inhibitors or diuretics AOR 0.63 (95% CI 0.41-0.95); secondary outcomes AOR varied from 0.50-0.98
Erler et al[42]	CKD[l] patients with ≥1 prescription exceeding recommended maximum dose AOR 0.46 (95% CI 0.26-0.82); CKD patients with ≥1 prescription exceeding recommended standard dose by >30% AOR 0.66 (95% CI 0.36-1.21)	NS differences in the numbers of patients with potentially dangerous or contraindicated medications
Clyne et al[43]	Percentage of PIP I: 52% vs C: 77%, *P*=.02, AOR 0.32 (95% CI 0.15-0.70); mean number of PIP C: 1.18 vs I: 0.70, *P*=.02	Odds of PIP AOR 0.30 (95% CI 0.14-0.68); NS differences for duplicate or long-term benzodiazepines
Cossette et al[40]	Drug cessation or dosage decrease: at 48h C: 15.9% vs 45.8%, AD[m] 30.0% (95% CI 13.8-46.1); at discharge C: 27.3% vs I: 48.1%, AD 20.8% (95% CI 4.6-37.0); drug cessation: at 48h C: 15.1% vs 51.9%, AD 36.8% (95% CI 15.6-57.9); at discharge C: 34.4% vs I: 45.2%, AD 10.7% (95% CI –10.5 to 31.9); dosage decrease: at 48h C: 17.2% vs 38.1%, AD 20.9% (95% CI 4.1-45.8); at discharge C: 15.8% vs I: 52.4%, AD 36.6% (95% CI 12.3-60.9)	____
Fried et al[32]	Proportion of medication reconciliation errors corrected C: 14.3% vs I: 48.4%, *P*<.001; proportion of ≥1 TRIM recommendations implemented C: 21.9% vs I: 29.7%, *P*=.42	___
O'Sullivan et al[44]	Patients with ≥1 PIP C: 84.6% vs I: 82%	___
Terrel et al[33]	Proportion of visits with a PIP C: 3.9% vs I: 2.6, *P*=.02, OR[n] 0.55 (95% CI 0.34-0.89), ARR[o] 1.3% (95% CI 0.4-2.3); proportion of all pre-	___

	scribed medications that were PIP C: 5.4% vs I: 3.4, *P*=.006, OR 0.59 (CI 95% 0.41-0.85), ARR 2.0% (95% CI 0.7-3.3)	
Study	**PIP[a] – or PIM[b] – related outcomes** **Changes in PIP or PIM drugs**	**Changes in specific PIP or PIM drugs**
Raebel et al[34]	Newly dispensed ≥1 PIP rate per 100 patients C: 2.20 vs I:1.85, *P*=.002, RRR[p] 16%; newly dispensed ≥1 PIP only for indications included in intervention rate per 100 patients C:1.50 vs I: 1.10, *P*<.001	Newly dispensed ≥1 PIP rate per 100 patients: amitriptyline C: 0.61 vs I: 0.38, *P*<.001; chlordiazepoxide C: 0.05 vs I: 0.04, *P*=.55; diazepam C: 1.38 vs I: 1.28, *P*=.32; doxepin C: 0.14 vs I: 0.11, *P*=.24; flurazepam C: 0.01 vs I: 0.01, *P*=.69; ketorolac C: 0.00 vs I: 0.01, *P*=.50; meperidine (oral) C: 0.01 vs I: 0.01, *P*=N/A[q]; oxycodone/aspirin C: 0.00 vs I: 0.00, *P*=N/A; newly dispensed ≥1 PIP only for indications included in intervention, rate per 100 patients: amitriptyline C: 0.59 vs I: 0.37, *P*<.001; chlordiazepoxide C: 0.05 vs I: 0.04, *P*=.55; diazepam C: 0.71 vs I: 0.56, *P*=.002; doxepin C: 0.13 vs I: 0.09, *P*=.17; flurazepam C: 0.01 vs I: 0.01, *P*=.69; ketorolac C: 0.00 vs I: 0.01, *P*=.50; meperidine (oral) C: 0.01 vs I: 0.01, *P*=N/A; oxycodone/aspirin C: 0.00 vs I: 0.00, *P*=N/A; dispensings of chlorpropamide, hydrocodone/aspirin, or piroxicam C: 0 vs I: 0
Crossover studies		
Peterson et al[35]	Prescription recommended daily dose C: 19% vs I: 29%, *P*<.001; prescription orders with 10- fold dosing C: 5.0% vs I: 2.8%, *P*<.001; prescriptions in agreement with recommendation C: 18.6% vs I: 29.3%, *P*<.001; prescription of non-recommended drugs C: 10.8% vs I: 7.6%, *P*<.001	Prescription orders with 10-fold dosing: benzodiazepines C: 3.5% vs I: 2.0%, *P*=.01; opiates C: 5.5% vs I: 2.8%, *P*<.001; neuroleptics C: 10.0% vs I: 7.5%, *P*=.35; prescriptions in agreement with recommendation: benzodiazepines C: 20.8% vs I: 28.2%, *P*<.001; opiates C: 16.6% vs I: 29%, *P*<.001; neuroleptics C: 22.5% vs I: 38%, *P*<.001
Pre-post intervention studies		
Ruhland et al[36]	----	Glyburide orders from total oral antidiabetic orders B[r]: 3.3% vs A[s]: 1.6%, *P*<.001; 17.8% patients transitioned off glyburide
Mattison et al[37]	Number of orders per total number of patients per day: not recommended medication B: 0.070 vs A: 0.054, *P*<.001; dose reduction medications B: 0.037 vs A: 0.037, *P*=.71; unflagged medications B: 0.033 vs A: 0.030, *P*=.03; number of orders per number of new patients per day: not recommended medication B: .333 vs A: 0.263, *P*<.001; dose reduction medications B: 0.182 vs A: 0.186, *P*=.51; unflagged medications B: 0.158 vs A: 0.148, *P*=.08	---
Lester et al[38]	---	>65 years prescription rates of: diphenhydramine B: 26.9% vs A: 20%, *P*<.001; metoclopramide B: 16.7% vs A: 12.5%, *P*<.001; antipsychotics B: 8.8% vs A: 9.2%, *P*=.80; ≥65 years: no significant changes for diphenhydramine, metoclopramide, or antipsychotics
Ghibelli et al[45]	Proportion of patients exposed to PIM at dis- charge B: 37.8% vs A: 11.6%; mean number of PIM per patient at discharge B: 0.4 vs A: 0.1	Proportion of patients exposed to PIM at discharge: high-dose short-acting benzodiazepines B: 21.6% vs A: 6.7%; ticlopidine B: 5.4% vs A: 0.0%; digoxin B: 5. 4% vs A: 1.7%; doxazosin B: 1.3% vs A: 1.7%; clonidine B: 1.3% vs A: 0.0%
Stevens et al[39]	Average percentage of PIMs per month: site 1 B: 11.9 vs A: 5.1, *P*<.001; site 2 B: 8.2 vs A: 4.5, *P*<.001; site 3 B: 8.9 vs A: 6.1, *P*=.007; site 4 B 7.4 vs A: 5.7, *P*=.04	---

[a]PIP: potentially inappropriate prescription; [b]PIM: potentially inappropriate medication; [c]C: comparator group; [d]I: intervention group; [e]RR: relative rate; [f]CI: confidence interval; [g]No data; [h]NSAID: nonsteroidal anti-inflammatory drug; [i]PPI: proton-pump inhibitor; [j]AOR: adjusted odds ratio; [k]ACE: angiotensin-converting enzyme; [l]CKD: chronic kidney disease; [m]AD: absolute difference; [n]OR: odds ratio; [o]ARR: absolute risk reduction; [p]RRR: relative risk reduction; [q]N/A: not applicable; [r]B: before; [s]A: after

Table 4 - Table 4 from "Reducing potentially inappropriate prescriptions for older patients using computerized decision support tools: Systematic Review"

Table 4 – Results of the included studies including number of prescriptions, adverse drug reactions, and potential drug-drug interactions (N=16)

Study	Overall number of prescriptions	Adverse drug reaction	PDDI[a]	Others
Randomized controlled trials				
Tamblyn et al[30]	---[b]	---	Number of PDDI started per 1000 visits C[c]: 1.5 vs I: 1.6, RR[d] 1.12 (CI[e] 95% 0.68-1.87); number of PPDI discontinued per 1000 visits C: 68.6 vs I[f]: 51.5 per 1000 visits, RR 1.33 (CI 95% 0.90-1.95)	Physicians with more computer problems downloaded information less often (*r*=−.31)
Price et al[31]	---	---	---	Description of 12 data quality probes; alert awareness: all participants in I were aware of STOPP[g] alerts, but not consistently; workflow and display: location on screen and workflow identified as barriers; study disruptiveness: considered as minimal
Avery et al[41]	---	---	---	Mean ICER[h] of intervention: at 6 months £65.6 (2.5- 97.5 percentile 58.2-73.0); at 12 months £66.5 (2.5-97.5 percentile 66.8-81.5)
Erler et al42	---	---	---	---
Clyne et al[43]	---	---	---	Beliefs about Medicine Questionnaire AOR[i] 0.16 (CI 95% - 1.85 to 1.07); 12. item Well-Being Questionnaire AOR – 0.41 (95% CI -0.80 to 1.07)
Cossette et al[40]	---	---	---	LOS[j] (median, IQR[k]) C: 9.5 (5-21) vs I: 10 (6-19), *P*=.9; in-hospital death C:11 (8.6%) vs I: 6 (4.8%), *P*=.3; 30- day post discharge ER visits C: 27 (21.1%) vs I: 27 (21.4%); 30-day post discharge readmissions C: 28 (21.9%) vs I: 20 (15.9%), *P*=.3
Fried et al[32]	Mean number of medications per patient C: 13.8 vs I: 13.3, *P*=.65	---	---	Mean patient active participation C: 2.7 vs I: 5.5, *P*=.001; percentage of patients assessment of care for chronic conditions score >10 C: 15.6% vs I: 29.7%, *P*=.06, OR[l] 2.73 (CI 95% 0.82-9.08); patient medication related; communication C: 3.6 vs I: 7.5, *P*<.001; mean clinician facilitative communication C: 0.67 vs I: 1.53, *P*=.02; mean clinician medication-related communication C: 4.6 vs I:7.3, *P*=.002; percentage >1 recommendations C: 32.8% vs I: 63.6%, *P*<.001; OR 3.33 (95% CI 1.37-8.04)
O'Sullivan et al[44]	Total number of medications C: 3747 vs I: 4192, *P*<.001; median (IQR) number of medications per patient C: 9(7-12) vs 12 (8-15), *P*<.001; number (%) of people with polypharmacy (≥ 5 medications); C: 346 (92.0) vs I: 346 (95.8), *P*=.44	Patients with ≥1 ADR[m] C: 20.7% vs I: 13.9%, *P*= 0.02, ARR[n] 6.8% (95% CI 1.5-12.3); RRR[o] 33.3% (95% CI; 7.7-51.7); NNT[p]15 (95% CI 8-68)	---	CDS[q] alerts 1000 in 296/361 patients; intervention group attended 54.8% of recommendations; median (IQR) LOS days C: 9 (5.16) vs I: 8 (5-13.5), P=.44; hospital mortality C: 4.5% vs I: 4.7%, P>.05; interrater reliability for application of WHO-UMC[r] ADR causality criteria k=0.81; Hallas ADR preventability criteria k=0.87; applications of Harfwig ADR; severity criteria k=0.56

Terrel et al[33]	---	---	---	CDS alerts 114 during 107 visits; 43% of recommendations accepted
Raebel et al[34]	---	---	---	---
Crossover studies				
Study	**Overall number of prescriptions**	**Adverse drug reaction**	**PDDI[a]**	**Others**
Peterson et al[35]	Median (IQR) orders per admission C: 2 (1-3 vs I: 4 2 (1-3), *P*=.43)	---	---	Number of altered mental status per 100 patient-days C: 21.9 vs I: 20.9, *P*=.17; median (IQR) LOS days C: 4 (2-6) vs I: 4 (2-6), *P*=.43; in-hospital fall rate C: 0.64 vs I: 0.28; falls per 100 patient-days, *P*<.001, AOR 0.50 (95% CI 0.30-0.82); fall injuries per 100 patient-days rate C: 0.17 vs I: 0.06, *P*=.09
Pre-post intervention studies				
Ruthland et al[36]	---	---	---	CDS tool alerted 101 times for 75 providers during encounters for 76 patients over 90 days; physicians were more likely to transition patients off glyburide vs other health care providers (46.2% vs 8.0%, *P*<.001)
Mattinson et al[37]	---	---	---	---
Lester et al[38]	---	---	---	---
Ghibelli et al[45]	---	---	Proportion of exposed to PDDI at discharge B[s]: 87.8% vs A[t]: 88.3%; mean number of PDDI per patient at discharge B: 4.5 vs A: 3.7	Median anticholinergic burden at discharge B: 1.5 vs A: 1.1
Stevens et al[39]	---	---	---	---

[a]PDDI: potential drug-drug interactions; [b]No data; [c]C: comparator group; [d]RR: relative rate; [e]CI: confidence interval.; [f]I: intervention group.; [g]STOPP: Screening Tool of Older People's Prescriptions.; [h]ICER: incremental cost-effectiveness ratio.; [i]AOR: adjusted odds ratio. ; [j]LOS: length of stay; [k]IQR: interquartile range; [l]OR: odds ratio; [m]ADR: adverse drug reaction; [n]ARR: absolute risk reduction; [o]RRR: relative risk reduction; [p]NNT: number needed to treat; [q]CDS: computerized decision support; [r]UMC: Uppsala Monitoring Centre; [s]B: before; [t]A: after.

Effects of Interventions

The CDS tools consistently reduced the number of PIPs started and the mean number of PIPs per patient, while also increasing PIM discontinuation and drug appropriateness. However, in several cases statistical significance was not achieved for some of the assessed measures, such as for PIM discontinuation in the Tamblyn et al article[30], for change in PIMs in the Price et al study[31], and other studies described in *Table 3*.

Number of prescriptions

With regard to the impact on the number of prescriptions, the RCT described by Fried et al[32] reported no significant reduction in the mean number of prescriptions in the group exposed to two Web

apps. One study obtained information on medications and chronic conditions from an electronic health record, and the second study used an interface for data chart review, a telephone-based patient assessment, a set of automated algorithms evaluating medication appropriateness, and a patient-specific medication management feedback report for the clinician. In a crossover study[35], there were no significant differences in the median number of medications prescribed per patient during the periods in which guided dosing of psychotropic medication was integrated into the Brigham Integrated Computer System.

In contrast, the RCT described by O'Sullivan et al[44] demonstrated that those in the intervention group (using CDS software structuring pharmacist review of medications designed to optimize geriatric pharmaceutical care) prescribed significantly fewer drugs (both total and median number of drugs). However, no impact was observed for the proportion of people with polypharmacy prescribed more than five drugs at once. This RCT was the only one addressing adverse drug reactions and it concluded that using this software significantly reduced the risk of adverse drug reactions. Furthermore, only 15 patients' medications needed to be reviewed to prevent one adverse drug reaction.

Number of Potential Drug-Drug Interaction

Only two studies assessed whether CDS tools could decrease the number of potential drug-drug interactions[30,44]. One CDS used in an RCT was found to decrease the initiation of PIP, but it did not have a similar impact on deprescription[30].

One pre-post intervention study observed that the proportion of patients exposed to potential drug-drug interactions increased after implementing a computer-based app that collects, stores, and automatically provides drug information to reduce or prevent PIPs[45]. However, the mean number of potential drug-drug interactions per patient at discharge was reduced. Statistical significance was not reported.

Other Measures

Other miscellaneous measures were reported in the studies examined, which should be highlighted. One RCT concluded that having computer problems was directly linked with PIP or PIM information download, and these computer problems could have an impact on the success of CDS tools[30]. Only one study described data quality probes; it found that professionals included in the intervention group were aware of STOPP alerts, although not in a consistent manner. Furthermore, the layout and impact on the workflow of the CDS tool were potential barriers to successful adherence[31].

Adherence to Computerized Decision Support Tools

Several RCTs reported the frequency of adherence to CDS recommendations by a health professional, with values ranging from 33% to 55%[32,33,44]. No significant reduction in the length of stay or intrahospital mortality was found in the RCT described by O'Sullivan et al[44]; in the Cossette et al study[40], the differences between the intervention and control groups were not statistically different. Similarly, a crossover study found no difference in the length of stay between periods when the CDS tool was either active or inactive[35]. Likewise, no difference was observed with respect to patients altered mental status or fall injuries. However, there was a significant decrease in the in-hospital rate.

The TRIM RCT concluded that the use of CDS tools significantly improved patients' active participation and facilitated communication between the clinician and the patient[32]. Another RCT found no significant impact on the Beliefs about Medicine Questionnaire or the 12-item Well-Being Questionnaire when general practitioners had access to information from a pharmacist and a medical review with Web-based pharmaceutical treatment algorithms and leaflets in addition to the usual care and simple, patient-level PIP postal feedback[43].

Cost-Effectiveness of Computerized Decision Support Tools

The cost-effectiveness of CDS tools was addressed in one RCT. The authors reported that there was a 95% probability that adding a pharmacist-led information technology complex intervention, in

addition to computer-generated simple feedback, could be cost-effective, resulting in a willingness to pay £75 per error avoided at 6 months[41].

Risk of Bias in the Studies Examined

The RCTs received a total score according to the Cochrane Collaboration Risk of Bias tool that ranged from 1[30,31] to 5[41,43]. The procedure to guarantee allocation concealment was unclear in eight of ten RCTs. Complete blinding of participants and personnel was not possible due to the nature of the intervention. Blinding for the outcome assessment was not conducted in five studies[31,34,40,41,44], and was unclear if it was successful in another two[30,42]. Both of these biases may have resulted in an overestimate of the CDS tools' impact on PIP or PIM reduction (see *Table 5*).

Table 5 - Table 5 from "Reducing potentially inappropriate prescriptions for older patients using computerized decision support tools: Systematic Review"

Table 5 - Risk of bias assessment (according to Cochrane Collaboration Risk of Bias tool) for the randomized controlled trial (n=10)

Study	Risk of bias items							Total score (max=7)
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	
Tamblyn et al[30]	?[a]	?	_[b]	?	?	+[c]	–	1
Price et al[31]	+	?	–	–	?	?	–	1
Avery et al[41]	+	+	–	–	+	+	+	5
Erler et al[42]	+	?	–	?	+	+	–	3
Clyne et al[43]	+	?	–	+	+	+	+	5
Cossette et al[40]	+	?	–	–	–	-	+	2
Fried et al[32]	–	–	–	+	+	+	?	3
O'Sullivan et al[44]	?	?	–	–	+	+	–	2
Terrel et al[33]	+	?	–	+	?	+	–	3
Raebel et al[34]	+	?	–	–	?	+	+	3

[a] ?: unclear risk of bias; [b] –: high risk of bias; [c] +: Low risk of bias.

Several studies did not report whether outcome data were available for all the participants included (n=4)[30,31,33,34]. Other biases were also found in five of the RCTs; namely, selection bias, performance bias, contamination, and underpowered sample sizes.

Regarding the pre-post intervention studies[36-39,45], they were considered high risk following the Cochrane Effective Practice and Organisation of Care[46]. For example, it is expected that pre-post intervention studies are more prone to the Hawthorne effect[47]. The Hawthorne effect happens when people (in this case, prescribers and patients) know they are being watched, which may lead to changes in behavior[47]. We consider that it is possible that being aware of one's study participation could have resulted in prescribers taking more care when prescribing medications.

Limited generalizability was also pointed out by several authors as a major limitation due to the context—single-center design—and the use of CDS tools that were created specifically for the study, which may not be available in other institutions.

Discussion

Principal Results

Despite the fact that withdrawal of PIPs is considered to be evidence-based[48], it is not an easy task[49]. CDS tools may play a role in supporting deprescription. From the 16 studies examined in this review, 10 were RCTs. Although RCTs represent stronger evidence, they lacked important data pertaining to clinical outcomes and presented a significant risk of bias (the total score of the studies using the Cochrane Collaboration Risk of Bias tool ranged from 1 to 5 with a mean value of 3). The most frequent biases included no blinding of health professionals and an unclear risk of breaking allocation concealment. If prescribers are not blinded, this can easily affect the deprescribing process. Health professionals may have been more susceptible to accepting the CDS tool recommendations. Alternatively, patients may have been more likely to agree with the withdrawal process. If a break in allocation concealment occurred, it is expected that investigators may have potentially included older adults that they considered best suited for the intervention group. Both types of bias may have led to an overestimation of the benefit of CDS tools.

We have also included five pre-post intervention studies. The nonrandomized nature of these studies is the major limitation of this analysis. The impact of CDS tools may be confounded by other changes that may have occurred in the institutions during the study periods.

We observed that almost two-thirds of the included studies were performed in the United States, and one-third were performed in European countries. This reflects the importance that has been given to this topic only in developed countries where electronic health record systems are widely available.

Overall Applicability and Quality of the Evidence

Seven studies were conducted in teaching hospitals and clinics[33,36-38,40,44,45], which may indicate potential bias. Teaching units are more prone to accept interventions in patient care, such as

changes in a prescription through the use of CDS tools. We can assume that these professionals may be more likely to change a patient's prescription and, therefore, to address PIPs. This tendency may result in an overestimate of the impact of the intervention, and we can only speculate as to what would be the impact in a nonteaching unit.

There is a balance between the number of studies conducted in primary care versus secondary care institutions, and only one was conducted in both. The impact of CDS on PIP or PIM reduction was similar between settings despite differences in the health professional and population characteristics. This suggests that the CDS tool might be successful in the context of a larger patient population.

The generalization of our results may be limited for several reasons. First, most studies used standard care as a comparator without providing additional details. In such a complex context, the management of older patients in institutions with several levels of care may mean that standard care could differ greatly between studies.

Second, the intervention varied greatly as a result of using different electronic systems, contents, and layouts. The intervention frequently included several features beyond the creation and application of a CDS tool itself.

Third, the main outcome definition was also diverse. Several studies used STOPP[31,32,40] and Beers Criteria[32,34,39,40,45] to define which medications were targeted. Both criteria are widely used worldwide, and although they do not provide a list of prohibited medications, they are an important tool for physicians due to their evidence-based rationale and constant updating. Nevertheless, the authors chose different groups of criteria for their outcome measures.

Fourth, the studies selected different participants and had widely variable sample sizes. Only two studies addressed potential drug-drug interactions[30,45] and one addressed adverse drug reactions[44]. Due to the increase of polypharmacy in older adults, the risk is higher for experiencing drug-drug interactions and adverse drug reactions. For the former, no significant impact was found, whereas for the latter, using a CDS tool significantly decreased the number of adverse drug reactions.

This tool, which included a clinical decision support software and a structured pharmacist review of medication[44], seems to be promising for aiding medication reconciliation activities. Most of the

reconciliation issues highlighted by this CDS tool were accepted by the health care professionals involved. In particular, the Erler et al study[42] should, in our opinion, have assessed these two topics because they studied a population with renal impairment, which is particularly susceptible to adverse drug reactions and drug interactions. Similarly, only two studies assessed the impact of CDS tools on length of stay[35,40], and two assessed intrahospital mortality[40,44]. No differences were found between those using a CDS tool and those not using a CDS tool. Cost-effectiveness was also assessed by one study, which reported a 95% probability of a CDS tool being cost-effective due to a willingness to pay £75 to prevent an adverse drug reaction in a 6-month period[41]. The study's results may have been underestimated due to low adherence to CDS recommendations. Three RCTs that evaluated adherence reported values fluctuating from 33% to 55%[32,33,44]. Finally, we consider the possibility that the Avery et al trial[41] could have explored the issue of prescription NSAIDs to patients with a history of asthma as a secondary outcome because the authors had information on both conditions (prescriptions of NSAIDs and a history of asthma). This analysis could yield interesting information about the patterns of prescribing NSAIDs to these patients.

Strengths and Limitations

This review presents some limitations. We have chosen to include both RCTs (n=10) and pre-post studies (n=6). We acknowledge that the latter provide a lower level of evidence. Nevertheless, they have assessed some outcomes for which no additional evidence exists. In addition, we have focused our search on articles having PIP modification outcomes, thus some studies assessing changes in PIM may have been missed.

Our search terms were more limited to PIP; therefore, this paper may have missed some studies regarding PIM. Nevertheless, no new articles were found when searching in the references from the included studies and in the grey literature

Major strengths of our study include the fact that we have followed the Cochrane Collaboration Handbook[50], which makes our study less susceptible to major biases and errors. Furthermore, no new references were found from searches in the grey literature, pertinent scientific meeting books of

abstracts, and the included studies' list of references, which suggests that our search strategy was exhaustive and all pertinent articles had been included.

However, the quality of the results of a systematic review is dependent on the available data. For all that was previously described, we believed that conducting a meta-analysis was not possible. Thus, only a narrative synthesis has been provided.

Comparison With Prior Work

To our knowledge, there are three previously published systematic reviews assessing the impact of CDS tools on PIP or PIM[51-27]. Due to an increase in the search period, the use of broader search criteria, and our overall methodology, we were able to include five additional RCTs[31,31,40,43,44]. These studies added evidence with new outcomes, such as well-being and patients' beliefs[43], reduction of adverse drug reactions[44], and users' perspectives[31].

The highlight of the findings in the more recent RCTs were as follows. In the study by Price et al[31], alerts with specific STOPP guideline content in electronic medical records positively changed PIPs (comparator: 0.1% versus intervention: 0.1%, *P*=.80), but not significantly. In the study by Clyne et al[43], the intervention consisted of Web-based pharmaceutical treatment algorithms that led to a lower percentage of PIPs (intervention: 52% versus comparator: 77%, *P*=.02). In the trial by Cossette et al[40], a computerized alert system-based pharmacist-physician intervention was able to significantly increase drug cessation or decrease dosage at discharge (comparator: 27.3% versus intervention: 48.1%; absolute

difference 20.8%, 95% CI 4.6-37.0). In the TRIM trial[32], the proportion of medication reconciliation errors was significantly diminished (comparator: 14.3% versus intervention: 48.4%, *P*<.001). In the article by O'Sullivan et al[44], clinical decision support software reduced adverse drug reactions among older patients (control patients: 20.7% versus intervention patients: 13.9%, *P*=.02). In sum, articles published since 2012 substantiated the value of CDS to improve PIP- or PIM-related outcomes.

The use of CDS tools had a positive impact on PIP independently of the outcome definition in the majority of the studies included in our analysis. However, statistical significance was not always achieved. Several possible sources of bias and experimental limitations were found in the included studies, and evidence is lacking regarding the impact of CDS tools in potential drug-drug interactions, adverse drug reactions, length of stay, mortality, and cost-effectiveness.

This research suggests that RCTs assessing the impact of CDS tools could be conducted in both primary and secondary health care settings using medication targets defined by Beers or STOPP criteria.

To replicate the intervention in different RCTs, a standard CDS tool could be developed. These CDS tools could promote communication between physicians and pharmaceutical servives. These RCTs could also assess adverse drug reactions, quality of life measurements, and patient and professional satisfaction, with a reasonable follow-up to clarify the clinical usefulness of these tools.

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CHAPTER 5.

TRANSLATION AND ADAPTATION OF THE STOPP-START SCREENING TOOL TO PORTUGUESE FOR DETECTING INAPPROPRIATE PRESCRIPTIONS IN OLDER PEOPLE: A PROTOCOL

Abstract

Introduction

Rational prescribing for older adults is a challenge because they usually exhibit multimorbility and multimedication. One available and reliable tool to tackle this issue consists of the Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START), which has been associated with improvements in clinical outcomes. Our goal here is to translate and validate the STOPP-START screening tool for use with Portuguese general practitioners/family physicians.

Methods and analysis

The study will be conducted in four phases: phase I – translation of the STOPP-START screening tool to Portuguese; phase II – data collection of the patient data; phase III – intrater reliability and agreement study; phase IV – inter-retar reliability and agreement study.

Ethics and dissemination

This study was approved by the Ethics Committee of the Central Health Region of Portugal (where the study will take place). Every participant will sign a written consent form. We intended to publish the full article in a related peer-reviewed journal, conference presentations, reports in a PhD thesis.

INTRODUCTION

In Organization for Economic Co-operation and Development countries, the number of older adults is increasing[1] as well as their life expectancy.[2,3]

Caring for older adults is a challenge for healthcare systems[4] because older adults are more likely to have more than one chronic disease.[5,6] For example, multimorbidity in the elderly can be higher than 90% in Portugal.[5] Therefore, adults aged ≥65 years are more likely to be prescribed with multiple drugs[7-9] and may be more susceptible to inappropriate medication use.[10-12]

Potentially inappropriate medications (PIMs) can be described as the use of medications that potentially have more risks than benefits even though safer pharmacological and non-pharmacological alternatives are available.[10] Potentially inappropriate prescription is a different concept than PIM, and includes the overprescription, underpre- scription and misprescription of medications (eg, inappropriate dose or duration).[13]

There are various tools to help physicians identify PIM such as the Beers Criteria[14] and the Potentially Inappropriate Medications in the Elderly list.[15] The combination of the Screening Tool of Older People's Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START)[16,17] is another widely used tool. One of the advantages of this tool is that it not only considers PIM, but also the indications to start an appropriate medication (START).

Versus other tools, some studies have shown that the STOPP-START tool can identify a significantly higher proportion of patients requiring hospitalization as a result of PIM- related adverse events,[16] can reduce the highest number of medications and can identify more potential major clinical issues.[18] The criteria for STOPP-START have been associated with improvement in prescribing quality and clinical outcomes.[19] These criteria have been adapted for other languages,

such as French.[20] In this adaptation, 50 data sets of patients hospitalised in an academic geriatrics department were analysed independently by one geriatrician and one general practitioner. They considered 87 STOPP-START criteria of the original version. The data sets involved 418 prescribed medications. The proportions of positive and negative inter-rater agreements were 99% and 95%, respectively, for STOPP and 99% and 88% for START; Cohen's coefficients were 0.95 for STOPP and 0.92 for START. The results indicated an excellent inter-rater agreement.

Inter-rater reliability of STOPP and START criteria was also tested between multiple physicians practising independently in Europe.[21] After translation of the criteria into their local language, doctors in Belgium, Czech Republic, Italy, Spain and Switzerland applied the criteria to 20 data sets selected from 200 patients aged ≥65 years of a university teaching hospital in Ireland. The median κ coefficients between raters were 0.93 (0.90 to 0.96) for STOPP criteria and 0.85 (0.82 to 0.91) for START criteria. The results demonstrated good inter-rater reliability of STOPP-START criteria. Therefore, the authors concluded that STOPP and START criteria are generalisable across different European countries and languages[21].

Reliability and agreement are different concepts but have been used without distinction in many studies.[22] Reliability can be defined as the ratio of variability between scores of the same subjects (by different raters or at different moments) to the total variability of all scores in the sample. Agreement is connected to the question about whether observations are similar or the degree to which they differ.

We aim to make the first translation and validation[23] of the English STOPP-START tool for portuguese family doctors. In the validation study, we deal with two aspects of reliability and agreement concepts: inter-rater reliability and agreement (different raters using the translated STOPP-START tool assess the same patients), and intra- rater reliability and agreement (the same rater using the translated STOPP-START tool assesses the same subjects at two different moments).

Methods and Analysis

Study Design

This study will be conducted in four phases as illustrated in *Figure 1* (timeline available in online supplemental appendix I). The first phase (phase I) is the translation to the portuguese language followed by data collection (phase II).

Phase III consists of an intrarater reliability and agreement study, and phase IV is an inter-rater reliability and agreement study. We made a preregistration on 'Open registries Network' (DOI 10.17605/OSF.IO/SK2RJ).

Phase I: Translation to Portuguese

The translation of the STOPP-START screening tool will follow the Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes Measures[20]. We have already obtained permission from STOPP-START's authors to translate and validate the tool for Portuguese. We will recruit a key in-country consultant who is a native Portuguese and fluent English speaker and will be the main contact to perform and help with the translation. This consultant will also have a background in health research and experience in translating English documents. We will obtain two independent translations of the STOPP-START. One will be done by the key in-country consultant, and the other will be performed by a forward translator who is also a native Portuguese and fluent English speaker.

The two translations will be reconciled by the research team to obtain a final consensus translation that will be back-translated.

The back-translation (from Portuguese to English) will be done by a professional translator who is a native speaker of English and fluent speaker of Portuguese. This translator will have no prior knowledge of the original English version. Afterwards, the back-translation will be compared with the original to identify any relevant differences.

In the final step, the reconciled Portuguese STOPP- START version will be distributed to a group of 15 general practitioners to verify if there are any interpretation issues. The research team will analyse the results from the application of the STOPP-START tool to prepare the final version.

Phase II: Data Collection

Design

This will be a cross-sectional, analytical study.

Setting

The study will be conducted in a primary care center in the Centre Region of Portugal.

The health united is located in Aveiro. Five family doctors follow a total of 8165 patients; 1625 patients aged ≥65 years.

Sample Sizing

To calculate the sample size for the validation study, we used the function CIBinary of the kappaSize package of R software[24]. For the intrarater study, we obtained a sample size of 334 subjects considering the following parameters: estimated κ value: 0.68[25]; error margin: 0.1; prevalence of each item of the START criteria: 0.25; number of moments: 2; and significance level: 5%. In the inter-rater study, we obtained a sample size of 205 subjects considering the following parameters: estimated κ value: 0.68[25]; error margin: 0.1; prevalence of each item of the START criteria: 0.25; number of raters: 3; and significance level: 5%. The 205 patients for inter-rater assessment will be randomly selected from the 334 subjects used for the intrarater evaluation.

Study Procedures

Recruiting of patients

Patients will be randomly selected (independent sampling using computer-generated random digits) from a list of patients aged ≥65 years from a primary care centre. They will be invited by telephone to participate in the study. The investigator or a previously trained research associate will then interview the patients in the general practitioner office. Recruitment will continue until 334 patients are enrolled.

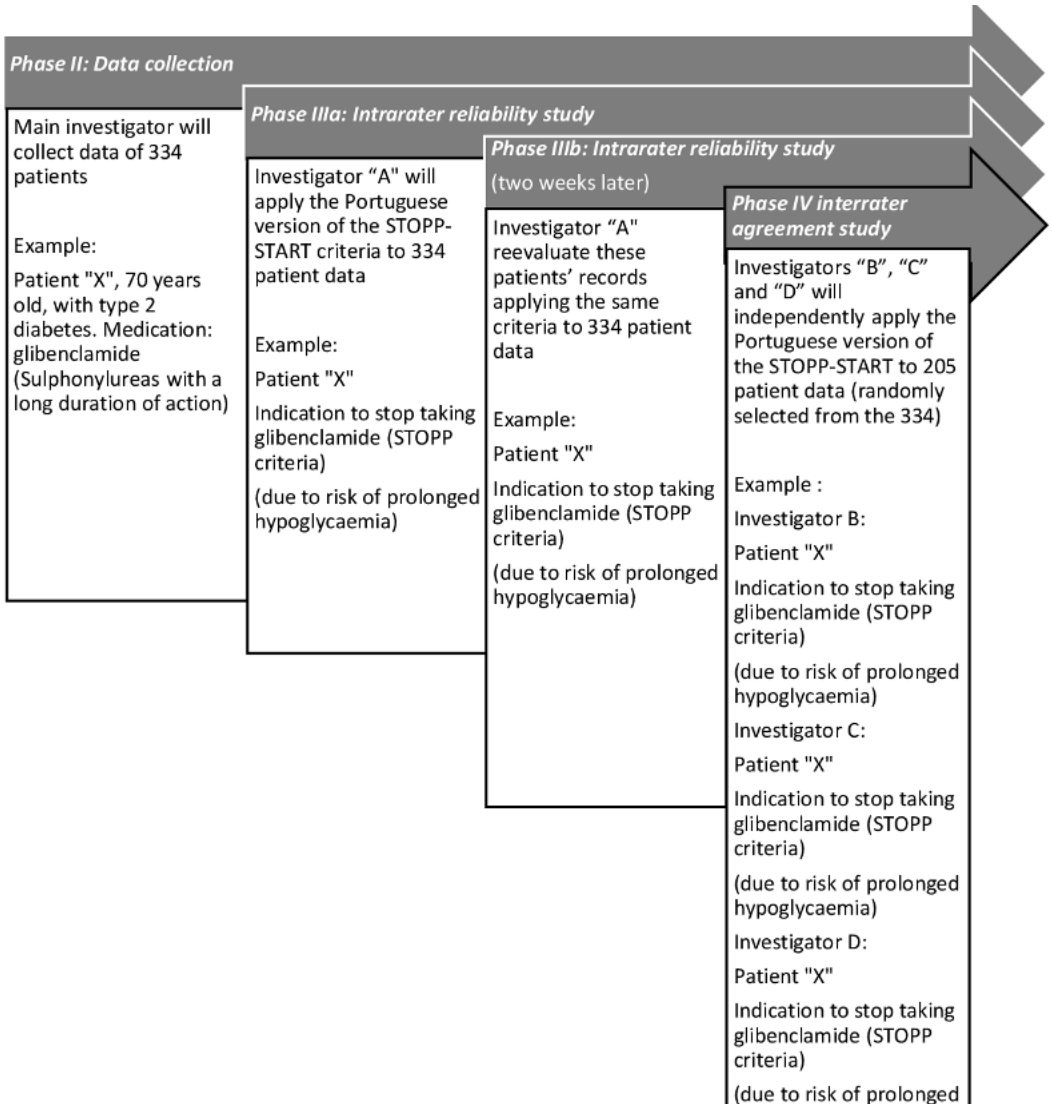

Figure 2 – Figure 1 from "START Screening Tool to Alert to Right Treatment; STOPP, Screenning Tool of Older People's Prescriptions"

STOPP, Screening Tool of Older People's Prescriptions

Exclusion criteria include incapacity or unwillingness to provide written informed consent, diagnostic of psychotic disorder, institutionalization and the presence of terminal illness.

At inclusion, the main investigator will collect sociodemographic patient data such as age, gender, educational level, labour status and marital status. Clinical data collection will include identification of total number of medications for chronic

diseases, any prescribed drugs, dosage, pharmaceutical dosage form and route of administration, the reason for taking medication, allergies, drug-related conditions and history of adverse drug reactions, and current or past conditions/diseases. A detailed list of current or past conditions/diseases that will be included is given II

The investigator will also collect the following information: presence or absence of ankle oedema, bone mineral density T-scores, history of influenza and pneumococcal vaccination, heart rate (beats per minute), and systolic blood and diastolic blood pressure (mm Hg).

The data are summarised in*Table 1*.

Table 6 - Table 1 from "Translation and Adaptation of the STOPP-START screening tool to Portuguese for detecting inappropriate prescriptions in older people: a protocol"

Table 1 – Patients data (phase II)

Patients' data	
Sociodemographic data	Gender
	Educational level
	Labour status
	Marital Status
Clinical Data	Number of medications for chronic diseases, prescribed drugs
	Pharmaceutical dosage form and route of administration, reason for taking medication
	Allergies
	Drug-related conditions
	Current or past conditions/diseases*
	Presence or absence ankle oedema
	Bone mineral density and T-scores
	History of influenza and pneumococcal vaccination heart rate (bpm)
	Systolic blood and diastolic blood pressure (mm Hg)
	Estimated glomerular filtration rate
	Serum K+ (mmol/L)
	Serum Na+ (mmol/L)

*Available at online supplemental appendix II.
bpm, beats per minute

Data Source

We will collect data using electronic health record consultations and clinical patient interviews.

Database

The information collected will not include information that might identify the patients. Each patient will be numbered from 1 to 334 to protect their identity.

To evaluate data obtained throughout the study, a data safety monitoring board will be set up that will be composed of two external investigators with board expertise in this clinical field and academic and scientific activities.

Following the Portuguese Clinical Research Law, all data recorded during the study will be stored for 5 years in a safe and proper place in the primary investigator's health centre after the closure of the investigation. All data containing participant codes will be destroyed after this period.

Phase III: Intrater reliability and agreement study

An independent researcher/family doctor (named investigator 'A') will apply the Portuguese version of the STOPP-START criteria to all the patients using the information collected in phase II.

Investigator 'A' is an independent researcher with more than 10 years of experience of clinical practice.

To ensure intrarater reliability and agreement, the same doctor will re-evaluate these patients' records applying the same criteria 2 weeks later to avoid recall bias.[26,27]

Phase IV: Inter-rater reliability and agreement study

Three independent investigators/family doctors (named investigators 'B', 'C' and 'D') will independently apply the Portuguese version of the STOPP-START using the data, collected in phase II, of 205 randomly selected participants[28]. These three physicians are based in different health units and they will only have contact with the corresponding author who will give them the comprised

data. Investigators 'B', 'C' and 'D' will independently assess the STOPP and START criteria in each of the 205 data sets and will be invited to give written comments if necessary.

Inter-rater agreement will be assessed by comparing the results of the three raters.

Statistical analysis

Data will be stored with Microsoft Excel software. Data analyses will be made with SPSS Statistics V.27.0 and the software R.

Categorical variables will be described by absolute and relative frequencies.

Continuous variables will be described by mean and SD if normally distributed or by median and IQR if not normally distributed. Normality will be assessed by observation of histograms and implementation of the Kolmogorov-Smirnov test.

Intrarater/inter-rater reliability will be measured using Cohen's κ coefficient and the respective 95% CI[22]. The Cohen's κ coefficient will be interpreted as poor ($k \leq 0.2$), fair ($0.21 \leq \kappa \leq 0.40$), moderate ($0.51 \leq \kappa \leq 0.6$), substantial ($0.61 \leq \kappa \leq 0.8$) and good ($0.81 \leq \kappa \leq 1.00$)[29]. Intrarater/inter-rater agreement will be assessed using agreement proportions and specific (positive and negative) agreement proportions and the respective 95% CI[22].

A p value less than or equal to 0.05 will be considered statistically significant.

Patient and public involvement

No patient or member of the public will be involved in the design of this protocol or the establishment of intervention and the outcome measures.

Discussion

Appropriate prescriptions for older patients are a quality standard for healthcare. General practitioners are the main prescribers and they struggle to identify PIM as well as potential prescribing omissions. The STOPP-START tool is an easy way to manage the care of older patients. It is easier for daily use when adapted for the language of the prescriber.

This study is innovative because it is the first development of a Portuguese version of the STOPP-START criteria. Our research will not be merely a translation but also an adaptation done by independent general practitioners that will potentially increase the use of this version in the primary care setting.

Our research has some limitations such as the fact that even though it will be Portuguese language adaption of the STOPP-START criteria, it is only focused on Portugal and may not apply to other countries where Portuguese is used. This adapted version of STOPP-START is exclusively focused towards primary healthcare centres.

ETHICS AND DISSEMINATION

Every participant will sign a written consent form (online supplemental appendix III). The identity of all participants will be protected throughout the study. The documents used to collect the data of the participants will contain only an identification code of each participant using a number from 1 to 334.

This protocol was approved on 30 July 2020 by the Ethics Committee of the Central Health Region of Portugal with the reference number 034-2020.

We intend to publish the full article in a related peer- reviewed journal, and results will also be disseminated in conference presentations, reports and in a PhD thesis.

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CHAPTER 6.

INNAPPROPRIATE PRESCRIPTIONS IN OLDER PEOPLE – TRANSLATION AND ADAPTATION TO PORTUGUESE OF THE STOPP/START SCREENING TOOL

Abstract

Inappropriate prescribing, which encompasses the prescription of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs), is a common problem for older people. The STOPP/START tool enables general practitioners, who are the main prescribers, to identify and reduce the incidence of PIMs and PPOs and appraise an older patient's prescribed drugs during the diagnosis process to improve the clinical care quality. This study aimed to translate and validate the STOPP/START screening tool to enable its use by Portuguese physicians. A translation-back translation method including the validation of the obtained Portuguese version was used. Intra- and inter-rater reliability and agreement analyses were used in the validation process. A dataset containing the information of 334 patients was analyzed by one GP twice within a 2-week interval, while a dataset containing the information of 205 patients was independently analyzed by three GPs. Intra-rater reliability assessment led to a Kappa coefficient (κ) of 0.70 (0.65–0.74) for the STOPP criteria and 0.60 (0.52–0.68) for the START criteria, considered to be substantial and moderate values, respectively. The results of the inter-rater reliability rating were almost perfect for all combinations of raters ($\kappa > 0.93$). The version of the STOPP/START criteria translated into Portuguese represents an improvement in managing the medications prescribed to the elderly. It provides clinicians with a screening tool for detecting potentially inappropriate prescribing in patients older than 65 years old that is reliable and easy to use.

1. INTRODUCTION

Today, it is globally accepted that adverse drug reactions (ADRs) are a public health problem and have a significant clinical impact related to morbidity and mortality, which results in the increased use of health services in developed countries[1,2]. ADRs are responsible for about 7% of all hospital admissions, many of which are considered preventable[2,3]. Additionally, about 2–3% of patients admitted with an ADR die as a result[2,4].

ADRs may occur in 6–20% of patients admitted to hospitals, increasing their hospitalization period; highly increasing the costs associated with healthcare[5]; indirectly impacting patients' and their families' economic, social context, and psychological well- being[6,7]; and leading to the discussion of patient participation and involvement in pharmacovigilance[8,9].

The number of older adults is increasing[10], as is their life expectancy[11,12], and these patients are more likely to have more than one chronic disease[13,14] and be prescribed multiple drugs, increasing their susceptibility to inappropriate medication use[15-21].

Inappropriate prescribing that encompasses potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) is a common problem for older people and is closely related to adverse events and ADRs[22]. Older adults are more prone to drug- related problems, as most take several medicines for multiple comorbidities, described as polypharmacy[23,24].

It is necessary to reduce PIMs and PPOs and improve clinical care quality[25]. The STOPP/START (Screening Tool of Older Persons' Prescriptions—STOPP; Screening Tool to Alert to Right Treatment—START) criteria for the use of potentially inappropriate medication in older people recognize the dual nature of inappropriate prescribing by including a list of PIMs (STOPP criteria) and PPOs (START criteria).

STOPP/START is a valid, reliable, and comprehensive screening tool that enables the prescribing physician to appraise an older patient's prescribed drugs in the context of their diagnosis[26]. Since the first publication of the STOPP/START criteria in 2008[26], the tool has been widely disseminated and

validated in many countries at different levels of healthcare (primary care, hospitals, nursing homes). The latest version (version 2) was published in 2014 and consists of 114 criteria, including 80 STOPP criteria and 34 START criteria[20,27]. These criteria are based on an up-to-date literature review and consensus validation among a European panel of experts[20]. The STOPP/START criteria were translated and adapted from English into several languages such as Czech, French[28-30], Italian, Spanish[31,32], and Dutch[33] to facilitate the local application of the criteria worldwide and have had a positive impact on patient evaluation[26].

This tool identifies potentially inappropriate prescriptions (PIPs)[34,35], identifying potentially inappropriate medicines through the STOPP criteria and identifying potential prescription omissions through the START criteria. The prevalence of patients with at least one instance of PIP identified by the STOPP criteria ranges from 21%[36] to 79%[37]. However, this range should be interpreted cautiously due to the heterogeneity of the sample population and study design between the different studies where this tool was assessed. The START criteria have identified at least one instance of PPO in 23%[36] to 74%[37] of patients.

A recent comparison of tools used to identify PIMs showed that the STOPP version 2 criteria identified substantially more PIMs than the EU (7)-PIM list[38], PRISCUS— Potentially Inappropriate Medications in the Elderly list[39-41], FORTA[39,40], and Beers criteria[25,42-46]. The STOPP/START criteria were found to be significantly associated with detecting adverse events in acutely ill older people, unlike the Beers criteria[20,42-45]. Compared to the Beers criteria or the prescribing indicators provided in the Elderly Aus- tralia criteria, the number and scope of drug-related problems identified were found to be best represented by the STOPP/START criteria[20,47,48]. Another advantage of this tool is that it considers PIMs and the indications to start an appropriate medication (START)[18].

A previous study from Gallagher et al., concluded that the STOPP/START criteria are generalizable across different European countries and languages[49]. Despite this, in other countries, such as in those with resource-limited healthcare settings, the original STOPP/START criteria might not be directly applicable; thus, modified versions of the STOPP/START criteria have been

developed and validated recently[24]. In Portugal, this tool has already been used by Portuguese authors, but the translation and adaptation of the criteria have never been carried out, and the original tool is still used[25,50-53]. The current study aimed to translate and validate the STOPP/START screening tool to enable its use by Portuguese general practitioners/family physicians.

2. Materials and Methods

This study was conducted in four phases. The first phase (phase I) was the translation and adaptation of the STOPP/START screening tool to the Portuguese language, followed by patient data collection (phase II). Phase III consisted of an intra-rater reliability and agreement study, and phase IV consisted of an inter-rater reliability and agreement study. Pre- registration on the 'Open Registries Network' was conducted (DOI10.17605/OSF.IO/SK2RJ (accessed on 31 March 2021), and the translation and adaptation of the STOPP/START screening tool to Portuguese has been described elsewhere[18].

2.1. Phase I: Translation and Adaptation of the STOPP/START Screening Tool to the Portuguese Language

The translation and adaptation of the STOPP/START screening tool followed the Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient- Reported Outcomes Measures[30]. The adaptation and translation were carried out based on the 2014 O'Mahony et al., version of STOPP/START[20]. Permission from the STOPP/START's authors to translate, adapt, and validate this tool for use in Portuguese was obtained by email. The final version was distributed to 15 general practitioners to verify if there were any interpretation issues and improve clarity. The research team analyzed the results obtained from applying the STOPP/START tool and prepared the final version. As a translation was needed, the chance for possible disagreements between raters was reduced by validating these translations before studying the intra-rater and inter-rater agreements. The detailed procedure was published previously in the protocol[18].

2.2. Phase II: Data Collection of Patient Data

Patients were randomly selected from a list of patients aged > 65 years old from a primary care center in the Centre Region of Portugal, following which a total of 8165 patients were followed, with 1625 aged over 65 years old. The sample size was calculated in the published protocol, and 334 subjects were randomly selected to participate in the study[26,54]. Exclusion criteria included incapacity or unwillingness to provide written informed con- sent, diagnosis of psychotic disorder, institutionalization, and the presence of terminal illness. Patients were interviewed during previously scheduled medical appointments. Every participant signed a written consent form (Supplementary Materials File S1). The identity of all participants was protected throughout the study.

Sociodemographic data such as age, sex, and educational level were collected and are shown in *Table 1*. Clinical data were collected by consulting health record registries and conducting interviews of clinical patients, including the identification of the total number of medications used for chronic diseases, any prescribed drugs, dosage, pharmaceutical dosage, pharmaceutical form and route of administration, reason for taking medication, allergies, drug-related conditions, history of adverse drug reactions, and current or past conditions/diseases. Other clinical information was also collected and described in the protocol but not used in the adaptation of the STOPP/START tool[18]. The information collected was input into a database, each patient was numbered from 1 to 334 by the main investigator, and the record of the coding was stored offline in an Excel 2016® spreadsheet. All data recorded during this study will be stored for 5 years after the closure of the investigation, following the Portuguese Clinical Research Law. After this period, data containing participant codes will be destroyed.

2.3. Phase III: Intra-Rater Reliability and Agreement Study

As previously proposed by Kottner et al.[55], reliability may be defined as the ability of a measurement to differentiate among subjects or objects, comprising the ratio of variability between subjects or objects to the total variability of all measurements in the sample[56,57]. Intra-rater agreement

assesses the extent to which the two responses from the same rater are concordant[58]. By definition, intra-rater reliability refers to the consistency of data recorded by the same rater, using the same scale, classification, instrument, or procedure, to assess the same subjects or objects at different times one rater over several trials. It is best determined when multiple trials are administered over a short period[55]. An independent researcher physician (named investigator/rater 'A') applied the Portuguese version of the STOPP/START criteria to all patient data collected in phase II. The investigator/rater 'A' was a family doctor with more than 10 years of experience in primary care, which included caring for and making daily prescriptions for older adults. To ensure intra-rater reliability and agreement, two weeks later, investigator A re-administered the tool. Both assessments of rater 'A' were used to study the intra-rater reliability.

Table 7 - Table 1 from "Inappropriate Prescriptions in Older People – Translation and Adaptation to Portuguese of the STOPP-START Screening Tool"

Table 1. Characteristics of patients (n = 334)

Variable	N (%)
Age, years mean (SD); min-max	74.2 (6.9); 65–99
65–69 years	105 (31.4%)
70–74 years	71 (21.3%)
75–79 years	78 (23.4%)
80–84 years	50 (15.0%)
85+ years	30 (9.0%)
Sex	
Women	159 (47.6%)
Men	175 (52.4%)
Educational level	
Early childhood, primary and lower secondary education (level 0–2)	316 (94.6%)
Upper secondary and post-secondary non-tertiary education (levels 3–4)	17 (5.1%)
Short-cycle tertiary education, Bachelor's, Master's, or Doctorate (levels 5–8)	1 (0.3%)
Number of medicines used	
0–1	57 (17.1%)
2 to 4 (Minor polypharmacy)	66 (19.8%)
5 to 9 (Major polypharmacy)	210 (62.8%)
10+ (Severe polypharmacy)	1 (0.3%)

Discrepancies in totals are due to rounding

2.4. Phase IV: Inter-Rater Reliability and Agreement Study

Inter-rater reliability refers to the consistency of data recorded by different raters, using the same scale, classification, instrument, or procedure, to assess the same subjects or objects. Inter-rater agreement assess the extent to which the responses of two or more independent raters are concordant[58]. In this specific study, intra-rater and inter-rater reliability assist in determining if the measurement tool produces results that can be used by a clinician to make decisions confidently[55].

Three independent researchers (named investigators/raters 'B', 'C', and 'D') independently applied the Portuguese version of STOPP/START using the data collected in phase II. The investigators/rater's 'B', 'C', and 'D' were family doctors with more than 10 years of experience in primary care. For the total of 334 subjects who participated in the intra-rater study, 205 patients were randomly selected for the inter-rater assessment[59]. These three physicians were independent investigators and only had contact with the authors to access the collected data. These investigators independently assessed the STOPP/START criteria in each of the 205 patients and were invited to provide written comments if necessary. Inter-rater agreement was assessed by comparing the results of the three raters. Between raters 'B', 'C', and 'D', an inter-rater reliability test was performed. Inter-rater reliability assessment is useful because observers will not necessarily interpret answers (or tools) in the same way and may disagree on how the constructed tool is used[60,61].

2.5. Statistical Analysis

Data were stored with Microsoft Excel 2016® software (Microsoft Corporation, Redmond, WA, USA). Data analyses were conducted using SPSS® V.27.0 (SPSS Inc, Chicago, IL, USA) and R. Studio® V.1.3093 (Integrated Development for R. Studio, PBC, Boston, USA, MA, USA). Categorical variables were described using absolute and relative frequencies, *n* (%). Quantitative variables were summarized by means and their respective standard deviations (SDs), along with minimum and maximum values (min-max). According to the "Guidelines for reporting reliability and agreement studies", reliability analyses and agreement analyses (intra- and inter-rater) were performed using Kappa statistics and proportions of a specific agreement, respectively[62-64]. The Kappa statistics were interpreted as poor if the score was ≤0.2, fair if it was 0.21–0.40, moderate if it was 0.51–0.6, substantial if it was 0.61–0.8, and good if it was 0.81–1.00. The proportion of specific agreement distinguishes agreement on positive (PPos) or negative (Pneg) proportions, which might have different implications in clinical practice[65]. The 95% confidence intervals (95% CI) were presented for Kappa statistics and agreement proportions[55].

Kappa statistics were used for the calculation of both inter- and intra-rater reliability[66]. The Kappa statistic is a coefficient of reliability for categorical data[67]. As the Kappa coefficient is known to be affected by rare observations, it may not always reflect the true agreement rates and will provide an underestimation of the actual agreement[68]. A simple solution for this problem is calculating the proportions of agreement and separating the agreement rates into positive and negative agreements, thus making it easier for readers to interpret the results[63,69].

3. RESULTS

A total of 334 patients were enrolled in this study. The patients' characteristics (age, sex, educational level, and number of medicines used) are described in *Table 1*.

Educational level was grouped according to the International Standard Classification of Education (ISCED 2011)[70]. The number of medicines used was grouped according to the definition of polypharmacy, grouping the number of medicines[23,71-73].

Intra-rater reliability and agreement involved the analysis of Rater A's evaluation of 334 patients' records and re-evaluation after a 2-week interval. Results are reported in *Table 2* (STOPP) and *3* (START). Inter-rater reliability and agreement analyses were performed by three different raters ('B', 'C', and 'D') who evaluated 205 randomized patients from the database. Each rater evaluated the same patients to allow for their comparison. The results obtained for the inter-rater reliability and agreement using the STOPP and START tools are shown in *Tables 2* and *3*, respectively.

Table 8 - Table 2 from "Inappropriate Prescriptions in Older People – Translation and Adaptation to Portuguese of the STOPP-START Screening Tool"

Table 2 - Intra- and inter-rater reliability and agreement based on the analysis of the STOPP criteria

		Agreement (%)		Reliability
STOPP criteria	Rater Combination	Ppos + (95% CI)	Pneg + (95% CI)	Kappa (95% CI)
Intra-rater	Rater A Rater A	94.2 (93.1–95.1)	75.2 (70.9–79.1)	0.70 (0.65–0.74)
Inter-rater	Rater B Rater C	99.8 (99.4–99.9)	98.9 (97.1–99.7)	0.99 (0.97–1.00)
	Rater B Rater D	99.6 (99.1–99.8)	97.8 (95.5–99.1)	0.97 (0.95–0.99)
	Rater C Rater D	99.5 (99.1–99.8)	97.5 (95.0–98.8)	0.97 (0.95–0.99)
	Rater B Rater C Rater D	99.6 (99.3–99.8)	98.1 (96.6–99.2)	0.98 (0.94–1.00)

+ **Ppos** agreement on positive proportions + **Pneg** agreement on positive negative proportions

Table 9 - Table 3 from "Inappropriate Prescriptions in Older People – Translation and Adaptation to Portuguese of the STOPP-START Screening Tool"

Table 3 - Intra- and Inter-rater reliability and agreement from the analysis of the START criteria

		Agreement (%)		Reliability
START Criteria	Rater Combination	Ppos + (95% CI)	Pneg + (95% CI)	Kappa (95% CI)
Intra-rater	Rater A Rater A	88.2 (85.4–90.6)	71.1 (64.5–76.8)	0.60 (0.52–0.68)
Inter-rater	Rater B Rater C	98.7 (97.3–99.4)	94.4 (88.6–97.7)	0.93 (0.87–0.99)
	Rater B Rater D	98.7 (97.3–99.4)	94.4 (88.6–97.7)	0.93 (0.87–0.99)
	Rater C Rater D	99.1 (97.9–99.7)	96.1 (90.1–98.7)	0.95 (0.91–1.00)
	Rater B Rater C Rater D	98.8 (97.9–99.6)	94.9 (90.8–98.2)	0.94 (0.87–1.00)

+ Ppos agreement on positive proportions **+ Pneg** agreement on positive negative proportions

For the STOPP criteria, the intra-rater reliability showed a Kappa coefficient of 0.70 [95% CI 0.65-0.74], considered substantial; the positive and negative proportions of agreement obtained were 94.2% [95% CI 93.1-95.1] and 75.2% [95% CI 70.9-79.1], respectively. The results obtained for the inter-rater reliability were almost perfect, with κ near to one in all possible combinations of raters. Inter-rater agreement determines the agreement between pairs of raters and all raters' judgments regarding the STOPP criteria.

For the START criteria, the intra-rater reliability showed a Kappa coefficient of 0.60 [0.52–0.68], considered a moderate value; the positive and negative proportions of agreement obtained were, respectively, 88.2% [85.4–90.6] and 71.1% [64.5–76.8]. The inter- rater reliability results were almost perfect, with κ near to one in all possible combinations of raters. Inter-rater agreement determines the agreement between pairs of raters and all raters' judgments regarding the START criteria.

The final version of the Portuguese adaptation of STOPP/START is presented in Supplementary Material File S2.

4. Discussion

This is to the best of our knowledge, the first study to translate and adapt the STOPP/START screening tool to Portuguese. The intra-rater reliability and inter-rater reliability scores obtained were not inferior to those obtained in previous studies conducted in other languages[28-33].

When testing reliability, several approaches are taken to determine consistency[74,75]. However, according to Innes et al., test–retest reliability, intra-rater reliability, and inter-rater reliability are the most common measures used among work-related assessments[74,75].

The first source of intra-rater inconsistency could be explained by various factors related to the assessment process. Rater A presented a high disagreement between two STOPP and START criteria evaluations. A major explanation was based on the analysis of the discrepancies. From 129 discrepancies seen between the first and second evaluation, 94 were related to proton pump inhibitors (F2 or A1 criteria without further investigation). In the second evaluation, with a better knowledge of the tool, the drug was properly assessed. Out of 119 discrepancies found in the evaluation on the START criteria, 51 were related to the introduction of vaccines in the second evaluation (I1 or I2 criteria were used). According to previous studies, a high level of familiarity is required to efficiently apply the STOPP/START criteria in clinical practice[49]. Additionally, raters could differ con- cerning their experience, specialties, and professional skills and have different perceptions regarding the knowledge required to use a particular item of the assessment tool. It is therefore important to highlight that the professionals that perform medication reviews with the STOPP/START tool should receive adequate training in order to use the tool appropriately[76,77].

One strength of this study is its innovation, with it representing the first development of a Portuguese version of the STOPP/START criteria. Our research was not merely a translation, but also an adaptation carried out by independent general practitioners that will hopefully increase the use of this version in the primary care setting. To ensure intra-rater reliability and agreement, the same doctor re-evaluated patients' records by applying the same criteria 2 weeks later, avoiding recall bias. Additionally, this study provides evidence for a near-perfect inter-rater reliability, meaning that raters almost always agree on whether to exclude/include medicines, although the reasons for these decisions were not necessarily similar. Finally, this version translated into Portuguese can be used by general practitioners or any other medical practitioner and could be used in countries where Portuguese is the main language. However, the differences in healthcare systems between countries; the different ranges of medicines

available; and differences in population characteristics, such as genetic or racial differences, should be considered.

One potential limitation was related to the fact that the adapted version of STOPP/START exclusively focuses on primary healthcare centers. The authors deliberately did not include patients with specific pathologies. It is important to clarify that this tool may not be appropriate for use in all population groups or in different healthcare settings, and the assessment tool should be evaluated in future studies, including in other populations with specific pathologies and in different contexts.

Furthermore, some of the randomized patients (n = 26, 8%) did not have any drugs prescribed, which would have reduced discrepancies between the raters when evaluating the STOPP criteria. Another potential limitation is the fact that the current tool was originally published in 2014, which means that there may be new medication and/or additional therapeutic indications that do not fit the current tool. Finally, the raters' decision to stop or start a drug based on this tool was a dichotomous decision and was not validated as either right or wrong from a clinical point of view. No assessment of clarity was performed, so a quality appraisal study should be conducted in the future to improve the clarity of clinical practice guidelines on a language level and enhance its clinical applicability[78].

In addition, using this tool, raters can point out different reasons for withdrawing or adding drugs without this changing the final decision. Since the criteria were applied to data from files in the absence of a clinical evaluation of patients by raters and prescriptions are subject to a certain variation in interpretation concerning the clinical heterogeneity observed in the elderly population, clinical evaluation was not performed by PPOs and the reasons for stopping and starting drugs were not compared[79].

5. Conclusions

The major research result of the current study was the adaptation of the STOPP/START (2014) criteria into Portuguese.

The objective of our research was not to test the tool in a Portuguese population. The use of this tool in this context may not lead to clinical differences for patients, or, at least, this was not the main objective for its use in this study.

The STOPP/START criteria have been proven to be a good tool for detecting potentially inappropriate prescriptions and improving prescription quality in older people in all healthcare settings, therefore leading to improved quality of life in patients, reducing the incidence of PIMs and PPOs, and improving clinical care quality. This research provides clinicians with a screening tool with which to detect potentially inappropriate prescribing in patients older than 65 years old that is easier to use for Portuguese native speakers. The tool is also useful for improving the training of medical students in managing polypharmacy[76] and can have a positive economic impact by reducing medicine expenditure in older patients[80,81]. This version in Portuguese represents a step forward in improving the management of medications in the elderly. The adaption of this tool will be useful not only for Portugal but also for other Portuguese-language countries.

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CHAPTER 7.
CONCLUSIONS AND FINAL REMARKS

Main conclusions

The main conclusions from the four papers included in this thesis can be summarized:

- CDS tools consistently reduced the number of potentially inappropriate prescriptions started;
- CDS tools reduced mean number of potentially inappropriate prescriptions per patient;
- CDS tools increased potentially inappropriate prescriptions discontinuation and drug appropriateness;
- The version of the STOPP/START criteria translated into Portuguese represents an improvement in managing the medications prescribed to the elderly;
- The translated STOPP/START screening tool provides Portuguese clinicians with a screening tool for detecting potentially inappropriate prescribing in patients older than 65 years old that is reliable and easy to use.

Analysis of Main Conclusions

To summarize the findings and have final reflections we will start by answering to our research questions.

Research question 1 and 2: In older adults, do CDS tools reduce potentially inappropriate medications? In older adults, do CDS tools improve clinical outcomes?

Previous studies reviewed strategies to deprescribe, such as multidisciplinary team and pharmacist medication reviews but did not focus on (CDS) Tools and reported substantial heterogeneity [1–3]. But we only found a 2012 review that focused on CDS [4].

Therefore, our study was a much-needed review to assess the impact of CDS tools on PIM and PIP in older patients.

Our study concluded that the use of CDS tools had a positive impact on PIP in the majority of the studies included in our analysis.

In fact, we proved that CDS tool consistently led to a reduction in the number of potentially inappropriate prescriptions started and mean number of PIPs per patient.

CDS tools also had an impact on deprescription of PIPS discontinuation and increased drug appropriateness.

Regarding clinical outcomes such as adverse drug reactions, length of stay, and mortality we could not find evidence to support the CDS tools.

Our review has some limitations due to the fact we included not only random clinical trials (RCTs) but also pre/post studies and a cross-over study. We considered that non-RCT studies have a high risk of bias. Nevertheless, we could have analyzed these studies with the ROBINS-I Risk of Bias In Non-randomised Studies of Interventions[5].

We also focused our search on articles having PIP modification outcomes; however, we may have missed studies addressing potentially inappropriate medications (PIM). A meta-analysis was not possible due to the significant heterogeneity among the systems used and the definitions of outcomes.

Our strengths were the fact that we have followed the Cochrane Collaboration Handbook[6] and the fact that no new references were found from searches in the grey literature, pertinent scientific

meeting books of abstracts, and the included studies' list of references, which suggests that our search strategy was exhaustive.

We also found five more RCTs[7–11] than the previously published revisions. These studies added evidence that support CDS tools regarding well-being and patients' beliefs, reduction of adverse drug reactions, and users' perspectives.

AIM: TO TRANSLATE AND VALIDATE A PORTUGUESE VERSION OF THE STOPP/START SCREENING TOOL

We identified many screening tools for the identification of the potential inappropriate medication such as the Medication Appropriateness Index[12], the Garfinkel[13], the LESS-CHRON criteria[14], the DBI[15], the European Union (EU)-PIM[7], the PRISCUS list[16], the FORTA (Fit fOR The Aged) IList[17,18], and the Beers criteria of the American Geriatrics Society (AGS)[19].

We focused our research on the STOPP/START that was first published in 2008[20] and was updated on 2014 (version 2)[21].

The STOPP/START has the advantage of identifying both PIMs (STOPP criteria) and potential prescribing omissions (START criteria), such as vaccines.

Therefore, our suggestion is that the STOPP/START is more useful than other criteria for the clinician who is taking care of older patient.

Despite its importance, our research discovered that there was no Portuguese adaptation of the tool which represented a missing information for doctors and patients.

We conducted a four phases study: The first phase (phase I) was the translation and adaptation of the STOPP/START screening tool into Portuguese followed by patient data collection (phase II). Phase III consisted of an intra-rater reliability and agreement study, and phase IV consisted of an inter-rater reliability and agreement study.

Our research was not merely a translation but also an adaptation carried out by independent doctors with clinical experience

Implications for Clinical Practice

Assuming that we interact with patients through digital technology[22] and that good prescribing includes deprescribing[23], we can now be more confident with the fact that computer decision tool help the doctors to identify potential inappropriate medication as well as prescription omissions.

The STOPP/START tool was adapted to Portuguese for the first time and can now be freely consulted. This document is useful not only for doctors but also for community pharmacists, nurses, and other healthcare professionals.

This tool is also important for the process of empowering patients and their caretakers. In fact, they can for the first time consult and actively check for the evidence that supports their medications.

Therefore, we hope that our work can help the shared decision of stop or start a medication in a clinical scenario.

Implications for Medical Education

The quaternary prevention is an evidence-based concept[24] and medical students and junior doctors should be able to define it correctly. That knowledge is more easily retained with problem-based learning.

The process of solving a clinical scenario is important to complement education and to simulate a real clinical scenario.

Our work was already used as a tool in a workshop for junior family doctors. In fact, the STOPP/START tool was applied and was useful for identifying potentially inappropriate medications and the evidence that supports the decision to stop the medication.

Implication for Research

Researcher interest is growing regarding the rational prescription of older adults[25–27].

Our studies add evidence for the complex process of appropriate prescription of older adults.

In fact, we found that computerized decision support tools may reduce potentially inappropriate prescriptions and potentially inappropriate medications.

More randomized controlled trials are needed to assess the impact of computerized decision support tools both in primary and secondary health care.

It is also important to implement studies with clear clinical outcomes such as mortality, hospital admissions and adverse drug reactions.

The future of research should also focus on high-quality and long-term clinical trials that measure patient-important outcomes, focus on patient involvement and perspectives, and generate evidence that helps implementing interventions in clinical practice[28].

We plan to design and accomplish a successful RCT for ordering tests[29]. In that study, one group of medical doctors would have a modified electronic prescription that suggests witch medications to stop or start based on the STOPP/START criteria and the control group will have access to the usual standard version of the software.

We also plan to implement research regarding junior doctors' perspectives in deprescribing and its importance on medical education.

Implication for Policymakers

Taking quality and secure care of older patients is a goal for society. Policymakers must decide the best use of the available resources to achieve such a goal.

Our investigation adds evidence to the decision by governments to implement computer decision support to help doctors to achieve evidence-based prescriptions.

Reducing costs by stopping a medication that is potentially inappropriate are important for patients and their families[30].

The STOPP/START tool available in Portuguese through our study could be a useful management tool for organizations that represent patients and health care ministries. In fact, it is an important support for future deprescribing guidelines[31, 32].

We proposed the integration of the Portuguese version of the STOPP/START tool into the software used by Portuguese doctors. This updated electronic prescription would contribute to the increase in both quality and safety of prescriptions. With this tool the prescription of older adults would be mainly of evidence-based. We propose that this software may contribute to the reduction of adverse drug reactions, hospitalizations, and morbidity and mortality.

With increasing healthcare related costs, it is a policymaker's duty to carefully allocate the available resources.

Our research gives policymaker's important tools that may help to reduce drug costs and increase effectiveness.

FINAL REMARKS

The present work combined different methods to answer the research questions.

That fact allowed the candidate the opportunity to learn the skills necessary to design two protocols: one for the systematic review and the other for the translation and adaptation of a tool.

The importance of peer review of the methods that are the most important section of an investigation are highlighted.

The success of this work is visible through the four publications that was only possible due to the team of researchers that generously accepted this challenge even during the coronavirus 2019 (COVID 19) pandemic.

The candidate hopes that this work is just the beginning of a line of research regarding evidence-based prescriptions for older adults. Many questions remain unanswered.

I was a medical student when I first came across the challenge of managing medications of older patients.

After realizing the magnitude of the problem, the candidate hopes to continue to pursuit the goal of helping patients through clinical and research routes.

Future research includes should focus on developing useful CDS tools software and more robust RCT´s focusing on patient-oriented outcomes.

This work is a small step along that path.

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APPENDICES

Appendix 1.

Portuguese Version of the STOPP/START Screening Tool (Supplementary file of article IV)

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MDPI

Supplementary Material S2

Inappropriate prescriptions in older people - Translation and adaptation to Portuguese of the STOPP/START screening tool

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Translation and adaptation from: [20] - O'Mahony D et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and Ageing. 2014;44(2):213-8.

Screening Tool of Older Persons' Prescriptions (STOPP) (Ferramenta de avaliação da prescrição de idosos) – versão 2 (2014).

As seguintes prescrições são potencialmente inadequadas para administração em doentes com 65 anos ou mais.

Secção A: Indicação de medicação

1. Qualquer medicamento prescrito sem indicação clínica baseada em evidência.
2. Qualquer medicamento prescrito para além da duração recomendada, sempre que a duração do tratamento estiver bem definida.
3. Qualquer prescrição de classe de medicamentos em duplicado, por exemplo, dois AINE (anti-inflamatórios não esteroides), (ISRS) inibidores seletivos da recaptação da serotonina (ISRS), diuréticos da ansa, inibidores da ECA (enzima conversora da angiotensina), anticoagulantes, em simultâneo (a otimização da monoterapia com uma única classe de medicamentos deve ser observada antes de considerar um novo agente).

Secção B: Sistema cardiovascular

1. Digoxina para insuficiência cardíaca com função ventricular sistólica normal (sem evidência clara de benefícios).
2. Verapamil ou diltiazem na insuficiência cardíaca classe III ou IV da *New York Heart Association* (NYHA) (pode agravar a insuficiência cardíaca).
3. Bloqueadores beta em combinação com verapamil ou diltiazem (risco de bloqueio cardíaco).
4. Bloqueador beta com bradicardia (<50/min), bloqueio auriculoventricular de segundo grau ou bloqueio auriculoventricular completo (risco de bloqueio atrioventricular completo, assistolia).
5. Amiodarona como terapêutica antiarrítmica de primeira linha em taquiarritmias supraventriculares (risco mais elevado de efeitos secundários do que bloqueadores beta, digoxina, verapamil ou diltiazem).
6. Diuréticos da ansa como tratamento de primeira linha para hipertensão (alternativas disponíveis mais seguras e mais eficazes).
7. Diuréticos da ansa para edema maleolar sem evidência clínica, bioquímica ou radiológica de insuficiência cardíaca, insuficiência hepática, síndrome nefrótica ou insuficiência renal (elevação das pernas e / ou compressão elástica degressiva, normalmente, mais adequadas).
8. Diuréticos tiazídicos na presença de hipocalemia significativa (ou seja, potássio (K+) sérico <3,0 mmol/l), hiponatremia (ou seja, sódio (Na+) sérico <130 mmol/l), hipercalcemia (ou seja, cálcio sérico corrigido >2,65 mmol/l) ou com antecedentes de gota (hipocalemia, hiponatremia, hipercalcemia e gota podem ser desencadeados por diuréticos tiazídicos).
9. Diuréticos da Ansa para tratamento da hipertensão na presença de incontinência urinária (pode exacerbar a incontinência).
10. Anti-hipertensores de ação central (por exemplo: metildopa, clonidina, moxonidina, rilmenidina, guanfacina), exceto em caso de intolerância clara a, ou falta de eficácia de, outras classes de anti-hipertensores (os anti-hipertensores de ação central são, geralmente, menos bem tolerados por pessoas mais idosas do que por pessoas mais jovens).

11. Inibidores da ECA (enzima conversora da angiotensina) ou bloqueadores do recetor da angiotensina em doentes com hipercalemia.
12. Antagonistas da aldosterona (por exemplo, espironolactona, epleronona) em simultâneo com medicamentos preservadores do potássio [por exemplo, IECA (inibidores da enzima conversora da angiotensina), ARB (bloqueadores do recetor da angiotensina), amilorida, triantereno)] sem monitorização do potássio sérico (risco de hipercalemia grave, ou seja, >6,0 mmol/l – o potássio sérico deve ser monitorizado regularmente, ou seja, pelo menos, de 6 em 6 meses).
13. Inibidores da fosfodiesterase 5 (por exemplo, sildenafil, taladafil, vardenafil) na insuficiência cardíaca grave caracterizada por hipotensão, ou seja, pressão arterial sistólica <90 mmHg, ou terapêutica conjunta com nitratos para angina de peito (risco de colapso cardiovascular).

Secção C: Medicamentos antiagregantes/anticoagulantes

1. Tratamento a longo prazo com ácido acetilsalicílico em doses superiores a 160 mg por dia (risco aumentado de hemorragia, sem evidência de aumento da eficácia).
2. Ácido acetilsalicílico com antecedentes de doença ulcerosa péptica sem terapêutica concomitante com IBP (inibidores da bomba de protões) (risco de recidiva de doença ulcerosa péptica).
3. Ácido acetilsalicílico, clopidogrel, dipiridamol, antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa com presença significativa de risco de hemorragia, ou seja, hipertensão grave não controlada, diátese hemorrágica, hemorragia espontânea recente não habitual (risco elevado de hemorragia).
4. Ácido acetilsalicílico mais clopidogrel como prevenção de AVC (Acidente Vascular Cerebral) secundário, a menos que o doente tenha um *stent* ou *stents* coronário(s) introduzido(s) nos 12 meses anteriores ou simultânea síndrome coronária aguda, ou tenha um elevado grau de estenose carotídea sintomática (não há evidência de benefício acrescentado à monoterapia com clopidogrel).
5. Ácido acetilsalicílico em combinação com antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa em doentes com fibrilhação auricular crónica (sem benefício acrescentado com o ácido acetilsalicílico).
6. Agentes antiagregantes com antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa em doentes com doença coronária, cerebrovascular ou arterial periférica estável (sem benefício acrescentado com terapêutica dupla).
7. Ticlopidina em quaisquer circunstâncias (clopidogrel e prasugrel têm eficácia similar, evidência mais sólida e menos efeitos secundários).
8. Antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa para primeira trombose venosa profunda sem fatores de risco permanentes (por exemplo, trombofilia) durante > 6 meses (sem acréscimo comprovado de benefícios).
9. Antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa para primeira embolia pulmonar sem fatores de risco permanentes (por exemplo, trombofilia) durante > 12 meses (sem acréscimo comprovado de benefícios).
10. AINE em combinação com antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa (risco de grande hemorragia gastrointestinal).
11. AINE conjuntamente com agente(s) antiplaquetário(s) sem profilaxia com IBP (risco aumentado de doença ulcerosa péptica).

Secção D: Sistema nervoso central e medicamentos psicotrópicos

1. Antidepressivos tricíclicos (ADT) com demência, glaucoma de ângulo fechado, anomalias da condução cardíaca, prostatismo ou antecedentes de retenção urinária (risco de agravar estas condições).
2. Início de ADT como tratamento antidepressivo de primeira linha (risco mais elevado de reações adversas ao medicamento com ADT do que com inibidores seletivos da recaptação da serotonina (ISRS) ou inibidores seletivos da recaptação da serotonina e da noradrenalina (ISRSN).
3. Neurolépticos com efeitos moderadamente marcados antimuscarínicos/anticolinérgicos (clorpromazina, clozapina, flupentixol, flufenazina, pipotiazina, promazina, zuclopentixol) com antecedentes de prostatismo ou retenção urinária (risco elevado de retenção urinária).
4. Inibidores seletivos da recaptação da serotonina (ISRS) com atual ou recente hiponatremia significativa, ou seja, Na+ sérico < 130 mmol/L (risco de exacerbar ou desencadear hiponatremia).

5. Benzodiazepinas durante ≥ 4 semanas (sem indicação para tratamento mais longo; risco de sedação prolongada, confusão, dificuldades de equilíbrio, quedas, acidentes de viação; todas as benzodiazepinas devem ser retiradas gradualmente se tomadas por mais de 4 semanas, porque existe o risco de provocar a síndrome de abstinência de benzodiazepinas se a administração das mesmas for interrompida abruptamente).
6. Antipsicóticos (ou seja, outros além da quetiapina ou clozapina) em doentes com parkinsonismo ou demência por corpos de *Lewy* (risco de sintomas extrapiramidais graves)).
7. Anticolinérgicos/antimuscarínicos para tratar efeitos secundários extrapiramidais de medicação neuroléptica (risco de toxicidade anticolinérgica).
8. Anticolinérgicos/antimuscarínicos em doentes com *delirium* ou demência (risco de exacerbar dificuldades cognitivas).
9. Antipsicótico neuroléptico em doentes com sintomas psicológicos e comportamentais da demência (SPCD), a menos que os sintomas sejam graves e outros tratamentos não farmacológicos tenham falhado (risco aumentado de AVC).
10. Neurolépticos como hipnóticos, a menos que os distúrbios do sono sejam devidos a psicose ou demência (risco de confusão, hipotensão, efeitos secundários extrapiramidais, quedas).
11. Inibidores da acetilcolinesterase com antecedentes conhecidos de bradicardia persistente (<60 batimentos/min), bloqueio cardíaco, ou síncope inexplicada, ou tratamento conjunto com medicamentos que reduzem o ritmo cardíaco, tais como betabloqueadores, digoxina, diltiazem, verapamil (risco de falha da condução cardíaca, síncope e lesão).
12. Fenotiazinas como tratamento de primeira linha, dado que existem alternativas mais seguras e mais eficazes (as fenotiazinas têm efeito sedativo, têm uma toxicidade antimuscarínica significativa em pessoas idosas, à exceção de proclorperazina para náuseas/vómitos/vertigens, clorpromazina para alívio de soluços persistentes e levomepromazina como antiemético em cuidados paliativos).
13. Agonistas da levodopa ou da dopamina para tremor essencial benigno (sem evidência de eficácia).
14. Anti-histamínicos de primeira geração (há atualmente outros anti-histamínicos mais seguros, menos tóxicos e amplamente disponíveis).

Secção E: Sistema renal. Os medicamentos seguintes são potencialmente inadequados em pessoas idosas com doença renal aguda ou crónica, com função renal abaixo dos níveis específicos da taxa de filtração glomerular estimada (TFGe) (consulte as tabelas do resumo das características do produto e as orientações do formulário local)

1. A digoxina numa dose a longo prazo superior a 125μg/dia e TFGe <30 ml/min/1,73m2 (risco de toxicidade da digoxina se os níveis plasmáticos não forem aferidos).
2. Inibidores diretos da trombina (por exemplo, dabigatrano) se TFGe <30 ml/min/1,73m2 (risco de hemorragia).
3. Inibidores do fator Xa (por exemplo, rivaroxabano, apixabano) se TFGe <15 ml/min/1,73m2 (risco de hemorragia).
4. AINE se TFGe <50 ml/min/1,73m2 (risco de deterioração da função renal).
5. Colquicina se TFGe <10 ml/min/1,73m2 (risco de toxicidade da colquicina).
6. Metformina se TFGe <30 ml/min/1,73m2 (risco de acidose láctica).

Secção F: Sistema gastrointestinal

1. Proclorperazina ou metoclopramida com parkinsonismo (risco de exacerbar os sintomas de parkinsonismo).
2. IBP para doença ulcerosa péptica não complicada ou esofagite péptica erosiva e dosagem terapêutica completa durante > 8 semanas (indicação para redução da dose ou descontinuação do tratamento mais cedo).
3. Medicamentos passíveis de provocar obstipação (por exemplo, medicamentos antimuscarínicos/anticolinérgicos, ferro por administração oral, opioides, verapamil, antiácidos à base de alumínio) em doentes com obstipação crónica quando estiverem disponíveis alternativas que não causem obstipação (risco de exacerbar a obstipação).

4. Doses de ferro elementar por administração oral superiores a 200 mg por dia (por exemplo, fumarato ferroso >600 mg/dia, sulfato ferroso >600 mg/dia, gluconato ferroso >1800 mg/dia; sem evidência de melhoria da absorção de ferro acima destas doses).

Secção G: Sistema respiratório

1. Teofilina como monoterapia para DPOC (doença pulmonar obstrutiva crónica) (alternativa mais segura, mais eficaz; risco de efeitos secundários devido a margem terapêutica estreita).
2. Corticosteróides sistémicos em vez de corticosteróides inalados para terapêutica de manutenção em DPOC moderada ou severa (exposição desnecessária a efeitos secundários sistémicos de corticosteróides a longo prazo e estão disponíveis terapêuticas inalatórias eficazes).
3. Broncodilatadores antimuscarínicos (por exemplo, ipratróprio, tiotróprio) com antecedentes de glaucoma de ângulo fechado (pode exacerbar o glaucoma) ou obstrução do fluxo urinário (pode causar retenção urinária).
4. Bloqueador beta não seletivo (quer por via oral quer por aplicação tópica para glaucoma) com antecedentes de asma com necessidade de tratamento (risco de aumentar broncoespasmos).
5. Benzodiazepinas com insuficiência respiratória aguda ou crónica, ou seja, pO2 <8,0 kPa ou <60 mmHg ± pCO2 >6,5 kPa ou >48,8 mmHg (risco de exacerbar a insuficiência respiratória).

Secção H: Sistema musculoesquelético

1. AINE que não seja agente seletivo da COX-2, com história de doença ulcerosa péptica ou hemorragia gastrointestinal, exceto com a administração simultânea de IBP ou antagonistas dos recetores H2 (risco de recidiva de úlcera péptica).
2. AINE com hipertensão grave (risco de exacerbar a hipertensão) ou insuficiência cardíaca grave (risco de exacerbar a insuficiência cardíaca).
3. AINE a longo prazo (>3 meses) para alívio dos sintomas de dor causada por osteoartrose, quando não se tiver tentado o paracetamol (analgésico simples, preferível e, normalmente, mais eficaz para alívio da dor).
4. Corticosteróides a longo prazo (>3 meses) em monoterapia para artrite reumatóide (risco de efeitos secundários sistémicos de corticosteroides).
5. Corticosteróides (outros que não sejam injeções intra-articulares periódicas para dor em apenas uma articulação) para osteoartrose (risco de efeitos secundários sistémicos de corticosteroides).
6. AINE a longo prazo ou colquicina (>3 meses) para tratamento crónico da gota, quando não houver contraindicações para um inibidor da xantina oxidase (o alopurinol ou febuxostate, dado que os inibidores da xantina oxidase são fármacos de primeira linha na profilaxia da crise aguda de gota).
7. AINE seletivos da COX-2 com doença cardiovascular concomitante (risco aumentado de enfarte do miocárdio e AVC).
8. AINE combinados com corticosteróides sem profilaxia com IBP (risco aumentado de doença ulcerosa péptica).
9. Bifosfonatos por administração oral em doentes com antecedentes de doença no trato gastrointestinal superior, ou seja, disfagia, esofagite, gastrite, duodenite, ou doença ulcerosa péptica, ou hemorragia do trato gastrointestinal superior (risco de recidiva/exacerbação de esofagite, úlcera esofágica, estenose do esófago).

Secção I: Sistema urogenital

1. Medicamentos antimuscarínicos na demência, ou dificuldades cognitivas crónicas (risco de aumento de confusão, agitação), ou glaucoma do ângulo fechado (risco de exacerbação aguda do glaucoma), ou prostatismo crónico (risco de retenção urinária).
2. bloqueadores alfa-1 seletivos em doentes com hipotensão ortostática sintomática ou síncope durante a micção (risco de provocar síncope recorrente).

Secção J. Sistema endócrino

1. Sulfonilureias com ação de longa duração (por exemplo, glibenclamida, clorpropamida, glimepirida) na diabetes *mellitus* tipo 2 (risco de hipoglicemia prolongada).
2. Tiazolidinedionas por exemplo, rosiglitazona, pioglitazona) em doentes com insuficiência cardíaca (risco de exacerbar a insuficiência cardíaca).

3. Bloqueadores beta na diabetes *mellitus* com episódios hipoglicémicos frequentes (risco de supressão dos sintomas hipoglicémicos).
4. Estrogénios com história de cancro da mama ou tromboembolismo venoso (risco aumentado de recidivas).
5. Estrogénios orais sem progesterona em doentes com o útero intacto (risco de cancro do endométrio).
6. Androgénios (hormonas do sexo masculino) na ausência de hipogonadismo primário ou secundário (risco de toxicidade por androgénios; não existem benefícios comprovados para além da indicação para hipogonadismo).

Secção K: Medicamentos que aumentam, previsivelmente, o risco de quedas em pessoas idosas

1. Benzodiazepinas (efeito sedativo, podem causar redução dos sentidos, dificuldades de equilíbrio).
2. Medicamentos neurolépticos (podem causar dispraxia durante a marcha, parkinsonismo).
3. Medicamentos vasodilatadores (por exemplo, bloqueadores dos recetores alfa-1, bloqueadores dos canais de cálcio, nitratos de longa duração de ação, inibidores da ECA, bloqueadores do recetor I da angiotensina) com hipotensão postural persistente, ou seja, queda frequente da pressão arterial sistólica ≥20mmHg (risco de síncope, quedas).
4. Medicamentos Z-hipnóticos, por exemplo, zopiclona, zolpidem, zaleplon (podem causar sedação prolongada durante o dia, ataxia).

Secção L: Medicamentos analgésicos

1. Utilização de opioides fortes transdérmicos (morfina, oxicodona, fentanilo, buprenorfina, diamorfina, metadona, tramadol, petidina, pentazocina) como terapêutica de primeira linha para dor ligeira (escada analgésica da Organização Mundial de Saúde não observada).
2. Utilização regular (distinto de quando necessário) de opióides sem fármacos laxantes em simultâneo (risco de obstipação grave).
3. Opióides de longa ação sem opióides de curta ação para combater a dor (risco de persistência de dor intensa).

Secção N: Carga medicamentosa antimuscarínica/anticolinérgica

Utilização concomitante de dois ou mais medicamentos com propriedades antimuscarínicas/ anticolinérgicas (por exemplo, antiespasmódicos das vias urinárias, antiespasmódicos intestinais, antidepressivos tricíclicos, anti-histamínicos de primeira geração (risco aumentado de toxicidade antimuscarínica/ anticolinérgica).

Screening Tool to Alert to Right Treatment (START), (Ferramenta de avaliação para alertar para o tratamento correcto) versão 2 (2014)

A menos que o estado clínico de um doente idoso seja terminal, requerendo, assim, uma abordagem farmacoterapêutica mais paliativa, as seguintes terapêuticas farmacológicas devem ser consideradas, quando não foram prescritas sem fundamento(s) clínico(s) válido(s). Presume-se que quem faz a prescrição observe todas as contraindicações específicas destas terapêuticas farmacológicas antes de as recomendar a doentes idosos.

Secção A: Sistema cardiovascular

1. Antagonistas da vitamina K, ou inibidores diretos da trombina, ou inibidores do fator Xa na presença de fibrilhação auricular crónica.
2. Ácido acetilsalicílico (75 mg - 160 mg, uma vez por dia) na presença de fibrilhação auricular crónica, quando estiverem contraindicados antagonistas da vitamina K, ou inibidores diretos da trombina ou inibidores do fator Xa.
3. Terapêutica antiagregante (Ácido acetilsalicílico, ou clopidogrel, ou prasugrel, ou ticagrelor) com antecedente de doença coronária, cerebral ou vascular periférica.
4. Terapêutica anti-hipertensora quando a pressão arterial sistólica for consistentemente >160 mmHg e/ou a pressão arterial diastólica for consistentemente >90 mmHg; se a pressão arterial sistólica for >140 mmHg e/ou a pressão arterial diastólica for >90 mmHg, em doente diabético.
5. Terapêutica com Estatinas com um historial documentado de doença coronária, cerebral ou vascular periférica, a menos que o estado do doente seja terminal ou com idade >85 anos.
6. Inibidores da enzima conversora da angiotensina (ECA) na insuficiência cardíaca sistólica e/ou doença arterial coronária documentada.
7. Bloqueador beta na doença cardíaca isquémica.
8. Bloqueador beta adequado (bisoprolol, nebivolol, metoprolol ou carvedilol) na insuficiência cardíaca sistólica estável.

Secção B: Sistema respiratório

1. Agonistas β2 inalados ou broncodilatadores antimuscarínicos usuais (por exemplo, ipratróprio, tiotróprio) para asma ligeira a moderada ou DPOC.
2. Corticosteróides inalados usuais para asma moderada a grave ou DPOC, quando FEV1 <50 % do valor previsto e ocorrerem exacerbações repetidas que exijam tratamento com corticosteróides orais.
3. Oxigénio de longa duração no domicílio com hipoxemia crónica documentada (ou seja, pO2 <8,0 kPa ou 60 mmHg ou SaO2 <89%).

Secção C: Sistema nervoso central e olhos

1. Levodopa ou um agonista da dopamina na doença de Parkinson idiopática com perturbações funcionais e consequente incapacidade.
2. Medicamento antidepressivo não ADT na presença de sintomas depressivos graves persistentes.
3. Inibidor da acetilcolinesterase (por exemplo, donepezilo, rivastigmina, galantamina) para demência de Alzheimer ligeira a moderada ou demência por corpos de Lewy (rivastigmina).
4. Prostaglandinas tópicas, prostamidas ou bloqueadores beta para glaucoma primário de ângulo aberto.
5. Inibidores seletivos da recaptação da serotonina (ou Inibidores seletivos da recaptação da serotonina e da noradrenalina (ISRSN) ou pregabalina, se ISRS estiverem contraindicados) para ansiedade grave persistente que interfira com o funcionamento independente.
6. Agonista da dopamina (ropinirol, ou pramipexol, ou rotigotina) para síndrome das pernas inquietas, quando estiverem excluídas a deficiência de ferro e a insuficiência renal grave.

Secção D: Sistema gastrointestinal

1. Inibidores da bomba de protões com doença de refluxo gastroesofágico grave ou estenose péptica que exija dilatação.
2. Suplementos de fibra (ou seja, farelos, ispágula, metilcelulose, estercúlia) para diverticulose com historial de obstipação.

Secção E: Sistema musculoesquelético

1. Medicamento antirreumático modificador da doença (MARMD) com doença reumática ativa e incapacitante.
2. Bifosfonatos, vitamina D e cálcio em doentes a tomar medicação corticosteroide sistémica a longo prazo.
3. Suplementos de vitamina D e cálcio em doentes com osteoporose conhecida e/ou fratura(s) de fragilidade anterior e/ou (índice T da densidade mineral óssea superior a -2,5 em vários locais).
4. Terapêutica anti-reabsortiva óssea ou anabolizante (por exemplo, bifosfonato, ranelato de estrôncio, teriparatida, denosumab) em doentes com osteoporose documentada, quando não existir qualquer contraindicação farmacológica ou do estado clínico (índice T da densidade mineral óssea - >2,5 em vários locais) e/ou historial anterior de fratura(s) de fragilidade.
5. Suplementos de vitamina D em pessoas idosas que estejam confinadas em casa ou que tenham sofrido quedas ou com osteopenia (índice T da densidade mineral óssea é >-1,0, porém <-2,5 em vários locais).
6. Inibidores da xantina oxidase (por exemplo, alopurinol, febuxostate) com antecedentes de episódios de gota recorrentes.
7. Suplementos de ácido fólico em doentes a tomar metotrexato.

Secção F: Sistema endócrino

1. Inibidor da ECA ou bloqueador do recetor da angiotensina (se for intolerante a inibidor da ECA) na diabetes com evidência de doença renal, ou seja, tira reagente positiva para proteinúria ou microalbuminúria (>30 mg/24 horas) marcadores bioquímicos séricos de insuficiência renal.

Secção G: Sistema urogenital

1. Bloqueador do recetor alfa-1 com prostatismo sintomático, quando a prostatectomia não for considerada necessária.
2. Inibidores da 5-alfa-redutase com prostatismo sintomático, quando a prostatectomia não for considerada necessária.
3. Estrogénio vaginal tópico ou estrogénio em óvulo vaginal para atrofia vaginal sintomática.

Secção H: Analgésicos

1. Opióides de elevada potência em dor moderada a intensa, quando o paracetamol, AINE ou opióides de baixa potência não forem adequados para a intensidade da dor ou não foram eficazes.
2. Laxantes em doentes que tomam opióides regularmente.

Secção I: Vacinas

1. Vacina tetravalente contra a gripe sazonal todos os anos.
2. Vacina pneumocócica pelo menos uma vez após os 65 anos, de acordo com as orientações nacionais.

References

20. O'Mahony, D.; O'Sullivan, D.; Byrne, S.; O'Connor, M.N.; Ryan, C.; Gallagher, P. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. *Age Ageing* **2014**, *44*, 213–218.

Appendix 2.

STOPP/START CRITERIA:

15 GPS FEEDBACK (PHASE I)

Anexo 3: Screening Tool of Older Persons' Prescriptions (STOPP) (Ferramenta de avaliação das prescrições em idosos) versão 2.

As seguintes prescrições são potencialmente inadequadas para administração em doentes com 65 anos ou mais.

Secção A: Indicação da medicação

1. Qualquer medicamento prescrito sem indicação clínica baseada em evidência.

2. Qualquer medicamento prescrito para além da duração recomendada, sempre que a duração do tratamento estiver bem definida.

3. Qualquer prescrição de classe de medicamentos em duplicado, por exemplo, dois anti-inflamatórios não esteróides (AINE) inibidores seletivos da recaptação da serotonina (SSRI), diuréticos de ansa, inibidores da enzima conversora da angiotensina (IECA), anticoagulantes, em simultâneo (a otimização da monoterapia com uma única classe de medicamentos deve ser observada antes de considerar um novo agente).

Secção B: Sistema cardiovascular

1. Digoxina para insuficiência cardíaca com função ventricular sistólica normal (sem evidência clara de benefícios).

2. Verapamil ou diltiazem na insuficiência cardíaca classe III ou IV da *New York Heart Association* (NYHA) (pode agravar a insuficiência cardíaca).

3. Bloqueador beta em combinação com verapamil ou diltiazem (risco de bloqueio cardíaco).

4. Bloqueador beta com bradicardia (<50/min), bloqueio atrioventricular de segundo grau ou bloqueio auriculoventricular completo (risco de bloqueio atrioventricular completo, assistolia).

5. Amiodarona como terapêutica antiarrítmica de primeira linha em taquiarritmias supraventriculares (risco mais elevado de efeitos secundários do que bloqueador beta, digoxina, verapamil ou diltiazem).

6. Diuréticos de ansa como tratamento de primeira linha para hipertensão (alternativas disponíveis mais seguras e mais eficazes).

7. Diuréticos de ansa para edema maleolar dependente do tornozelo sem evidência clínica, bioquímica ou radiológica de insuficiência cardíaca, insuficiência hepática, síndrome

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nefrótica ou insuficiência renal (elevação das pernas e / ou compressão elástica degressiva, normalmente, mais adequadas).

8. Diuréticos tiazídicos na presença de hipocalemia significativa (ou seja, K+ sérico <3,0 mmol/l), hiponatremia (ou seja, Na+ sérico <130 mmol/l), hipercalcemia (ou seja, cálcio sérico >2,65 mmol/l) ou com antecedentes de gota (hipocalemia, hiponatremia, hipercalcemia e gota podem ser desencadeados por diuréticos tiazídicos).

9. Diuréticos de ansa para tratamento da hipertensão na presença de incontinência urinária (pode exacerbar a incontinência).

10. Anti-hipertensores de ação central (por exemplo, metildopa, clonidina, moxonidina, rilmenidina, guanfacina), exceto em caso de intolerância clara a, ou falta de eficácia de, outras classes de anti-hipertensores (os anti-hipertensores de ação central são, geralmente, menos bem tolerados por pessoas mais idosas do que por pessoas mais jovens).

11. Inibidores da enzima conversora da angiotensina (IECA) ou bloqueadores do recetor da angiotensina em doentes com hipercalemia.

12. Antagonistas da aldosterona (por exemplo espironolactona, epleronona) em simultâneo com medicamentos preservadores do potássio [por exemplo IECA (inibidores da enzima conversora da angiotensina), ARB (bloqueadores do recetor da angiotensina), amilorida, triantereno) sem monitorização do potássio sérico (risco de hipercalemia grave, ou seja, >6,0 mmol/l – o potássio sérico deve ser monitorizado regularmente, ou seja, pelo menos, de 6 em 6 meses).

13. Inibidores da fosfodiesterase 5 (por exemplo, sildenafil, taladafil, vardenafil) na insuficiência cardíaca grave caracterizada por hipotensão, ou seja, pressão arterial sistólica <90 mmHg, ou terapêutica conjunta com nitratos para angina de peito (risco de colapso cardiovascular).

Secção C: Medicamentos antiplaquetários/anticoagulantes

1. Tratamento a longo prazo com ácido acetilsalicílico em doses superiores a 160 mg por dia (risco aumentado de hemorragia, sem evidência de aumento da eficácia).

2. Ácido acetilsalicílico com antecedentes de doença ulcerosa péptica sem terapêutica concomitante com IBP (inibidores da bomba de protões) (risco de recidiva de doença ulcerosa péptica).

3. Ácido acetilsalicílico (Aspirina), clopidogrel, dipiridamole, antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa com presença significativa de risco de hemorragia, ou seja, hipertensão grave não controlada, diátese hemorrágica, hemorragia espontânea recente não habitual) (risco elevado de hemorragia).

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4. Aspirina mais clopidogrel como prevenção secundária de AVC, a menos que o doente tenha *stent(s)* coronário(s) introduzido(s) nos 12 meses anteriores ou síndrome coronária aguda em simultâneo, ou tenha uma estenose carotídea de elevado grau sintomática (não há evidência de benefício acrescentado à monoterapia com clopidogrel).

5. Ácido acetilsalicílico em combinação com antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa em doentes com fibrilhação auricular crónica (sem benefício acrescentado com a ácido acetilsalicílico).

6. Agentes antiplaquetários com antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa em doentes com doença coronária, cerebrovascular ou arterial periférica estável (sem benefício acrescentado com terapêutica dupla).

7. Ticlopidina em quaisquer circunstâncias (clopidogrel e prasugrel têm eficácia similar, evidência mais sólida e menos efeitos secundários).

8. Antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa para primeira trombose venosa profunda sem fatores de risco permanentes (por exemplo, trombofilia) durante > 6 meses (sem acréscimo comprovado de benefícios).

9. Antagonistas da vitamina K, inibidores diretos da trombina ou inibidores do fator Xa para primeira embolia pulmonar sem fatores de risco permanentes (por exemplo, trombofilia) durante > 12 meses (sem acréscimo comprovado de benefícios).

10. AINE e antagonistas da vitamina K, combinados com inibidores diretos da trombina ou inibidores do fator Xa (risco de grande hemorragia gastrointestinal).

11. AINE conjuntamente com agentes antiplaquetários sem profilaxia com IBP (risco aumentado de doença ulcerosa péptica).

Secção D: Sistema nervoso central e medicamentos psicotrópicos

1. Antidepressivos tricíclicos (ADT) com demência, glaucoma de ângulo fechado, anomalias da condução cardíaca, prostatismo ou antecedentes de retenção urinária (risco de agravar estas condições).

2. Início de antidepressivos tricíclicos (ADT) como tratamento antidepressivo de primeira linha (risco mais elevado de reações adversas ao medicamento com ADT do que com inibidores seletivos da recaptação da serotonina (SSRI) ou inibidores seletivos da recaptação da serotonina e da noradrenalina (SNRI).

3. Neurolépticos com efeitos moderadamente marcados antimuscarínicos/anticolinérgicos (clorpromazina, clozapina, flupentixol, flufenazina, pipotiazina, promazina, zuclopentixol) com antecedentes de prostatismo ou retenção urinária (risco elevado de retenção urinária).

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4. Inibidores seletivos da recaptação da serotonina (SSRI) com hiponatremia significativa atual ou recente, ou seja, Na+ sérico 130 mmol/L (risco de exacerbar ou desencadear hiponatremia).

5. Benzodiazepinas durante ≥ 4 semanas (sem indicação para tratamento mais longo; risco de sedação prolongada, confusão, dificuldades de equilíbrio, quedas, acidentes de viação; todas as benzodiazepinas devem ser retiradas gradualmente se tomadas por mais de 4 semanas, porque existe o risco de provocar a síndrome de abstinência de benzodiazepinas se a administração das mesmas for interrompida abruptamente).

6. Antipsicóticos (ou seja, outros além da quetiapina ou clozapina) em doentes com parkinsonismo ou demência por corpos de *Lewy* (risco de sintomas extrapiramidais graves).

7. Anticolinérgicos/antimuscarínicos para tratar efeitos secundários extrapiramidais de medicação neuroléptica (risco de toxicidade anticolinérgica).

8. Anticolinérgicos/antimuscarínicos em doentes com *delirium* ou demência (risco de exacerbar dificuldades cognitivas).

9. Antipsicótico neuroléptico em doentes com sintomas psicológicos e comportamentais da demência (SPCD), a menos que os sintomas sejam graves e outros tratamentos não farmacológicos tenham falhado (risco aumentado de AVC).

10. Neurolépticos como hipnóticos, a menos que os distúrbios do sono sejam devidos a psicose ou demência (risco de confusão, hipotensão, efeitos secundários extrapiramidais, quedas).

11. Inibidores da acetilcolinesterase com antecedentes conhecidos de bradicardia persistente (<60 batimentos/min), bloqueio cardíaco, ou síncope inexplicada, ou tratamento conjunto com medicamentos que reduzem o ritmo cardíaco, tais como betabloqueadores, digoxina, diltiazem, verapamil (risco de falha da condução cardíaca, síncope e lesão).

12. Fenotiazinas como tratamento de primeira linha, dado que existem alternativas mais seguras e mais eficazes (as fenotiazinas têm efeito sedativo, têm uma toxicidade antimuscarínica significativa em pessoas idosas, à exceção de proclorperazina para náuseas/vómitos/vertigens, clorpromazina para alívio de soluços persistentes e levomepromazina como antiemético em cuidados paliativos).

13. Levodopa ou agonistas da dopamina para tremor essencial ou benigno (sem evidência de eficácia).

14. Anti-histamínicos de primeira geração (anti-histamínicos mais seguros, menos tóxicos, atualmente, amplamente disponíveis).

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Secção E: Sistema renal. Os medicamentos seguintes são potencialmente inadequados em pessoas idosas com doença renal aguda ou crónica, com função renal abaixo dos níveis específicos da taxa de filtração glomerular estimada (TFGe) (consulte as tabelas do resumo das características do produto e as orientações do formulário local)

1. A digoxina numa dose a longo prazo superior a 125µg/dia se TFGe <30 ml/min/1,73m2 (risco de toxicidade da digoxina se os níveis plasmáticos não forem aferidos).

2. Inibidores diretos da trombina (por exemplo dabigatrano) se TFGe <30 ml/min/1,73m2 (risco de hemorragia).

3. Inibidores do fator Xa (por exemplo rivaroxabano, apixabano) se TFGe <15 ml/min/1,73m2 (risco de hemorragia).

4. AINE se TFGe <50 ml/min/1,73m2 (risco de deterioração da função renal).

5. Colquicina se TFGe <10 ml/min/1,73m2 (risco de toxicidade da colquicina).

6. Metformina se TFGe <30 ml/min/1,73m2 (risco de acidose láctica).

Secção F: Sistema gastrointestinal

1. Proclorperazina ou metoclopramida com parkinsonismo (risco de exacerbar os sintomas de parkinsonismo).

2. IBP para doença ulcerosa péptica não complicada ou esofagite péptica erosiva e dosagem terapêutica completa durante >8 semanas (indicação para redução da dose ou descontinuação do tratamento mais cedo).

3. Medicamentos passíveis de provocar obstipação (por exemplo, medicamentos antimuscarínicos/anticolinérgicos, ferro por administração oral, opióides, verapamil, antiácidos à base de alumínio) em doentes com obstipação crónica quando estiverem disponíveis alternativas que não causem obstipação (risco de exacerbar a obstipação).

4. Doses de ferro elementar por administração oral superiores a 200 mg por dia (por exemplo, fumarato ferroso >600 mg/dia, sulfato ferroso >600 mg/dia, gluconato ferroso >1800 mg/dia; sem evidência de melhoria da absorção do ferro acima destas doses).

Secção G: Sistema respiratório

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1. Teofilina como monoterapia para DPOC (doença pulmonar obstrutiva crónica) (alternativa mais segura, mais eficaz; risco de efeitos secundários devido a margem terapêutica estreita).

2. Corticosteróides sistémicos em vez de corticosteróides inalados para terapêutica de manutenção em DPOC moderada ou severa (exposição desnecessária a efeitos secundários sistémicos de corticosteróides a longo prazo e estão disponíveis terapêuticas inalatórias eficazes).

3. Broncodilatadores antimuscarínicos (por exemplo, ipratróprio, tiotróprio) com antecedentes de glaucoma de ângulo fechado (pode exacerbar o glaucoma) ou obstrução do fluxo urinário (pode causar retenção urinária).

4. Bloqueador beta não seletivo (quer por via oral quer por aplicação tópica para glaucoma) com antecedentes de asma com necessidade de tratamento (risco de aumentar broncoespasmo).

5. Benzodiazepinas com insuficiência respiratória aguda ou crónica, ou seja, pO2 <8,0 kPa ± pCO2 >6,5 kPa (risco de exacerbar a insuficiência respiratória).

Secção H: Sistema musculoesquelético

1. Medicamento anti-inflamatório não esteróide (AINE) que não seja agente seletivo da COX-2, com historial de doença ulcerosa péptica ou hemorragia gastrointestinal, exceto com a administração simultânea de IBP ou antagonistas dos recetores H2 (risco de recidiva de úlcera péptica).

2. AINE com hipertensão grave (risco de exacerbar a hipertensão) ou insuficiência cardíaca grave (risco de exacerbar a insuficiência cardíaca).

3. AINE a longo prazo (>3 meses) para alívio dos sintomas de dor causada por osteoartrose, quando não se tiver tentado o paracetamol (analgésico simples, preferível e, normalmente, mais eficaz para alívio da dor).

4. Corticosteróides a longo prazo (>3 meses) em monoterapia para artrite reumatóide (risco de efeitos secundários sistémicos de corticosteróides).

5. Corticosteróides (outros que não sejam injeções intra-articulares periódicas para dor em apenas uma articulação) para osteoartrose (risco de efeitos secundários sistémicos de corticosteróides).

6. AINE a longo prazo ou colquicina (>3 meses) para tratamento crónico da gota, quando não houver contraindicações para um inibidor da xantina oxidase (por exemplo, alopurinol, febuxostate) (os inibidores da xantina oxidase são a primeira opção no que respeita a medicação profilática para a gota).

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7. AINE seletivos da COX-2 com doença cardiovascular concomitante (risco aumentado de enfarte do miocárdio e AVC).

8. AINE combinados com corticosteróides sem profilaxia com IBP (risco aumentado de doença ulcerosa péptica).

Eliminou: corticosteroides

9. Bifosfonatos por administração oral em doentes com antecedentes de doença no trato gastrointestinal superior, ou seja, disfagia, esofagite, gastrite, duodenite, ou doença ulcerosa péptica, ou hemorragia do trato gastrointestinal superior (risco de recidiva/exacerbação de esofagite, úlcera esofágica, estenose do esófago).

Secção I: Sistema urogenital

1. Medicamentos antimuscarínicos na demência, ou dificuldades cognitivas crónicas (risco de aumento de confusão, agitação), ou glaucoma do ângulo fechado (risco de exacerbação aguda do glaucoma), ou prostatismo crónico (risco de retenção urinária).

Eliminou: com

2. Bloqueadores alfa seletivos dos recetores alfa-1 em doentes com hipotensão ortostática sintomática ou síncope durante a micção (risco de provocar síncope recorrente).

Secção J. Sistema endócrino

1. Sulfonilureias com ação de longa duração (por exemplo, glibenclamida, clorpropamida, glimepirida) na diabetes *mellitus* tipo 2 (risco de hipoglicemia prolongada).

2. Tiazolidenedionas (por exemplo, rosiglitazona, pioglitazona) em doentes com insuficiência cardíaca (risco de exacerbar a insuficiência cardíaca).

3. Bloqueadores beta na diabetes *mellitus* com episódios hipoglicémicos frequentes (risco de supressão dos sintomas hipoglicémicos).

4. Estrogénios com historial de cancro da mama ou tromboembolismo venoso (risco aumentado de recidivas).

5. Estrogénios orais sem progesterona em doentes com o útero intacto (risco de cancro do endométrio).

6. Androgénios (hormonas do sexo masculino) na ausência de hipogonadismo primário ou secundário (risco de toxicidade por androgénios; não existem benefícios comprovados para além da indicação para hipogonadismo).

Secção K: Medicamentos que aumentam, previsivelmente, o risco de quedas em pessoas idosas

1. Benzodiazepinas (efeito sedativo, podem causar redução dos sentidos, dificuldades de equilíbrio).

2. Medicamentos neurolépticos (podem causar dispraxia durante a marcha, parkinsonismo).

3. Medicamentos vasodilatadores (por exemplo, bloqueadores dos recetores alfa-1, bloqueadores dos canais de cálcio, nitratos de longa duração de ação, inibidores da ECA, bloqueadores do recetor I da angiotensina) com hipotensão postural persistente, ou seja, queda frequente da pressão arterial sistólica ≥20mmHg (risco de síncope, quedas).

4. Medicamentos Z-hipnóticos, por exemplo, zopiclona, zolpidem, zaleplon (podem causar sedação prolongada durante o dia, ataxia).

Secção L: Medicamentos analgésicos

1. Utilização de opióides fortes orais ou transdérmicos (morfina, oxicodona, fentanilo, buprenorfina, diamorfina, metadona, tramadol, petidina, pentazocina) como terapêutica de primeira linha para dor ligeira (escada analgésica da Organização Mundial de Saúde não observada).

2. Utilização regular de opióides (distinga-se de quando necessário) sem laxantes em simultâneo (risco de obstipação grave).

3. Opióides de longa ação sem opióides de curta ação de resgate para dor intensa (risco de persistência de dor intensa).

Secção N: Carga medicamentosa antimuscarínica/anticolinérgica

Utilização concomitante de dois ou mais medicamentos com propriedades antimuscarínicas/anticolinérgicas (por exemplo, antiespasmódicos das vias urinárias, antiespasmódicos intestinais, antidepressivos tricíclicos, anti-histamínicos de primeira geração (risco aumentado de toxicidade antimuscarínica/anticolinérgica)).

Anexo: 4: **Screening Tool to Alert to Right Treatment (START), (Ferramenta de avaliação da adequação do tratamento) versão 2.**

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Eliminou: laxativos

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Eliminou: para combater a dor

Eliminou: para alertar para o tratamento certo

A menos que o estado clínico de um doente idoso seja terminal, requerendo, assim, uma abordagem farmacoterapêutica mais paliativa, as seguintes terapêuticas farmacológicas devem ser consideradas, quando omitidas sem fundamento(s) clínico(s) válido(s). Presume-se que quem faz a prescrição observe todas as contraindicações específicas destas terapêuticas farmacológicas antes de as recomendar a doentes idosos.

Secção A: Sistema cardiovascular

1. Antagonistas da vitamina K, ou inibidores diretos da trombina, ou inibidores do fator Xa na presença de fibrilhação auricular crónica.

2. Ácido acetilsalicílico (75 mg - 160 mg, uma vez por dia) na presença de fibrilhação auricular crónica, quando estiverem contraindicados antagonistas da vitamina K, ou inibidores diretos da trombina ou inibidores do fator Xa.

3. Terapêutica antiagregante (ácido acetilsalicílico, ou clopidogrel, ou prasugrel, ou ticagrelor) quando antecedente de doença coronária, cerebral ou vascular periférica.

4. Terapêutica anti-hipertensora quando a pressão arterial sistólica for consistentemente >160 mmHg e/ou a pressão arterial diastólica for consistentemente >90 mmHg, se a pressão arterial sistólica for >140 mmHg e/ou a pressão arterial diastólica for >90 mmHg, em doente diabético.

5. Terapêutica com estatinas, com um historial documentado de doença coronária, cerebral ou vascular periférica, a menos que o estado do doente seja terminal ou com idade > 85 anos.

6. Inibidores da enzima conversora da angiotensina (ECA) na insuficiência cardíaca sistólica e/ou doença arterial coronária documentada.

7. Bloqueador beta na doença cardíaca isquémica.

8. Bloqueador beta adequado (bisoprolol, nebivolol, metoprolol ou carvedilol) na insuficiência cardíaca sistólica estável.

Secção B: Sistema respiratório

1. Agonistas β2 inalados ou broncodilatadores antimuscarínicos usuais (por exemplo, ipratróprio, tiotróprio) para asma ligeira a moderada ou DPOC.

2. Corticosteróides inalados usuais para asma moderada a grave ou DPOC, quando FEV1 <50 % do valor previsto e ocorrerem exacerbações repetidas que exijam tratamento com corticosteróides orais.

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Eliminou: Corticosteroides

Eliminou: corticosteroides

3. Oxigénio de longa duração no domicílio com hipoxemia crónica documentada (ou seja, pO2 <8,0 kPa ou 60 mmHg ou SaO2 <89%)

Secção C: Sistema nervoso central e olhos

1. Levodopa ou um agonista da dopamina na doença de *Parkinson* idiopática com perturbações funcionais e resultante incapacidade.

2. Medicamento antidepressivo não ADT, na presença de sintomas depressivos graves persistentes.

3. Inibidor da acetilcolinesterase (por exemplo, donepezil, rivastigmina, galantamina) para demência de *Alzheimer* ligeira a moderada ou demência por corpos de *Lewy* (rivastigmina).

4. Prostaglandinas tópicas, prostamidas ou bloqueadores beta para glaucoma primário de ângulo aberto.

5. Inibidores seletivos da recaptação da serotonina (ou SNRI, ou pregabalina, se SSRI estiverem contraindicados) para ansiedade grave persistente que interfira com a independência funcional.

6. Agonista da dopamina (ropinirol, ou pramipexol, ou rotigotina) para síndrome das pernas inquietas, quando estiverem excluídas a deficiência de ferro e a insuficiência renal grave.

Secção D: Sistema gastrointestinal

1. IBP na doença de refluxo gastroesofágico grave ou estenose péptica que exija dilatação.

2. Suplementos de fibra (ou seja, farelos, ispágula, metilcelulose, estercúlia) para diverticulose com historial de obstipação.

Secção E: Sistema musculoesquelético

1. Medicamento antirreumático modificador da doença (MARMD) na doença reumática ativa, incapacitante.

2. Bifosfonatos e vitamina D mais cálcio em doentes a tomar medicação corticosteróide sistémica a longo prazo.

3. Suplementos de vitamina D mais cálcio em doentes com osteoporose conhecida e/ou fratura(s) de fragilidade anterior(es) e/ou índice T da densidade mineral óssea superior a -2,5 em vários locais.

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4. Terapêutica anti-reabsortiva óssea ou anabolizante (por exemplo, bifosfonato, ranelato de estrôncio, teriparatida, denosumab) em doentes com osteoporose documentada, quando não existir qualquer contraindicação farmacológica ou do estado clínico (índice T da densidade mineral óssea - >2,5 em vários locais) e/ou historial anterior de fratura(s) de fragilidade.

Eliminou: por

5. Suplementos de vitamina D em pessoas idosas que estejam confinadas em casa, que tenham sofrido quedas ou com osteopenia (índice T da densidade mineral óssea é >-1,0, porém <-2,5 em vários locais).

6. Inibidores da xantina oxidase (por exemplo, alopurinol, febuxostate) se antecedentes de episódios de gota frequentes.

Eliminou: com

7. Suplementos de ácido fólico em doentes a tomar metotrexato.

Secção F: Sistema endócrino

1. Inibidor da ECA ou bloqueador do recetor da angiotensina (se for intolerante a inibidor da ECA) na diabetes com evidência de doença renal, ou seja, tira reagente positiva para proteinúria ou microalbuminúria (>30 mg/24 horas) com ou sem marcadores bioquímicos séricos de insuficiência renal.

Eliminou: bioquímica sérica.

Secção G: Sistema urogenital

1. Bloqueador do recetor alfa-1 com prostatismo sintomático, quando a prostatectomia não for considerada necessária.

2. Inibidores da 5-alfa-redutase com prostatismo sintomático, quando a prostatectomia não for considerada necessária.

3. Estrogénio vaginal tópico ou estrogénio em pessário vaginal para atrofia vaginal sintomática.

Secção H: Analgésicos

1. Opióides de elevada potência em dor moderada a intensa, quando o paracetamol, AINE ou opióides de baixa potência não forem adequados para a intensidade da dor ou não foram eficazes.

Eliminou: o

Eliminou: o

2. Laxantes em doentes que tomam opióides regularmente.

Eliminou: o

Secção I: Vacinas

1. Vacina trivalente contra a gripe sazonal todos os anos.

2. Vacina pneumocócica, pelo menos, uma vez, após os 65 anos, de acordo com as orientações nacionais.

Appendix 3.

Manuscript published at BMJ Open

Computerised decision to reduce inappropriate medication in the elderly: a systematic review with meta analysis protocol (additional paper)

BMJ Open

Computerised decision to reduce inappropriate medication in the elderly: a systematic review with meta-analysis protocol

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ABSTRACT

Introduction Life expectancy continues to increase in developed countries. Elderly people are more likely to consume more medications and become vulnerable to age-related changes in drugs' pharmacokinetics and pharmacodynamics. Recent studies have identified opportunities and barriers for deprescribing potentially inappropriate medications. It has already been demonstrated that computerised decision support systems can reduce physician orders for unnecessary tests. We will systematically review the available literature to understand if computerised decision support is effective in reducing the use of potentially inappropriate medications, thus having an impact on health outcomes.

Methods and analysis A systematic review will be conducted using MEDLINE, CENTRAL, EMBASE and Web of Science databases, as well as the grey literature assessing the effectiveness of computer decision support interventions in deprescribing inappropriate medication, with an impact on health outcomes in the elderly. The search will be performed during January and February 2018. Two reviewers will conduct articles' screening, selection and data extraction, independently and blind to each other. Eligible sources will be selected after discussing non-conformities. All extracted data from the included articles will be assessed based on studies' participants, design and setting, methodological quality, bias and any other potential sources of heterogeneity. This review will be conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement of quality for reporting systematic reviews and meta-analyses.

Ethics and dissemination As a systematic review, this research is exempt from ethical approval. We intend to publish the full article in a related peer-reviewed journal and present it at international conferences.

PROSPEROregistration number CRD42017067021.

Strengths and limitations of this study

- We aim to clarify whether new technologies, namely computerised decision systems, can help in reducing inappropriate medication in the elderly.
- This protocol was written following the recently published Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- We will conduct a comprehensive systematic review on this clinical topic using, if possible, meta-analytic methods.
- Studies with high heterogeneity and varying quality may limit the quality of evidence for this systematic review.

INTRODUCTION

In developed countries, ageing population is increasing.[1] Caring for older adults is a challenge for healthcare providers, as they are more likely to have multimorbidities[2 3] and to consume more medication.[4]

Polypharmacy, defined as 'the use of multiple drugs administered to the same patient, most commonly seen in elderly patients,'[5 6] although frequent has a negative impact on senior health.[7 8] There is an increased risk of drug interactions and prescriptions of potentially inappropriate medications,[4] changes in pharmacokinetics and pharmacodynamics and limited generalisation of clinical research results due to common exclusion of subjects aged more than 65 years old.[9] So, prescribing medication for elderly patients should be evidence based and particularly cautious.

In several cases it is urgent to deprescribe, this is to begin 'the process of withdrawal of inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes.'[10]

Inappropriate medication prescription, meaning 'the practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist,'[5 11] can be reduced by several

interventions.[12] However, they are not widely known and therefore used. In one hand, general practitioners report interest in learning and using more mobile technologies to assist in clinical care[13]; on the other hand, they refer an insufficient emphasis on geriatric pharmacotherapy training.[14]

It has already been shown that computerised decision support systems can reduce physicians' orders of unnecessary tests.[15] This systematic review aims to determine if computerised decision support is effective in reducing potentially inappropriate medication prescription in the elder population.

Other studies have addressed strategies to improve care of elderly in what concerns inappropriate medication prescription.[12 16] In 2013, one synthesis study identified eight randomised controlled trials (RCT), two cluster RCTs and two controlled before-and-after studies.[9] In 2015, another study included 12 RCTs.[13] Both studies reported high heterogeneity on the included studies. However, these studies have not focused on computerised decision support systems. In addition, we consider that since the last study search, more adequate studies have been published and that, for the first time, a meta-analysis will be possible to conduct.

METHODS AND ANALYSIS

Eligibility criteria

In this systematic review, we will select (1) interventional studies, such as RCTs, non-randomised controlled studies and quasirandomised controlled studies; (2) those that include participants aged 65 years or more, to whom one or more regular medications were prescribed, and (3) assess the impact of computerised decision support systems in withdrawal of potentially inappropriate medication prescription. On the other hand, studies including only moribund, terminal or palliative participants will be excluded. Studies published or in press will be included independent of the language, year of publication and setting in which it was conducted (hospitals, nursing centres, communities, and so on). Potentially inappropriate medications will be defined using the Beers criteria[17] and STOPP/START criteria.[18]

Information sources

Our sources of information will include electronic databases (namely MEDLINE, CENTRAL, EMBASE, Web of Science), trial registries, different types of grey literature and contact with specialists in the field. If further data are needed, authors of the selected articles will be contacted. The search will be performed in January and February 2018. The search will have no language restrictions. In those cases that none of the research team members are able to translate the included study, we will first contact the authors to ascertain if the main data are available in other languages and seek to translate whenever necessary. A second search using all identified keywords and proprietary names of computerised decision support systems will then be undertaken across all included databases.

Search strategy

Our initial search syntax in CENTRAL will be: (1) MeSH descriptor: [Medical Informatics Applications] explode all trees; (2) Computer decision support; (3) MeSH descriptor: [Deprescriptions] explode all trees; (4) MeSH descriptor: [Inappropriate Prescribing] explode all trees; (5) no. 1 or 2; (6) no. 3 or 4; (7) no. 5 and no. 6.

For PubMed, the query will be "(Medical Informatics Applications [MeSH Terms] OR (medical AND informatics AND applications)) AND ((Deprescriptions [Mesh Terms] OR deprescription OR deprescribing OR Inappropriate Prescribing [Mesh Terms] OR (inappropriate AND prescribing*) OR (inappropriate AND prescription*) OR (over* AND prescribing*)) OR medication errors [MeSH Terms] OR (error* AND medication) OR (drug AND use AND error*) AND (decision support systems, clinical [MeSH Terms] OR 'clinical decision support systems' OR (clinical AND decision AND support*) OR decision making, computer-assisted [MeSH Terms] OR (computer AND assisted AND decision AND making) OR (medical AND computer AND assisted AND decision AND making) OR medical order entry systems [MeSH Terms] OR (medical AND order entry systems) OR (medications AND alert AND systems) OR 'computorized physician order entry systems' OR 'computorized provider order entry systems' OR 'computorized physician order entry' OR 'computorized provider order entry')."

For Web of Science the query will be "TS=('Medical Informatics Applications' OR (medical AND informatics AND applications)) AND TS=((Deprescriptions OR deprescription OR deprescribing OR 'Inappropriate Prescribing' OR (inappropriate AND prescribing*) OR (inappropriate AND prescription*) OR (over* AND prescribing*)) OR 'medication errors' OR (error* AND medication) OR (drug AND use AND error*) AND TS=('clinical decision support systems' OR (clinical AND decision AND support*) OR decision making, computer-assisted [MeSH Terms] OR (computer AND assisted AND decision AND making) OR (medical AND computer AND assisted AND decision AND making) OR 'medical order entry systems' OR (medical AND order entry systems) OR (medications AND alert AND systems) OR 'computorized physician order entry systems' OR 'computorized provider order entry systems' OR 'computorized physician order entry' OR 'computorized provider order entry')."

Study selection process

The selection process procedure will be made by two reviewers following several steps.

First, they will independently review the title and abstract of each reference. Each one will be categorised into either relevant, unsure or irrelevant. If a reference

is considered irrelevant by the two authors it will be eliminated.

In the next phase, the two authors will review the full text of the remaining references and each one will independently select which articles should be included.

The two authors will compare their selected articles and discuss any disagreement in each phase.

If the two reviewers cannot reach an agreement all the authors of the paper will make the final decision.

Data extraction and management

Once the articles to be included are selected, data will be extracted and entered into data sheets independently by two reviewers. These two sheets, including their differences, will be checked by a third reviewer.

The following information will be extracted from each article: (1) study characteristics, intervention type; type of study; country, setting, follow-up duration; (2) participants' number and age; and (3) clinical outcomes. The primary outcome to be considered is the effect of intervention on withdrawal of potentially inappropriate medications (discontinuation rate). The authors will give priority to the following outcomes, by order of importance: mortality, hospitalisation, any reported adverse drug withdrawal effects and quality of life measurements.

Any potential difference among reviewers will be discussed with the team, and if not resolved, the manuscript authors will be contacted. Also, if required data are missing from the article or are incomplete or unclear, inquiries will similarly be sent to the authors.

Risk of bias

Two reviewers will assess, independently and blinded to each other, the risk of bias by applying the Cochrane Collaboration Risk of Bias tool to all the included studies.[19]

Data synthesis

The final report will present the available data of the computer decision to support in reducing inappropriate medication prescription in older adults.

Each outcome will be combined and calculated using the statistical software RevMan V.5.1,[20] according to statistical guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions.[21]

If we are able to include a group of studies that are sufficiently comparable and reliable we will conduct a meta-analysis. We consider that we should use a random effects model taking in consideration the previous systematic reviews' results. We expect to encounter a sufficient number of studies, reporting a sufficient number of events, but that are not completely comparable (concerning the intervention, context and population).

If heterogeneity is severe (I^2 superior to 40%–50%) and studies' results are strongly biased, we will not perform a meta-analysis; thus, a narrative, qualitative summary will be done instead.

Effect sizes and 95% CI will be expressed as ORs. When a study reports zero event in both arms, we will consider using zero-cell correction methods.

Subgroup analyses will be used to explore possible sources of heterogeneity based on the following: setting, type of software, medication and participants' clinical characteristics.

Regarding subgroups, we assume it will be relevant to include subgroups regarding the tool used by software to identify targets: STOPP/START criteria subgroup and the Beers criteria. We will also conduct metaregression to evaluate whether the covariates have significant influence on heterogeneity.

Forest plots will be produced when three or more studies are included in a meta-analysis. Data in tables will be presented by therapeutic class based on the Anatomical Therapeutic Classification codes.

Studies rated as having a high risk of bias will be included in the narrative synthesis but not on our meta-analysis and discussed in detail.

A systematic narrative synthesis will be provided in the text and tables to summarise and explain the characteristics and findings of the studies; it will explore the relationship within and between studies, in line with guidance from the Centre for Reviews and Dissemination.

To determine whether publication bias is present, we will include funnel plot and statistical tests in the assessment, namely Begg's test and Egger's test.

We will also ascertain if each RCT had its protocol published before recruitment of patients was initiated.

The quality of evidence for all outcomes will be judged with the Grading of Recommendations Assessment, and the Development and Evaluation working group methodology.[22]

The final paper will be prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[23 24]

ETHICS AND DISSEMINATION

As a systematic review, this research is exempt from ethical approval. We intend to publish the full article in a related peer-reviewed journal and present it in international conferences.

DISCUSSION

Although electronic health records are common in clinical practice, there is a lack of evidence of computer decision support systems regarding health outcomes. Deprescribing potentially inappropriate medication in the elderly is particularly difficult, although computer support may be an important tool. This systematic review will help identify the success of computerised decision support to reduce inappropriate medication prescription. Therefore, this review will be relevant for patients, health professionals and policymakers. One potential limitation of this study will be if we find a limited number of studies

with considerable differences regarding their characteristics and methodology. This may impair our conclusions and impede meta-analysis. In addition, depending on the data available and obtained results we may not be able to define which is the best decision support available.

Contributors LM had the original idea for the systematic review. LM, TM and ISS wrote the protocol and reviewed the search strategy. LM, TM, ISS, MMS and CM reviewed the protocol.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This research is exempt from ethical approval.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 4.

MANUSCRIPT PUBLISHED AT JMIR

REDUCING POTENTIALLY INAPPROPRIATE PRESCRIPTIONS FOR OLDER PATIENTS USING COMPUTERISED DECISION SUPPORT TOOLS: SYSTEMATIC REVIEW

Review

Reducing Potentially Inappropriate Prescriptions for Older Patients Using Computerized Decision Support Tools: Systematic Review

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Abstract

Background: Older adults are more vulnerable to polypharmacy and prescriptions of potentially inappropriate medications. There are several ways to address polypharmacy to prevent its occurrence. We focused on computerized decision support tools.

Objective: The available literature was reviewed to understand whether computerized decision support tools reduce potentially inappropriate prescriptions or potentially inappropriate medications in older adult patients and affect health outcomes.

Methods: Our systematic review was conducted by searching the literature in the MEDLINE, CENTRAL, EMBASE, and Web of Science databases for interventional studies published through February 2018 to assess the impact of computerized decision support tools on potentially inappropriate medications and potentially inappropriate prescriptions in people aged 65 years and older.

Results: A total of 3756 articles were identified, and 16 were included. More than half (n=10) of the studies were randomized controlled trials, one was a crossover study, and five were pre-post intervention studies. A total of 266,562 participants were included; of those, 233,144 participants were included and assessed in randomized controlled trials. Intervention designs had several different features. Computerized decision support tools consistently reduced the number of potentially inappropriate prescriptions started and mean number of potentially inappropriate prescriptions per patient. Computerized decision support tools also increased potentially inappropriate prescriptions discontinuation and drug appropriateness. However, in several studies, statistical significance was not achieved. A meta-analysis was not possible due to the significant heterogeneity among the systems used and the definitions of outcomes.

Conclusions: Computerized decision support tools may reduce potentially inappropriate prescriptions and potentially inappropriate medications. More randomized controlled trials assessing the impact of computerized decision support tools that could be used both in primary and secondary health care are needed to evaluate the use of medication targets defined by the Beers or STOPP (Screening Tool of Older People's Prescriptions) criteria, adverse drug reactions, quality of life measurements, patient satisfaction, and professional satisfaction with a reasonable follow-up, which could clarify the clinical usefulness of these tools.

Trial Registration: International Prospective Register of Systematic Reviews (PROSPERO) CRD42017067021; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017067021

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KEYWORDS

deprescriptions; medical informatics applications; potentially inappropriate prescription; potentially inappropriate medication; computerized decision support

Introduction

The older adult population is increasing in developed countries [1], and people worldwide are living longer [2,3]. According to the World Health Organization, people aged 60 years and older in 2020 will outnumber children younger than 5 years. In 2050, the world's population aged 60 years and older is expected to total 2 billion [2].

The aging of populations increases the pressure on health care systems, which should be aligned with the needs of older populations [4]. Older patients are more likely to have more than one chronic condition, known as multimorbidity [5,6]. The prevalence of multimorbidity is more than 90% in older patients [5]. Having more than one chronic condition requires the use of several medications. Thus, older adults are more vulnerable to polypharmacy [7], meaning the use of multiple drugs administered to the same patient [8,9], in addition to prescriptions of potentially inappropriate medications (PIMs) [10-12]. A PIM can be described as a medication use that has potentially more risks than benefits with a safer alternative available [10].

Potentially inappropriate prescription (PIP) is a broader concept than PIM, because it includes over-, under-, and misprescribing (eg, inappropriate dose or duration). It is defined as "the prescribing of medication that could introduce a significant risk of an adverse event, in particular when there is an equally or more effective alternative with lower risk available" [13].

Due to changes in pharmacokinetics and pharmacodynamics, older people are more prone to drug interactions and adverse drug reactions [14,15]. Adverse drug reactions are considered a public health problem in older patients and a cause of disability and mortality [15]. Deprescribing is defined as "the process of withdrawal of inappropriate medication, supervised by a health care professional, with the goal of managing polypharmacy and improving outcomes" [16].

There are several ways to address polypharmacy to prevent its occurrence [17-23]. This review focused on computerized decision support (CDS) tools. Bates et al [24] defined CDS systems as computer-based systems providing "passive and active referential information as well as reminders, alerts, and guidelines." Payne [25] added that CDS tools can be defined as "computer applications designed to aid clinicians in making diagnostic and therapeutic decisions in patient care." CDS tools may have a positive impact on health care, such as reducing physicians' orders of unnecessary tests [26].

Previous studies reviewed such strategies, such as multidisciplinary team medication reviews, pharmacist medication reviews, computerized clinical decision support systems, and multifaceted approaches and reported substantial heterogeneity in the included studies, but did not focus on CDS [19,21]. One systematic review that did focus on CDS systems included studies published only through 2012, and new studies have been published since then [27]. This systematic review aims to clarify whether CDS tools can help in reducing PIPs or PIMs to improve clinical outcomes in older adults.

Methods

Eligibility Criteria

The systematic review was conducted according to a protocol previously published [28] and registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD42017067021). We searched for interventional controlled studies (type of study) with participants aged 65 years or older (population) that assessed whether CDS tools (intervention) could diminish PIM (outcome). Moribund or terminal participants were excluded along with those requiring palliative care. No other restriction was applied.

Search Methods

We searched MEDLINE, CENTRAL, EMBASE, and Web of Science for studies published through February 2018 without language restrictions. Specific queries were used according to each database's requirements that were described in detail elsewhere [29]. Trial registries, different types of grey literature, and contact with specialists in the field were also performed. The reference lists of all included studies were searched to identify any potentially pertinent study that might not have been identified by previous methods. References were checked from previously published systematic reviews.

Selection Process

Articles were selected by applying the criteria to the title and abstract of each study. Studies that were selected at this stage were then assessed in their entirety. Each stage was conducted by two researchers blindly and independently. Two reviewers (LM and TM) examined the titles and abstracts and did the full-text screening. When disagreement occurred, it was resolved through consensus.

Data Collection Process

For all the included studies, characterization of data and results were exported into a datasheet by one of the authors (LM) and confirmed by the other (MS).

Type of Data Collected

Studies were characterized according to setting, intervention, comparison definition, study duration, number of included participants overall and in each study group, the proportion of missing data, participants' mean age, the proportion of male individuals, and deprescribing target. Outcomes retrieved from each study were categorized as PIP- or PIM-related and by overall number of prescriptions, adverse drug reactions, and potential drug-drug interactions.

Analysis of Results and Assessment of the Risk of Bias

Possible bias in randomized controlled trials (RCTs) was independently identified using the Cochrane Collaboration Risk

of Bias tool [29] by two researchers (TM and LM). This assessment was confirmed by other authors (IV and MS). Risk of bias was determined with regard to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and other biases.

The included articles did not permit the performance of a meta-analysis because there were not a minimum of three studies using the same deprescribing target. Thus, only a narrative synthesis was performed. We have summarized the main features and results of all the included studies, discussed their limitations, and proposed future research avenues.

Results

Description of the Studies

Using our search strategy, 3756 articles were identified through MEDLINE, Central, EMBASE, and Web of Science databases. One article was identified through contact with specialists. After duplicates were removed, 2819 articles remained. The titles and abstracts were screened, and 2767 studies were excluded. Of these, 52 articles were selected to assess eligibility and their full text was analyzed. Of these, 36 articles were excluded. Ultimately, we included 16 studies in our systematic review. No new article was found by searching in the included studies' reference lists, trial registries, or grey literature. The article selection process and reasons for exclusion are described in Figure 1.

The characteristics of the included studies are described in Table 1. More than half (10/16) of the included studies were RCTs, one was a crossover study, and five were pre-post intervention studies. Most studies were conducted in North America (Canada and United States; n=11) [30-40]. The remaining were conducted in Europe (n=5) [41-45].

Six studies were conducted exclusively in secondary health care institutions [35,37,38,40,44,45]. In two studies, only emergency department participants were included [33,39]. In total, six studies were performed exclusively in primary health care institutions [30-32,41-43], one study took place in a health maintenance organization [34], and one study included participants from both secondary and primary health care institutions [36]. Six studies took place at teaching hospitals [36-38,40,44,45].

Most commonly, the standard of care was the only comparator (n=11). The interventional design was always based on a CDS tool, which was usually included in the electronic medical record with several different features. In some cases (n=6), complex interventions were performed that included training and engagement sessions and/or leaflet provision.

The RCTs had an inclusion period ranging from 3 to 30 months (see Table 2). The crossover study included four on-off periods with a 6-week duration [33]. The pre-post intervention studies frequently compared different time periods.

Figure 1. Flow diagram on search and article inclusion, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

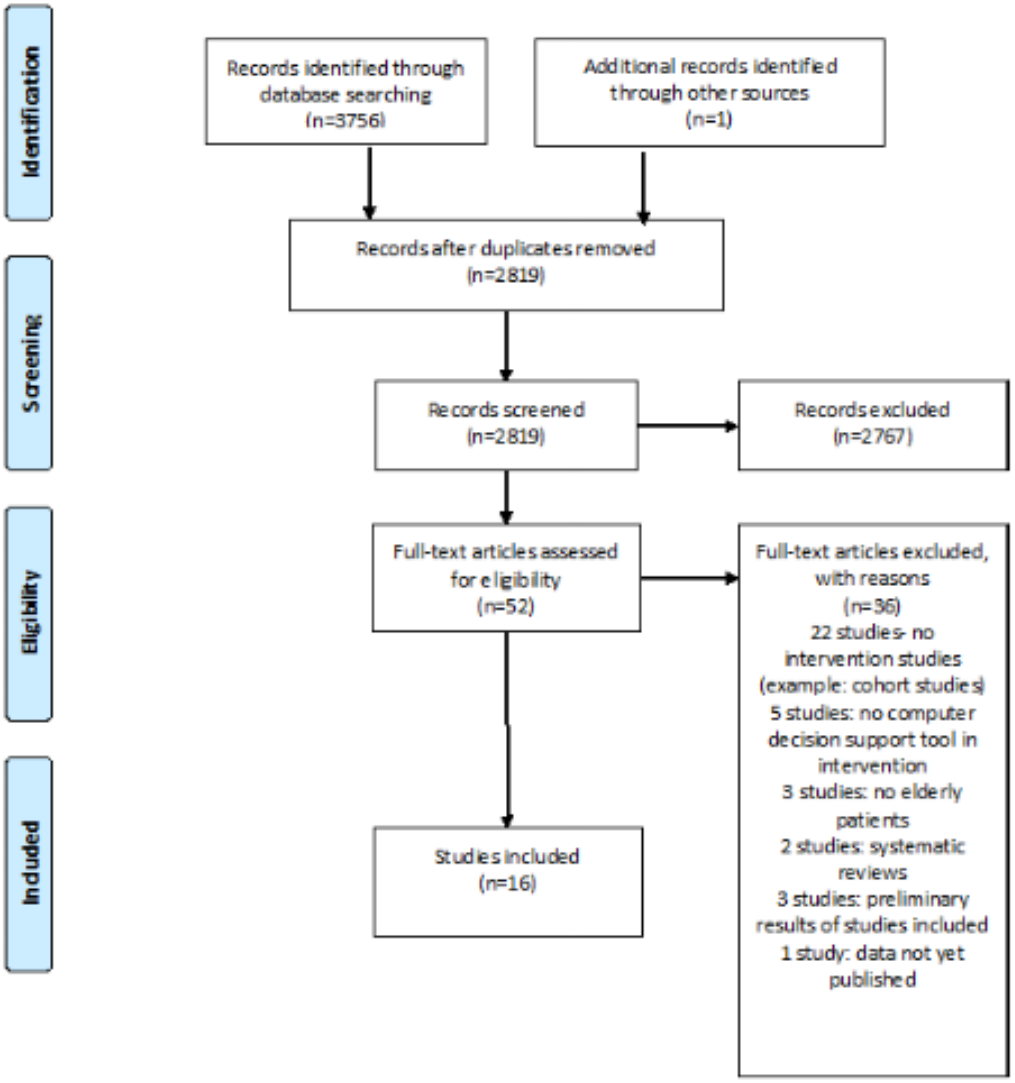

Table 1. Descriptions of the included studies in the systematic review (N=16).

Author, year; (study); country	Setting	Comparator	Intervention	Deprescribing target
Randomized controlled trials				
Tamblyn et al [30], 2003; Canada	PHC[a]	Usual care[b]	Computerized decision support tool providing alert identified problem + presented possible consequences + provided alternative therapy	PIP[c] (159 clinically relevant PIPs in the elderly defined by expert consensus)
Price et al [31], 2017; Canada	PHC (8 GP[d])	Usual care	Clinical decision support tool showing alert with specific STOPP[e] guideline content in electronic medical record	PIPs (40 STOPP criteria)
Avery et al [41], 2012; (PINCER); UK	PHC (72 GP)	Computer-generated simple feedback	PINCER; comparator + pharmacist-led information technology complex intervention	PIPs on NSAIDs[f], beta blockers, ACE[g] inhibitors, or loop diuretics
Erler et al [42], 2012; Germany	PHC (46 GP)	Usual care	Interactive 1-hour workshop for physicians on detection and management of CKD[h] + provision of desktop checklist of medications to be reduced or avoided + patient information leaflets + training in the use of software "DOSING"	Prescription exceeding recommended standard; daily dosage >30% or recommended; maximum daily dose in CKD patients
Clyne et al [43], 2015; (OPTI-SCRIPT); Ireland	PHC (21 GP)	Usual care + simple, patient-level PIP postal feedback	Comparator + academic detailing with pharmacist + medicine review with Web-based pharmaceutical treatment algorithms + leaflets	PIPs using 28 criteria from the study
Cossette et al [40], 2017; Canada	SHC[i] (teaching hospital)	Usual care	KT[j] strategy; distribution of educational materials + in-services by geriatricians + computerized alert systems pharmacist-physician	7 PIMs[k] based Beers and STOPP geriatric criteria and drugs with anticholinergic properties or acting on the central nervous system
Fried et al [32], 2017; (TRIM); USA	PHC (Veterans Affairs; medical center)	Usual care only and usual care with telephonic patient assessment	2 Web apps: (1) extracts information on medications and chronic conditions from the electronic health record, (2) interface for data chart review and telephonic patient assessment + a set of automated algorithms evaluating medication appropriateness + patient-specific medication management feedback report for the clinician	Medication appropriateness based on range of criteria, including feasibility in context of patient's cognition and social support, potential overtreatment of DM[l] or hypertension, "traditional" PIMs according to Beers and STOPP criteria, inappropriate renal dosing, and patient report of adverse medication effects
O'Sullivan et al [44], 2016; Ireland	SHC (teaching hospital)	Usual medical and pharmaceutical care	Clinical decision support software supported structured pharmacist review of medication designed to optimize geriatric pharmaceutical care	Medicines associated with "nontrivial" adverse drug reactions (according to WHO)
Terrel et al [33], 2009; USA	ED[m] (teaching hospital)	Computerized; physician order entry without alerts	Computer-assisted decision support alert when PIM was being prescribed + rationale + recommended safer substitute therapies. If physician chose to continue, second menu displayed to query most important reason	9 high-use and high-impact PIMs[n]
Raebel et al [34], 2007; USA	HMO[o] (18 medical offices + 21 pharmacies)	Usual care	Medication alert generated from PIMS not allowing prescription label to be printed until the pharmacist actively determined whether prescription should be dispensed; pharmacists should communicate notifications to prescribing clinicians	Newly prescribed PIMs based on the Beers, Zhan and Kaiser Performance Care Management Institute lists of medications to be avoided in older people[p]
Crossover studies				

Author, year; (study); country	Setting	Comparator	Intervention	Deprescribing target
Peterson et al [35], 2005; USA	SHC	Usual computerized order entry	Guided dosing of psychotropic medication integrated in Brigham Integrated Computer System	Benzodiazepines, opiates, and neuroleptics
Pre-post intervention studies				
Ruhland et al [36], 2017; USA	SHC + PHC; (1 teaching hospital + 2 community hospital + 31 clinics)	Usual care	Clinical decision support system creating an alert + rational and; alternative medication through Epic (an integrated electronic medical record)	PIMs on glyburide
Mattinson et al [37], 2010; USA	SHC (teaching hospital)	Usual care	Medication-specific warning system (advised alternative medication or dose reduction)	PIMs on medications not recommended for use in older patients (not recommended medications) and those for which only a reduced dose was advised (dose-reduction medications)
Lester et al [38], 2015; USA	SHC (teaching hospital)	Computerized physician order entry without alerts	Computerized; physician order entry with pop-up alerts for selected PIPs containing links to articles relevant to the alert	PIPs on diphenhydramine, metoclopramide, and antipsychotics
Ghibelli et al [45], 2013; (INTERcheck); Italy	SHC (teaching hospital)	Analysis without any interference	Computer-based application (INTERCheck) that collects, stores and automatically; provides drug information to reduce or prevent PIPs	PIMs from 2003 Beers Criteria; potential DDIs[q]; and Anticholinergic Cognitive Burden Scale
Stevens et al [39], 2017; (EQUiPPED); USA	ED (10 Veterans Affairs; medical centers)	Usual care	EQUiPPED interventions: education + informatics-based clinical decision support + individual provider feedback	PIMs from 2012 Beers Criteria category 1 (to avoid in all older adults)

[a]PHC: primary health care.

[b]Each physician was given a computer, printer, health record software, and access to the internet.

[c]PIP: potentially inappropriate prescription.

[d]GP: general practice.

[e]STOPP: Screening Tool of Older People's Prescriptions.

[f]NSAID: nonsteroidal anti-inflammatory drug.

[g]ACE: angiotensin-converting enzyme.

[h]CKD: chronic kidney disease.

[i]SHC: secondary health care.

[j]KT: knowledge translation.

[k]PIM: potentially inappropriate medication.

[l]DM: diabetes mellitus.

[m]ED: emergency department.

[n]High-use and high-impact PIMs: promethazine, diphenhydramine, diazepam, propoxyphene with acetaminophen, hydroxyzine, amitriptyline, cyclobenzaprine, clonidine, indomethacin.

[o]HMO: health maintenance organization.

[p]Examples of medications to be avoided in older people: amitriptyline, chlordiazepoxide, chlorpropamide, diazepam, doxepin, flurazepam, aspirin in combination with hydrocodone or oxycodone, ketorolac, oral meperidine, and piroxicam.

[q]DDI: drug-drug interaction.

Table 2. Characterization of the included studies in the systematic review, including study type, study duration, sample size, and participant demographics (N=16).

Study	Study duration (months); date range	Sample size, N	Participants, n			Outcome missing data, n (%)
				Age (years), mean (SD)	Gender (male), n (%)	
Randomized controlled trials						
Tamblyn et al [30]	13; (01/1997-02/1998)	12,560	C[a]: 6276; I[b]: 6284	C: 75 (6); I: 75 (6)	C: 2248 (36); I: 2439 (39)	N/R[c]
Price et al [31]	8; (02-10/2015)	81,905	C:37,615; I: 44,290	N/R; all >65 years	N/R	N/R
Avery et al [41]	6 (and 12)	480,942	C: 37,659; I: 34,413	N/R	N/R	C: 22 (0.06); I: 28 (0.08) for outcome 3
Erler et al [42]	6	404	C: 206; I: 198	C: 80 (9); I: 81 (6)	C: 63 (31); I: 81 (41)	C: 9 (4); I: 0 (0)
Clyne et al [43]	6; (10/2012-09/2013)	196	C: 97; I: 99	C: 76 (5); I: 77 (5)	C: 50 (52); I: 55 (56)	C: 3 (3); I: 3 (3)
Cossette et al [40]	10 weeks; (09/2015-12/2015)	321	C: 133; I: 139	C: 81 (7); I: 82 (8)	C: 53 (41); I:48 (38)	C: 5 (4); I: 13 (9)
Fried et al [32]	3; (10/2014-01/2016)	156	C1: 36; C2: 39; I: 81	<70 years C: 25 (39); I: 27 (42)	C: 63 (99); I: 63 (99)	C1: 4 (11); C2:7 (18); I: 17 (21)
O'Sullivan et al [44]	13; (06/2011-07/2012)	737	C: 361; I: 376	C: 78b; (IQR 72-84); I: 77; (IQR 71-83)	C: 190 (51); I: 180 (50)	C: 17 (5); I: 17 (5)
Terrel et al [33]	30; (12/01/2005-07/07/2007)	5162	C: 2515; I: 2647	C: 74 (7); I: 74 (7)	C: 880 (35); I: 929 (35)	N/R
Raebel et al [34]	12; (18/05/2005-17/05/2006)	59,680	C: 29,840; I: 29,840	C: 74; (5-95 percentile 66-88); I: (5-95 percentile 66-88)	C: 12,843 (43); I: 12704 (43)	N/R
Crossover studies						
Peterson et al [35]	4 × 6 week on-off periods; (08/10/2001-16/05/2002)	3718	C: 1925; I: 1793	C: 75 (7); I: 75 (7)	C: 905 (47); I: 843 (47)	N/R
Pre-post intervention studies						
Ruhland et al [36]	3 + 3; (B[d]: 01/12/2014-28/02/2015); A[e]: 01/03/2015-31/05/2015)	N/R	101 patients with activated alert	75	N/R	N/A[f]
Mattison et al [37]	6 + 41.5; (B: 1/06-29/11/2014; A: 17/03/2015-30/08/2008)	N/R	N/R	N/R; all >65 years	N/R	N/R
Lester et al [38]	12 + 24; (B: Q2 2010; A: Q2s 2011-2013)	29,465	B: 6604; A: 22,861	<75 years; B: 5279 (80); A: 15,633 (68)	N/R	N/R
Ghibelli et al [45]	2 + 2; (B: 04 to 05/2012; A: 06 to 07/2012)	134	B: 74; A: 60	B: 81; A: 81	B: 27 (36); A: 25 (42)	B: 0 (0); A: 0 (0)
Stevens et al [39]	>6 + >12	N/R	N/R	N/R; all >65 years	N/R	N/R

[a]C: comparator group.

[b]I: intervention group.

[c]N/R: not reported.

[d]B: before.

[e]A: after.

[f]N/A: not applicable.

A total of 233,144 participants were included and assessed in RCTs (mean sample size: 21,199; range 196-72,072 participants). The crossover study included 3718 individuals. The pre-post intervention studies included more than 29,700 participants. However, some studies did not report a raw number of participants included in each study period. There was no information regarding whether missing data influenced the outcome assessment in eight studies (50%).

According to our inclusion criteria, all individuals were older than 65 years of age. The mean age in the selected studies was approximately 75 years. Females were often more prevalent, especially in larger studies.

The deprescribing target varied among the studies, and several papers used more than one criterion [30,32-34,40,45]. PIM was defined in some papers using internationally recognized criteria, such as the Beers Criteria (n=5) [32,34,39,40,45], the Screening Tool of Older People's Prescriptions (STOPP) criteria (n=3) [31,32,40], and the Anticholinergic Cognitive Burden Scale (n=1) [45]. In other studies (n=4), some group medications were specifically the target, such as benzodiazepines, opiates, and neuroleptics [35]; glyburide [36]; nonsteroidal anti-inflammatory drugs (NSAIDs), beta blockers, angiotensin-converting enzyme (ACE) inhibitors, or loop diuretics [41]; and diphenhydramine, metoclopramide, and antipsychotics [38].

Results of the Studies

The main results of the included studies are described in Tables 3 and 4. Several definitions and units were used to measure the impact of CDS tools on changes in PIP and PIM drugs (overall or concerning specific drugs). Studies assessed the following PIP- or PIM-related outcomes: number of PIMs started per 1000 visits [30], number of PIMs discontinued per 1000 visits [30], proportion of discontinued PIMs [30], percentage of PIMs [43], mean number of PIMs, risk of receiving a prescription for a drug exceeding the recommended maximum dose [42], risk of receiving a prescription for a drug exceeding the recommended standard doses [42], proportion of reconciliation errors corrected [32], proportion of recommendations implemented [32,33], proportion of patients with at least one PIM, and/or proportion of all prescribed medications that were PIM [33].

Table 3. Results of the included studies including changes in potentially inappropriate prescriptions or medications (N=16).

Study	PIP[a]- or PIM[b]-related outcomes	
	Changes in PIP or PIM drugs	Changes in specific PIP or PIM drugs
Randomized controlled trials		
Tamblyn et al [30]	Number of PIP started per 1000 visits C[c]: 52.2 vs I[d]: 43.8, RR[e] 0.82 (CI[f] 95% 0.69 −0.98); PIP discontinuation C: 44.5% vs I: 47.5%, RR: 1.14 (95% CI 0.98-1.33); number of PIP discontinued per 1000 visits C: 67.4 vs I: 71.4, RR 1.06 (95% CI 0.89-1.26)	Number of PIP started per 1000 visits: drug-disease contraindication C: 18.4 vs I: 16.6, RR 0.89 (CI 95% 0.72-1.10); drug-age contraindication C: 13.7 vs I: 10.7, RR 0.77 (CI 95% 0.59-1.00); excessive duration therapy C: 17.1 vs I: 13.3, RR 0.78 (CI 95% 0.61-0.99); therapeutic duplication C: 6.8 vs I: 6.1, RR 0.87 (CI 95% 0.69-1.11); number of PIP discontinued per 1000 visits: drug-disease contraindication C: 57.9 vs I: 62.6, RR 1.08 (CI 95% 0.85-1.36); drug-age contraindication C: 42.9 vs I: 40.7, RR 0.94 (CI 95% 0.79-1.13); excessive duration therapy C: 32.6 vs I: 32.3, RR 1.00 (CI 95% 0.77-1.29); therapeutic duplication C: 334.0 vs I: 317.1, RR 0.94 (CI 95% 0.59-1.51)
Price et al [31]	Change in PIP C: 0.1% vs I: 0.1%, *P*=.80	
Avery et al [41]	—[g]	At 6 months: history of peptic ulcer prescribed an NSAID[h] without a PPI/history of peptic ulcer without PPI[i] AOR[j] 0.58 (95% CI 0.38-0.89); asthma prescribed a β blocker/asthma AOR 0.73 (95% CI 0.58-0.91); aged ≥75 years long-term ACE[k] inhibitors or loop diuretics without urea and electrolyte monitoring in the previous 15 months aged ≥75 years receiving long-term ACE inhibitors or diuretics AOR 0.51 (95% CI 0.34-0.78); secondary outcomes AOR varied from 0.39-0.96; at 12 months: history of peptic ulcer prescribed an NSAID without a PPI/history of peptic ulcer without PPI AOR 0.91 (95% CI 0.59-1.39); asthma prescribed a β blocker/asthma AOR 0.78 (95% CI 0.63-0.97); aged ≥75 years receiving long-term ACE inhibitors or loop diuretics without urea and electrolyte monitoring in the previous 15 months aged ≥75 years receiving long-term ACE inhibitors or diuretics AOR 0.63 (95% CI 0.41-0.95); secondary outcomes AOR varied from 0.50-0.98
Erler et al [42]	CKD[l] patients with ≥1 prescription exceeding recommended maximum dose AOR 0.46 (95% CI 0.26-0.82); CKD patients with ≥1 prescription exceeding recommended standard dose by >30% AOR 0.66 (95% CI 0.36-1.21)	NS differences in the numbers of patients with potentially dangerous or contraindicated medications
Clyne et al [43]	Percentage of PIP I: 52% vs C: 77%, *P*=.02, AOR 0.32 (95% CI 0.15-0.70); mean number of PIP C: 1.18 vs I: 0.70, *P*=.02	Odds of PIP AOR 0.30 (95% CI 0.14-0.68); NS differences for duplicate or long-term benzodiazepines
Cossette et al [40]	Drug cessation or dosage decrease: at 48h C: 15.9% vs 45.8%, AD[m] 30.0% (95% CI 13.8-46.1); at discharge C: 27.3% vs I: 48.1%, AD 20.8% (95% CI 4.6-37.0); drug cessation: at 48h C: 15.1% vs 51.9%, AD 36.8% (95% CI 15.6-57.9); at discharge C: 34.4% vs I: 45.2%, AD 10.7% (95% CI −10.5 to 31.9); dosage decrease: at 48h C: 17.2% vs 38.1%, AD 20.9% (95% CI 4.1-45.8); at discharge C: 15.8% vs I: 52.4%, AD 36.6% (95% CI 12.3-60.9)	—
Fried et al [32]	Proportion of medication reconciliation errors corrected C: 14.3% vs I: 48.4%, *P*<.001; proportion of ≥1 TRIM recommendations implemented C: 21.9% vs I: 29.7%, *P*=.42	—
O'Sullivan et al [44]	Patients with ≥1 PIP C: 84.6% vs I: 82%	—
Terrel et al [33]	Proportion of visits with a PIP C: 3.9% vs I: 2.6, *P*=.02, OR[n] 0.55 (95% CI 0.34-0.89), ARR[o] 1.3% (95% CI 0.4-2.3); proportion of all prescribed medications that were PIP C: 5.4% vs I: 3.4, *P*=.006, OR 0.59 (CI 95% 0.41-0.85), ARR 2.0% (95% CI 0.7-3.3)	—

Study	PIP[a]- or PIM[b]-related outcomes	
	Changes in PIP or PIM drugs	Changes in specific PIP or PIM drugs
Raebel et al [34]	Newly dispensed ≥1 PIP rate per 100 patients C: 2.20 vs I:1.85, *P*=.002, RRR[p] 16%; newly dispensed ≥1 PIP only for indications included in intervention rate per 100 patients C:1.50 vs I: 1.10, *P*<.001	Newly dispensed ≥1 PIP rate per 100 patients: amitriptyline C: 0.61 vs I: 0.38, *P*<.001; chlordiazepoxide C: 0.05 vs I: 0.04, *P*=.55; diazepam C: 1.38 vs I: 1.28, *P*=.32; doxepin C: 0.14 vs I: 0.11, *P*=.24; flurazepam C: 0.01 vs I: 0.01, *P*=.69; ketorolac C: 0.00 vs I: 0.01, *P*=.50; meperidine (oral) C: 0.01 vs I: 0.01, *P*=N/A[q]; oxycodone/aspirin C: 0.00 vs I: 0.00, *P*=N/A; newly dispensed ≥1 PIP only for indications included in intervention, rate per 100 patients: amitriptyline C: 0.59 vs I: 0.37, *P*<.001; chlordiazepoxide C: 0.05 vs I: 0.04, *P*=.55; diazepam C: 0.71 vs I: 0.56, *P*=.002; doxepin C: 0.13 vs I: 0.09, *P*=.17; flurazepam C: 0.01 vs I: 0.01, *P*=.69; ketorolac C: 0.00 vs I: 0.01, *P*=.50; meperidine (oral) C: 0.01 vs I: 0.01, *P*=N/A; oxycodone/aspirin C: 0.00 vs I: 0.00, *P*=N/A; dispensings of chlorpropamide, hydrocodone/aspirin, or piroxicam C: 0 vs I: 0
Crossover studies		
Peterson et al [35]	Prescription recommended daily dose C: 19% vs I: 29%, *P*<.001; prescription orders with 10-fold dosing C: 5.0% vs I: 2.8%, *P*<.001; prescriptions in agreement with recommendation C: 18.6% vs I: 29.3%, *P*<.001; prescription of nonrecommended drugs C: 10.8% vs I: 7.6%, *P*<.001	Prescription orders with 10-fold dosing: benzodiazepines C: 3.5% vs I: 2.0%, *P*=.01; opiates C: 5.5% vs I: 2.8%, *P*<.001; neuroleptics C: 10.0% vs I: 7.5%, *P*=.35; prescriptions in agreement with recommendation: benzodiazepines C: 20.8% vs I: 28.2%, *P*<.001; opiates C: 16.6% vs I: 29%, *P*<.001; neuroleptics C: 22.5% vs I: 38%, *P*<.001
Pre-post intervention studies		
Ruhland et al [36]	—	Glyburide orders from total oral antidiabetic orders B[r]: 3.3% vs A[s]: 1.6%, *P*<.001; 17.8% patients transitioned off glyburide
Mattison et al [37]	Number of orders per total number of patients per day: not recommended medication B: 0.070 vs A: 0.054, *P*<.001; dose reduction medications B: 0.037 vs A: 0.037, *P*=.71; unflagged medications B: 0.033 vs A: 0.030, *P*=.03; number of orders per number of new patients per day: not recommended medication B: .333 vs A: 0.263, *P*<.001; dose reduction medications B: 0.182 vs A: 0.186, *P*=.51; unflagged medications B: 0.158 vs A: 0.148, *P*=.08	—
Lester et al [38]	—	>65 years prescription rates of: diphenhydramine B: 26.9% vs A: 20%, *P*<.001; metoclopramide B: 16.7% vs A: 12.5%, *P*<.001; antipsychotics B: 8.8% vs A: 9.2%, *P*=.80; ≥65 years: no significant changes for diphenhydramine, metoclopramide, or antipsychotics
Ghibelli et al [45]	Proportion of patients exposed to PIM at discharge B: 37.8% vs A: 11.6%; mean number of PIM per patient at discharge B: 0.4 vs A: 0.1	Proportion of patients exposed to PIM at discharge: high-dose short-acting benzodiazepines B: 21.6% vs A: 6.7%; ticlopidine B: 5.4% vs A: 0.0%; digoxin B: 5. 4% vs A: 1.7%; doxazosin B: 1.3% vs A: 1.7%; clonidine B: 1.3% vs A: 0.0%

Study	PIP[a]- or PIM[b]-related outcomes	
	Changes in PIP or PIM drugs	Changes in specific PIP or PIM drugs
Stevens et al [39]	Average percentage of PIMs per month: site 1 B: 11.9 vs A: 5.1, *P*<.001; site 2 B: 8.2 vs A: 4.5, *P*<.001; site 3 B: 8.9 vs A: 6.1, *P*=.007; site 4 B: 7.4 vs A: 5.7, *P*=.04	—

[a]PIP: potentially inappropriate prescription.
[b]PIM: potentially inappropriate medication.
[c]C: comparator group.
[d]I: intervention group.
[e]RR: relative rate.
[f]CI: confidence interval.
[g]No data.
[h]NSAID: nonsteroidal anti-inflammatory drug.
[i]PPI: proton-pump inhibitor.
[j]AOR: adjusted odds ratio.
[k]ACE: angiotensin-converting enzyme.
[l]CKD: chronic kidney disease.
[m]AD: absolute difference.
[n]OR: odds ratio.
[o]ARR: absolute risk reduction.
[p]RRR: relative risk reduction.
[q]N/A: not applicable.
[r]B: before.
[s]A: after.

Table 4. Results of the included studies including number of prescriptions, adverse drug reactions, and potential drug-drug interactions (N=16).

Study	Overall number of prescriptions	Adverse drug reaction	PDDI[a]	Others
Randomized controlled trials				
Tamblyn et al [30]	—[b]	—	Number of PDDI started per 1000 visits C[c]: 1.5 vs I: 1.6, RR[d] 1.12 (CI[e] 95% 0.68-1.87); number of PPDI discontinued per 1000 visits C: 68.6 vs I[f]: 51.5 per 1000 visits, RR 1.33 (CI 95% 0.90-1.95)	Physicians with more computer problems downloaded information less often (r=−.31)
Price et al [31]	—	—	—	Description of 12 data quality probes; alert awareness: all participants in I were aware of STOPP[g] alerts, but not consistently; workflow and display: location on screen and workflow identified as barriers; study disruptiveness: considered as minimal
Avery et al [41]	—	—	—	Mean ICER[h] of intervention: at 6 months £65.6 (2.5-97.5 percentile 58.2-73.0); at 12 months £66.5 (2.5-97.5 percentile 66.8-81.5)
Erler et al [42]	—	—	—	—
Clyne et al [43]	—	—	—	Beliefs about Medicine Questionnaire AOR[i] 0.16 (CI 95% −1.85 to 1.07); 12-item Well-Being Questionnaire AOR −0.41 (95% CI −0.80 to 1.07)
Cossette et al [40]	—	—	—	LOS[j] (median, IQR[k]) C: 9.5 (5-21) vs I: 10 (6-19), *P*=.9; in-hospital death C:11 (8.6%) vs I: 6 (4.8%), *P*=.3; 30-day post discharge ER visits C: 27 (21.1%) vs I: 27 (21.4%); 30-day postdischarge readmissions C: 28 (21.9%) vs I: 20 (15.9%), *P*=.3
Fried et al [32]	Mean number of medications per patient C: 13.8 vs I: 13.3, *P*=.65	—	—	Mean patient active participation C: 2.7 vs I: 5.5, *P*=.001; percentage of patients assessment of care for chronic conditions score >10 C: 15.6% vs I: 29.7%, *P*=.06, OR[l] 2.73 (CI 95% 0.82-9.08); patient medication-related; communication C: 3.6 vs I: 7.5, *P*<.001; mean clinician facilitative communication C: 0.67 vs I: 1.53, *P*=.02; mean clinician medication-related communication C: 4.6 vs I:7.3, *P*=.002; percentage >1 recommendations C: 32.8% vs I: 63.6%, *P*<.001; OR 3.33 (95% CI 1.37-8.04)
O'Sullivan et al [44]	Total number of medications C: 3747 vs I: 4192, *P*<.001; median (IQR) number of medications per patient C: 9 (7-12) vs 12 (8-15), *P*<.001; number (%) of people with polypharmacy (≥5 medications); C: 346 (92.0) vs I: 346 (95.8), *P*=.44	Patients with ≥1 ADR[m] C: 20.7% vs I: 13.9%, *P*= 0.02, ARR[n] 6.8% (95% CI 1.5-12.3); RRR[o] 33.3% (95% CI; 7.7-51.7); NNT[p] 15 (95% CI 8-68)	—	CDS[q] alerts 1000 in 296/361 patients; intervention group attended 54.8% of recommendations; median (IQR) LOS days C: 9 (5-16) vs I: 8 (5-13.5), *P*=.44; hospital mortality C: 4.5% vs I: 4.7%, *P*>.05; interrater reliability for application of WHO-UMC[r] ADR causality criteria k= 0.81; Hallas ADR preventability criteria k= 0.87; application of Hartwig ADR; severity criteria k=0.56
Terrel et al [33]	—	—	—	CDS alerts 114 during 107 visits; 43% of recommendations accepted
Raebel et al [34]	—	—	—	—
Crossover studies		—	—	—

Study	Overall number of prescriptions	Adverse drug reaction	PDDI[a]	Others
Peterson et al [35]	Median (IQR) orders per admission C: 2 (1-3) vs I: 4 2 (1-3), *P*=.43	—	—	Number of altered mental status per 100 patient-days C: 21.9 vs I: 20.9, *P*=.17; median (IQR) LOS days C: 4 (2-6) vs I: 4 (2-6), *P*=.43; in-hospital fall rate C: 0.64 vs I: 0.28; falls per 100 patient-days, *P*<.001, AOR 0.50 (95% CI 0.30-0.82); fall injuries per 100 patient-days rate C: 0.17 vs I: 0.06, *P*=.09
Pre-post intervention studies		—	—	—
Ruhland et al [36]	—	—	—	CDS tool alerted 101 times for 75 providers during encounters for 76 patients over 90 days; physicians were more likely to transition patients off glyburide vs other health care providers (46.2% vs 8.0%, *P*<.001)
Mattison et al [37]	—	—	—	—
Lester et al [38]	—	—	—	—
Ghibelli et al [45]	—	—	Proportion of patients exposed to PDDI at discharge B[s]: 87.8% vs A[t]: 88.3%; mean number of PDDI per patient at discharge B: 4.5 vs A: 3.7	Median anticholinergic burden at discharge B: 1.5 vs A: 1.1
Stevens et al [39]	—	—	—	—

[a]PDDI: potential drug-drug interactions.
[b]No data.
[c]C: comparator group.
[d]RR: relative rate.
[e]CI: confidence interval.
[f]I: intervention group.
[g]STOPP: Screening Tool of Older People's Prescriptions.
[h]ICER: incremental cost-effectiveness ratio.
[i]AOR: adjusted odds ratio.
[j]LOS: length of stay.
[k]IQR: interquartile range.
[l]OR: odds ratio.
[m]ADR: adverse drug reaction.
[n]ARR: absolute risk reduction.
[o]RRR: relative risk reduction.
[p]NNT: number needed to treat.
[q]CDS: computerized decision support.
[r]UMC: Uppsala Monitoring Centre.
[s]B: before.
[t]A: after.

Effects of Interventions

The CDS tools consistently reduced the number of PIPs started and the mean number of PIPs per patient, while also increasing PIM discontinuation and drug appropriateness. However, in several cases statistical significance was not achieved for some of the assessed measures, such as for PIM discontinuation in the Tamblyn et al article [30], for change in PIMs in the Price et al study [31], and other studies described in Table 3.

Number of Prescriptions

With regard to the impact on the number of prescriptions, the RCT described by Fried et al [32] reported no significant reduction in the mean number of prescriptions in the group exposed to two Web apps. One study obtained information on medications and chronic conditions from an electronic health record, and the second study used an interface for data chart review, a telephone-based patient assessment, a set of automated algorithms evaluating medication appropriateness, and a

patient-specific medication management feedback report for the clinician. In a crossover study [35], there were no significant differences in the median number of medications prescribed per patient during the periods in which guided dosing of psychotropic medication was integrated into the Brigham Integrated Computer System.

In contrast, the RCT described by O'Sullivan et al [44] demonstrated that those in the intervention group (using CDS software structuring pharmacist review of medications designed to optimize geriatric pharmaceutical care) prescribed significantly fewer drugs (both total and median number of drugs). However, no impact was observed for the proportion of people with polypharmacy prescribed more than five drugs at once. This RCT was the only one addressing adverse drug reactions and it concluded that using this software significantly reduced the risk of adverse drug reactions. Furthermore, only 15 patients' medications needed to be reviewed to prevent one adverse drug reaction.

Number of Potential Drug-Drug Interaction

Only two studies assessed whether CDS tools could decrease the number of potential drug-drug interactions [30,44]. One CDS used in an RCT was found to decrease the initiation of PIP, but it did not have a similar impact on deprescription [30].

One pre-post intervention study observed that the proportion of patients exposed to potential drug-drug interactions increased after implementing a computer-based app that collects, stores, and automatically provides drug information to reduce or prevent PIPs [45]. However, the mean number of potential drug-drug interactions per patient at discharge was reduced. Statistical significance was not reported.

Other Measures

Other miscellaneous measures were reported in the studies examined, which should be highlighted. One RCT concluded that having computer problems was directly linked with PIP or PIM information download, and these computer problems could have an impact on the success of CDS tools [30]. Only one study described data quality probes; it found that professionals included in the intervention group were aware of STOPP alerts, although not in a consistent manner. Furthermore, the layout and impact on the workflow of the CDS tool were potential barriers to successful adherence [31].

Adherence to Computerized Decision Support Tools

Several RCTs reported the frequency of adherence to CDS recommendations by a health professional, with values ranging from 33% to 55% [32,33,44]. No significant reduction in the length of stay or intrahospital mortality was found in the RCT described by O'Sullivan et al [44]; in the Cosstte et al study [40], the differences between the intervention and control groups were not statistically different. Similarly, a crossover study found no difference in the length of stay between periods when the CDS tool was either active or inactive [35]. Likewise, no difference was observed with respect to patients' altered mental status or fall injuries. However, there was a significant decrease in the in-hospital rate.

The TRIM RCT concluded that the use of CDS tools significantly improved patients' active participation and facilitated communication between the clinician and the patient [32]. Another RCT found no significant impact on the Beliefs about Medicine Questionnaire or the 12-item Well-Being Questionnaire when general practitioners had access to information from a pharmacist and a medical review with Web-based pharmaceutical treatment algorithms and leaflets in addition to the usual care and simple, patient-level PIP postal feedback [43].

Cost-Effectiveness of Computerized Decision Support Tools

The cost-effectiveness of CDS tools was addressed in one RCT. The authors reported that there was a 95% probability that adding a pharmacist-led information technology complex intervention, in addition to computer-generated simple feedback, could be cost-effective, resulting in a willingness to pay £75 per error avoided at 6 months [41].

Risk of Bias in the Studies Examined

The RCTs received a total score according to the Cochrane Collaboration Risk of Bias tool that ranged from 1 [30,31] to 5 [41,43]. The procedure to guarantee allocation concealment was unclear in eight of ten RCTs. Complete blinding of participants and personnel was not possible due to the nature of the intervention. Blinding for the outcome assessment was not conducted in five studies [31,34,40,41,44], and was unclear if it was successful in another two [30,42]. Both of these biases may have resulted in an overestimate of the CDS tools' impact on PIP or PIM reduction (see Table 5).

Table 5. Risk of bias assessment (according to Cochrane Collaboration Risk of Bias tool) for the randomized controlled trials (n=10).

Study	Risk of bias items							Total score (max=7)
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	
Tamblyn et al [30]	?[a]	?	–[b]	?	?	+[c]	–	1
Price et al [31]	+	?	–	–	?	?	–	1
Avery et al [41]	+	+	–	–	+	+	+	5
Erler et al [42]	+	?	–	?	+	+	–	3
Clyne et al [43]	+	?	–	+	+	+	+	5
Cossette et al [40]	+	?	–	–	–	-	+	2
Fried et al [32]	–	–	–	+	+	+	?	3
O'Sullivan et al [44]	?	?	–	–	+	+	–	2
Terrel et al [33]	+	?	–	+	?	+	–	3
Raebel et al [34]	+	?	–	–	?	+	+	3

[a]?: unclear risk of bias.

[b]–: high risk of bias.

[c]+: Low risk of bias.

Several studies did not report whether outcome data were available for all the participants included (n=4) [30,31,33,34]. Other biases were also found in five of the RCTs; namely, selection bias, performance bias, contamination, and underpowered sample sizes.

Regarding the pre-post intervention studies [36-39,45], they were considered high risk following the Cochrane Effective Practice and Organisation of Care [46]. For example, it is expected that pre-post intervention studies are more prone to the Hawthorne effect [47]. The Hawthorne effect happens when people (in this case, prescribers and patients) know they are being watched, which may lead to changes in behavior [47]. We consider that it is possible that being aware of one's study participation could have resulted in prescribers taking more care when prescribing medications.

Limited generalizability was also pointed out by several authors as a major limitation due to the context—single-center design—and the use of CDS tools that were created specifically for the study, which may not be available in other institutions.

Discussion

Principal Results

Despite the fact that withdrawal of PIPs is considered to be evidence-based [48], it is not an easy task [49]. CDS tools may play a role in supporting deprescription. From the 16 studies examined in this review, 10 were RCTs. Although RCTs represent stronger evidence, they lacked important data pertaining to clinical outcomes and presented a significant risk of bias (the total score of the studies using the Cochrane Collaboration Risk of Bias tool ranged from 1 to 5 with a mean value of 3). The most frequent biases included no blinding of health professionals and an unclear risk of breaking allocation concealment. If prescribers are not blinded, this can easily affect the deprescribing process. Health professionals may have been more susceptible to accepting the CDS tool recommendations. Alternatively, patients may have been more likely to agree with the withdrawal process. If a break in allocation concealment occurred, it is expected that investigators may have potentially included older adults that they considered best suited for the intervention group. Both types of bias may have led to an overestimation of the benefit of CDS tools.

We have also included five pre-post intervention studies. The nonrandomized nature of these studies is the major limitation of this analysis. The impact of CDS tools may be confounded by other changes that may have occurred in the institutions during the study periods.

We observed that almost two-thirds of the included studies were performed in the United States, and one-third were performed in European countries. This reflects the importance that has been given to this topic only in developed countries where electronic health record systems are widely available.

Overall Applicability and Quality of the Evidence

Seven studies were conducted in teaching hospitals and clinics [33,36-38,40,44,45], which may indicate potential bias. Teaching units are more prone to accept interventions in patient care, such as changes in a prescription through the use of CDS tools. We can assume that these professionals may be more likely to change a patient's prescription and, therefore, to address PIPs. This tendency may result in an overestimate of the impact of the intervention, and we can only speculate as to what would be the impact in a nonteaching unit.

There is a balance between the number of studies conducted in primary care versus secondary care institutions, and only one was conducted in both. The impact of CDS on PIP or PIM reduction was similar between settings despite differences in the health professional and population characteristics. This

suggests that the CDS tool might be successful in the context of a larger patient population.

The generalization of our results may be limited for several reasons. First, most studies used standard care as a comparator without providing additional details. In such a complex context, the management of older patients in institutions with several levels of care may mean that standard care could differ greatly between studies.

Second, the intervention varied greatly as a result of using different electronic systems, contents, and layouts. The intervention frequently included several features beyond the creation and application of a CDS tool itself.

Third, the main outcome definition was also diverse. Several studies used STOPP [31,32,40] and Beers Criteria [32,34,39,40,45] to define which medications were targeted. Both criteria are widely used worldwide, and although they do not provide a list of prohibited medications, they are an important tool for physicians due to their evidence-based rationale and constant updating. Nevertheless, the authors chose different groups of criteria for their outcome measures.

Fourth, the studies selected different participants and had widely variable sample sizes. Only two studies addressed potential drug-drug interactions [30,45] and one addressed adverse drug reactions [44]. Due to the increase of polypharmacy in older adults, the risk is higher for experiencing drug-drug interactions and adverse drug reactions. For the former, no significant impact was found, whereas for the latter, using a CDS tool significantly decreased the number of adverse drug reactions.

This tool, which included a clinical decision support software and a structured pharmacist review of medication [44], seems to be promising for aiding medication reconciliation activities. Most of the reconciliation issues highlighted by this CDS tool were accepted by the health care professionals involved. In particular, the Erler et al study [42] should, in our opinion, have assessed these two topics because they studied a population with renal impairment, which is particularly susceptible to adverse drug reactions and drug interactions. Similarly, only two studies assessed the impact of CDS tools on length of stay [35,40], and two assessed intrahospital mortality [40,44]. No differences were found between those using a CDS tool and those not using a CDS tool. Cost-effectiveness was also assessed by one study, which reported a 95% probability of a CDS tool being cost-effective due to a willingness to pay £75 to prevent an adverse drug reaction in a 6-month period [41]. The study's results may have been underestimated due to low adherence to CDS recommendations. Three RCTs that evaluated adherence reported values fluctuating from 33% to 55% [32,33,44]. Finally, we consider the possibility that the Avery et al trial [41] could have explored the issue of prescription NSAIDs to patients with a history of asthma as a secondary outcome because the authors had information on both conditions (prescriptions of NSAIDs and a history of asthma). This analysis could yield interesting information about the patterns of prescribing NSAIDs to these patients.

Strengths and Limitations

This review presents some limitations. We have chosen to include both RCTs (n=10) and pre-post studies (n=6). We acknowledge that the latter provide a lower level of evidence. Nevertheless, they have assessed some outcomes for which no additional evidence exists. In addition, we have focused our search on articles having PIP modification outcomes, thus some studies assessing changes in PIM may have been missed.

Our search terms were more limited to PIP; therefore, this paper may have missed some studies regarding PIM. Nevertheless, no new articles were found when searching in the references from the included studies and in the grey literature

Major strengths of our study include the fact that we have followed the Cochrane Collaboration Handbook [50], which makes our study less susceptible to major biases and errors. Furthermore, no new references were found from searches in the grey literature, pertinent scientific meeting books of abstracts, and the included studies' list of references, which suggests that our search strategy was exhaustive and all pertinent articles had been included.

However, the quality of the results of a systematic review is dependent on the available data. For all that was previously described, we believed that conducting a meta-analysis was not possible. Thus, only a narrative synthesis has been provided.

Comparison With Prior Work

To our knowledge, there are three previously published systematic reviews assessing the impact of CDS tools on PIP or PIM [51-27]. Due to an increase in the search period, the use of broader search criteria, and our overall methodology, we were able to include five additional RCTs [31,32,40,43,44]. These studies added evidence with new outcomes, such as well-being and patients' beliefs [43], reduction of adverse drug reactions [44], and users' perspectives [31].

The highlight of the findings in the more recent RCTs were as follows. In the study by Price et al [31], alerts with specific STOPP guideline content in electronic medical records positively changed PIPs (comparator: 0.1% versus intervention: 0.1%, P=.80), but not significantly. In the study by Clyne et al [43], the intervention consisted of Web-based pharmaceutical treatment algorithms that led to a lower percentage of PIPs (intervention: 52% versus comparator: 77%, P=.02). In the trial by Cossette et al [40], a computerized alert system-based pharmacist-physician intervention was able to significantly increase drug cessation or decrease dosage at discharge (comparator: 27.3% versus intervention: 48.1%; absolute difference 20.8%, 95% CI 4.6-37.0). In the TRIM trial [32], the proportion of medication reconciliation errors was significantly diminished (comparator: 14.3% versus intervention: 48.4%, P<.001). In the article by O'Sullivan et al [44], clinical decision support software reduced adverse drug reactions among older patients (control patients: 20.7% versus intervention patients: 13.9%, P=.02). In sum, articles published since 2012 substantiated the value of CDS to improve PIP- or PIM-related outcomes.

Conclusions

The use of CDS tools had a positive impact on PIP independently of the outcome definition in the majority of the studies included in our analysis. However, statistical significance was not always achieved. Several possible sources of bias and experimental limitations were found in the included studies, and evidence is lacking regarding the impact of CDS tools in potential drug-drug interactions, adverse drug reactions, length of stay, mortality, and cost-effectiveness.

This research suggests that RCTs assessing the impact of CDS tools could be conducted in both primary and secondary health care settings using medication targets defined by Beers or STOPP criteria.

To replicate the intervention in different RCTs, a standard CDS tool could be developed. These CDS tools could promote communication between physicians and pharmaceutical servives. These RCTs could also assess adverse drug reactions, quality of life measurements, and patient and professional satisfaction, with a reasonable follow-up to clarify the clinical usefulness of these tools.

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Conflicts of Interest

None declared.

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Abbreviations

CDS: computerized decision support
NSAID: nonsteroidal anti-inflammatory drugs
PDDI: potential drug-drug interaction
PIM: potentially inappropriate medications
PIP: potentially inappropriate prescriptions
RCT: randomized controlled trial

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Appendix 5.

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Translation and adaptation of the STOPP-START screening tool to Portuguese for detecting inappropriate prescriptions in older people: a protocol

BMJ Open

Translation and adaptation of the STOPP-START screening tool to Portuguese for detecting inappropriate prescriptions in older people: a protocol

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ABSTRACT

Introduction Rational prescribing for older adults is a challenge because they usually exhibit multimorbidity and multimedication. One available and reliable tool to tackle this issue consists of the Screening Tool of Older People's Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START), which has been associated with improvements in clinical outcomes. Our goal here is to translate and validate the STOPP-START screening tool for use with Portuguese general practitioners/family physicians.

Methods and analysis The study will be conducted in four phases: phase I—translation of the STOPP-START screening tool to Portuguese; phase II—data collection of patient data; phase III—intrarater reliability and agreement study; and phase IV—inter-rater reliability and agreement study.

Ethics and dissemination This study was approved by the Ethics Committee of the Central Health Region of Portugal (where the study will take place). Every participant will sign a written consent form. We intend to publish the full article in a related peer-reviewed journal, conference presentations, reports and in a PhD thesis.

Strengths and limitations of this study

- This study will develop the first Portuguese version of the Screening Tool of Older People's Prescriptions and the Screening Tool to Alert to Right Treatment criteria.
- This is the first study in a Portuguese primary care setting that aims to develop a useful tool for the appropriate prescription of older patients.
- The main limitation of the study is that it is focused on Portugal and it may not apply to other countries where Portuguese is not the main language.

INTRODUCTION

In Organisation for Economic Co-operation and Development countries, the number of older adults is increasing[1] as well as their life expectancy.[2 3]

Caring for older adults is a challenge for healthcare systems[4] because older adults are more likely to have more than one chronic disease.[5 6] For example, multimorbidity in the elderly can be higher than 90% in Portugal.[5] Therefore, adults aged ≥65 years are more likely to be prescribed with multiple drugs[7–9] and may be more susceptible to inappropriate medication use.[10–12]

Potentially inappropriate medications (PIMs) can be described as the use of medications that potentially have more risks than benefits even though safer pharmacological and non-pharmacological alternatives are available.[10] Potentially inappropriate prescription is a different concept than PIM, and includes the overprescription, underprescription and misprescription of medications (eg, inappropriate dose or duration).[13]

There are various tools to help physicians identify PIM such as the Beers Criteria[14] and the Potentially Inappropriate Medications in the Elderly list.[15] The combination of the Screening Tool of Older People's Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START)[16 17] is another widely used tool. One of the advantages of this tool is that it not only considers PIM, but also the indications to start an appropriate medication (START).

Versus other tools, some studies have shown that the STOPP-START tool can identify a significantly higher proportion of patients requiring hospitalisation as a result of PIM-related adverse events,[16] can reduce the highest number of medications and can identify more potential major clinical issues.[18] The criteria for STOPP-START have been associated with improvement in prescribing quality and clinical outcomes.[19] These criteria have been adapted for other languages, such as French.[20] In this adaptation, 50 data sets of patients hospitalised in an academic geriatrics

department were analysed independently by one geriatrician and one general practitioner. They considered 87 STOPP-START criteria of the original version. The data sets involved 418 prescribed medications. The proportions of positive and negative inter-rater agreements were 99% and 95%, respectively, for STOPP and 99% and 88% for START; Cohen's κ coefficients were 0.95 for STOPP and 0.92 for START. The results indicated an excellent inter-rater agreement.

Inter-rater reliability of STOPP and START criteria was also tested between multiple physicians practising independently in Europe.[21] After translation of the criteria into their local language, doctors in Belgium, Czech Republic, Italy, Spain and Switzerland applied the criteria to 20 data sets selected from 200 patients aged ≥65 years of a university teaching hospital in Ireland. The median κ coefficients between raters were 0.93 (0.90 to 0.96) for STOPP criteria and 0.85 (0.82 to 0.91) for START criteria. The results demonstrated good inter-rater reliability of STOPP-START criteria. Therefore, the authors concluded that STOPP and START criteria are generalisable across different European countries and languages.[21]

Reliability and agreement are different concepts but have been used without distinction in many studies.[22] Reliability can be defined as the ratio of variability between scores of the same subjects (by different raters or at different moments) to the total variability of all scores in the sample. Agreement is connected to the question about whether observations are similar or the degree to which they differ.

We aim to make the first translation and validation[23] of the English STOPP-START tool for Portuguese family doctors. In the validation study, we deal with two aspects of reliability and agreement concepts: inter-rater reliability and agreement (different raters using the translated STOPP-START tool assess the same patients), and intra-rater reliability and agreement (the same rater using the translated STOPP-START tool assesses the same subjects at two different moments).

METHODS AND ANALYSIS

Study design

This study will be conducted in four phases as illustrated in figure 1 (timeline available in online supplemental appendix I). The first phase (phase I) is the translation to the Portuguese language followed by data collection (phase II).

Phase III consists of an intrarater reliability and agreement study, and phase IV is an inter-rater reliability and agreement study. We made a preregistration on 'Open registries Network' (DOI 10.17605/OSF.IO/SK2RJ).

Phase I: translation to Portuguese

The translation of the STOPP-START screening tool will follow the Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes Measures.[20] We have already obtained permission from STOPP-START's authors to translate and validate the tool for Portuguese. We will recruit a key in-country consultant who is a native Portuguese and fluent English speaker and will be the main contact to perform and help with the translation. This consultant will also have a background in health research and experience in translating English documents. We will obtain two independent translations of the STOPP-START. One will be done by the key in-country consultant, and the other will be performed by a forward translator who is also a native Portuguese and fluent English speaker.

The two translations will be reconciled by the research team to obtain a final consensus translation that will be back-translated.

The back-translation (from Portuguese to English) will be done by a professional translator who is a native speaker of English and fluent speaker of Portuguese. This translator will have no prior knowledge of the original English version. Afterwards, the back-translation will be compared with the original to identify any relevant differences.

In the final step, the reconciled Portuguese STOPP-START version will be distributed to a group of 15 general practitioners to verify if there are any interpretation issues. The research team will analyse the results from the application of the STOPP-START tool to prepare the final version.

Phase II: data collection

Design

This will be a cross-sectional, analytical study.

Setting

The study will be conducted in a primary care centre in the Centre Region of Portugal.

The health unit is located in Aveiro. Five family doctors follow a total of 8165 patients; 1625 patients aged ≥65 years.

Sample size

To calculate the sample size for the validation study, we used the function CIBinary of the kappaSize package of R software.[24] For the intrarater study, we obtained a sample size of 334 subjects considering the following parameters: estimated κ value: 0.68[25] ; error margin: 0.1; prevalence of each item of the START criteria: 0.25; number of moments: 2; and significance level: 5%. In the inter-rater study, we obtained a sample size of 205 subjects considering the following parameters: estimated κ value: 0.68[25] ; error margin: 0.1; prevalence of each item of the START criteria: 0.25; number of raters: 3; and significance level: 5%. The 205 patients for inter-rater assessment will be randomly selected from the 334 subjects used for the intrarater evaluation.

Study procedures

Recruitment of patients

Patients will be randomly selected (independent random sampling using computer-generated random digits) from

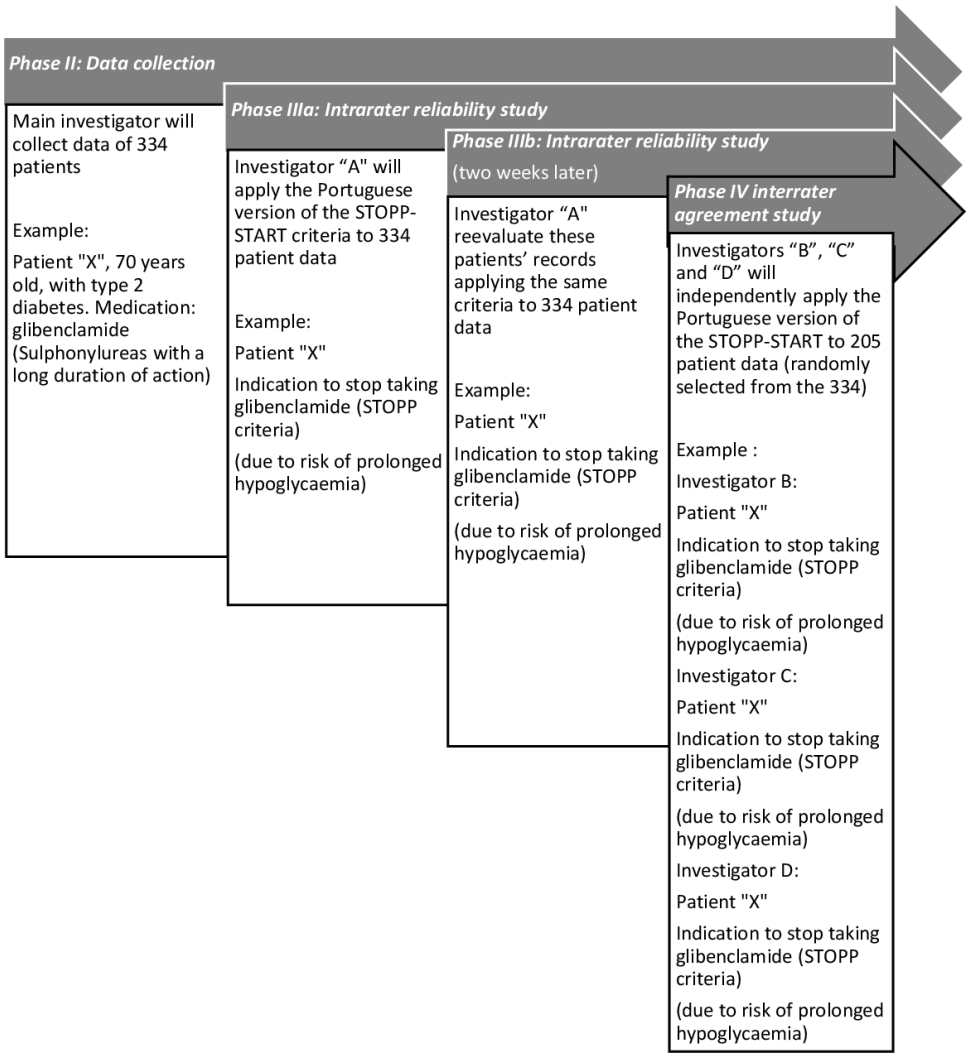

Figure 1 Flow chart and example. START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions.

a list of patients aged ≥65 years from a primary care centre. They will be invited by telephone to participate in the study. The investigator or a previously trained research associate will then interview the patients in the general practitioner office. Recruitment will continue until 334 patients are enrolled.

Exclusion criteria include incapacity or unwillingness to provide written informed consent, diagnostic of psychotic disorder, institutionalisation and the presence of terminal illness.

At inclusion, the main investigator will collect sociodemographic patient data such as age, gender, educational level, labour status and marital status. Clinical data collection will include identification of total number of medications for chronic diseases, any prescribed drugs, dosage, pharmaceutical dosage form and route of administration, the reason for taking medication, allergies, drug-related conditions and history of adverse drug reactions, and current or past conditions/diseases. A detailed list of current or past conditions/diseases that will be included is given in the online supplemental appendix II.

The investigator will also collect the following information: presence or absence of ankle oedema, bone mineral density T-scores, history of influenza and pneumococcal vaccination, heart rate (beats per minute), and systolic blood and diastolic blood pressure (mm Hg).

The data are summarised in table 1.

Data source

We will collect data using electronic health record consultations and clinical patient interviews.

Database

The information collected will not include information that might identify the patients. Each patient will be numbered from 1 to 334 to protect their identity.

To evaluate data obtained throughout the study, a data safety monitoring board will be set up that will be composed of two external investigators with board expertise in this clinical field and academic and scientific activities.

Table 1 Patients' data (phase II)

Patients' data	
Sociodemographic data	Age Gender Educational level Labour status Marital status
Clinical data	Number of medications for chronic diseases, prescribed drugs Pharmaceutical dosage form and route of administration, reason for taking medication Allergies Drug-related conditions History of adverse drug reactions Current or past conditions/diseases* Presence or absence of ankle oedema Bone mineral density T-scores History of influenza and pneumococcal vaccination heart rate (bpm) Systolic blood and diastolic blood pressure (mm Hg) Estimated glomerular filtration rate Serum K+ (mmol/L) Serum Na+ (mmol/L)

*Available at online supplemental appendix II.
bpm, beats per minute.

Following the Portuguese Clinical Research Law, all data recorded during the study will be stored for 5 years in a safe and proper place in the primary investigator's health centre after the closure of the investigation. All data containing participant codes will be destroyed after this period.

Phase III: intrarater reliability and agreement study

An independent researcher/family doctor (named investigator 'A') will apply the Portuguese version of the STOPP-START criteria to all the patients using the information collected in phase II.

Investigator 'A' is an independent researcher with more than 10 years of experience of clinical practice.

To ensure intrarater reliability and agreement, the same doctor will re-evaluate these patients' records applying the same criteria 2 weeks later to avoid recall bias.[26 27]

Phase IV: inter-rater reliability and agreement study

Three independent investigators/family doctors (named investigators 'B', 'C' and 'D') will independently apply the Portuguese version of the STOPP-START using the data, collected in phase II, of 205 randomly selected participants.[28] These three physicians are based in different health units and they will only have contact with the corresponding author who will give them the comprised data. Investigators 'B', 'C' and 'D' will independently assess the STOPP and START criteria in each of the 205 data sets and will be invited to give written comments if necessary. Inter-rater agreement will be assessed by comparing the results of the three raters.

Statistical analysis

Data will be stored with Microsoft Excel software. Data analyses will be made with SPSS Statistics V.27.0 and the software R.

Categorical variables will be described by absolute and relative frequencies.

Continuous variables will be described by mean and SD if normally distributed or by median and IQR if not normally distributed. Normality will be assessed by observation of histograms and implementation of the Kolmogorov-Smirnov test.

Intrarater/inter-rater reliability will be measured using Cohen's κ coefficient and the respective 95% CI.[22] The Cohen's κ coefficient will be interpreted as poor ($\kappa \leq 0.2$), fair ($0.21 \leq \kappa \leq 0.40$), moderate ($0.51 \leq \kappa \leq 0.6$), substantial ($0.61 \leq \kappa \leq 0.8$) and good ($0.81 \leq \kappa \leq 1.00$).[29] Intrarater/inter-rater agreement will be assessed using agreement proportions and specific (positive and negative) agreement proportions and the respective 95% CI.[22]

A p value less than or equal to 0.05 will be considered statistically significant.

Patient and public involvement

No patient or member of the public will be involved in the design of this protocol or the establishment of intervention and the outcome measures.

DISCUSSION

Appropriate prescriptions for older patients are a quality standard for healthcare. General practitioners are the main prescribers and they struggle to identify PIM as well as potential prescribing omissions. The STOPP-START tool is an easy way to manage the care of older patients. It is easier for daily use when adapted for the language of the prescriber.

This study is innovative because it is the first development of a Portuguese version of the STOPP-START criteria. Our research will not be merely a translation but also an adaptation done by independent general practitioners that will potentially increase the use of this version in the primary care setting.

Our research has some limitations such as the fact that even though it will be Portuguese language adaption of the STOPP-START criteria, it is only focused on Portugal and may not apply to other countries where Portuguese is used. This adapted version of STOPP-START is exclusively focused towards primary healthcare centres.

ETHICS AND DISSEMINATION

Every participant will sign a written consent form (online supplemental appendix III). The identity of all participants will be protected throughout the study. The documents used to collect the data of the participants will

contain only an identification code of each participant using a number from 1 to 334.

This protocol was approved on 30 July 2020 by the Ethics Committee of the Central Health Region of Portugal with the reference number 034-2020.

We intend to publish the full article in a related peer-reviewed journal, and results will also be disseminated in conference presentations, reports and in a PhD thesis.

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Appendix 6.

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INAPPROPRIATE PRESCRIPTIONS IN OLDER PEOPLE – TRANSLATION AND ADAPTATION TO PORTUGUESE OF THE STOPP/START SCREENING TOOL

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Article

Inappropriate Prescriptions in Older People—Translation and Adaptation to Portuguese of the STOPP/START Screening Tool

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Abstract: Inappropriate prescribing, which encompasses the prescription of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs), is a common problem for older people. The STOPP/START tool enables general practitioners, who are the main prescribers, to identify and reduce the incidence of PIMs and PPOs and appraise an older patient's prescribed drugs during the diagnosis process to improve the clinical care quality. This study aimed to translate and validate the STOPP/START screening tool to enable its use by Portuguese physicians. A translation-back translation method including the validation of the obtained Portuguese version was used. Intra- and inter-rater reliability and agreement analyses were used in the validation process. A dataset containing the information of 334 patients was analyzed by one GP twice within a 2-week interval, while a dataset containing the information of 205 patients was independently analyzed by three GPs. Intra-rater reliability assessment led to a Kappa coefficient (κ) of 0.70 (0.65–0.74) for the STOPP criteria and 0.60 (0.52–0.68) for the START criteria, considered to be substantial and moderate values, respectively. The results of the inter-rater reliability rating were almost perfect for all combinations of raters ($\kappa > 0.93$). The version of the STOPP/START criteria translated into Portuguese represents an improvement in managing the medications prescribed to the elderly. It provides clinicians with a screening tool for detecting potentially inappropriate prescribing in patients older than 65 years old that is reliable and easy to use.

Keywords: geriatric medicine; quality in health care; general medicine; STOPP/START

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1. Introduction

Today, it is globally accepted that adverse drug reactions (ADRs) are a public health problem and have a significant clinical impact related to morbidity and mortality, which results in the increased use of health services in developed countries [1,2]. ADRs are responsible for about 7% of all hospital admissions, many of which are considered preventable [2,3]. Additionally, about 2–3% of patients admitted with an ADR die as a result [2,4].

ADRs may occur in 6–20% of patients admitted to hospitals, increasing their hospitalization period; highly increasing the costs associated with healthcare [5]; indirectly impacting patients' and their families' economic, social context, and psychological well-being [6,7]; and leading to the discussion of patient participation and involvement in pharmacovigilance [8,9].

The number of older adults is increasing [10], as is their life expectancy [11,12], and these patients are more likely to have more than one chronic disease [13,14] and be prescribed multiple drugs, increasing their susceptibility to inappropriate medication use [15–21].

Inappropriate prescribing that encompasses potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) is a common problem for older people and is closely related to adverse events and ADRs [22]. Older adults are more prone to drug-related problems, as most take several medicines for multiple comorbidities, described as polypharmacy [23,24].

It is necessary to reduce PIMs and PPOs and improve clinical care quality [25]. The STOPP/START (Screening Tool of Older Persons' Prescriptions—STOPP; Screening Tool to Alert to Right Treatment—START) criteria for the use of potentially inappropriate medication in older people recognize the dual nature of inappropriate prescribing by including a list of PIMs (STOPP criteria) and PPOs (START criteria).

STOPP/START is a valid, reliable, and comprehensive screening tool that enables the prescribing physician to appraise an older patient's prescribed drugs in the context of their diagnosis [26]. Since the first publication of the STOPP/START criteria in 2008 [26], the tool has been widely disseminated and validated in many countries at different levels of healthcare (primary care, hospitals, nursing homes). The latest version (version 2) was published in 2014 and consists of 114 criteria, including 80 STOPP criteria and 34 START criteria [20,27]. These criteria are based on an up-to-date literature review and consensus validation among a European panel of experts [20]. The STOPP/START criteria were translated and adapted from English into several languages such as Czech, French [28–30], Italian, Spanish [31,32], and Dutch [33] to facilitate the local application of the criteria worldwide and have had a positive impact on patient evaluation [26].

This tool identifies potentially inappropriate prescriptions (PIPs) [34,35], identifying potentially inappropriate medicines through the STOPP criteria and identifying potential prescription omissions through the START criteria. The prevalence of patients with at least one instance of PIP identified by the STOPP criteria ranges from 21% [36] to 79% [37]. However, this range should be interpreted cautiously due to the heterogeneity of the sample population and study design between the different studies where this tool was assessed. The START criteria have identified at least one instance of PPO in 23% [36] to 74% [37] of patients.

A recent comparison of tools used to identify PIMs showed that the STOPP version 2 criteria identified substantially more PIMs than the EU (7)-PIM list [38], PRISCUS—Potentially Inappropriate Medications in the Elderly list [39–41], FORTA [39,40], and Beers criteria [25,42–46]. The STOPP/START criteria were found to be significantly associated with detecting adverse events in acutely ill older people, unlike the Beers criteria [20,42–45]. Compared to the Beers criteria or the prescribing indicators provided in the Elderly Australia criteria, the number and scope of drug-related problems identified were found to be best represented by the STOPP/START criteria [20,47,48]. Another advantage of this tool is that it considers PIMs and the indications to start an appropriate medication (START) [18].

A previous study from Gallagher et al., concluded that the STOPP/START criteria are generalizable across different European countries and languages [49]. Despite this, in other countries, such as in those with resource-limited healthcare settings, the original STOPP/START criteria might not be directly applicable; thus, modified versions of the STOPP/START criteria have been developed and validated recently [24]. In Portugal, this tool has already been used by Portuguese authors, but the translation and adaptation of the criteria have never been carried out, and the original tool is still used [25,50–53]. The current study aimed to translate and validate the STOPP/START screening tool to enable its use by Portuguese general practitioners/family physicians.

2. Materials and Methods

This study was conducted in four phases: The first phase (phase I) was the translation and adaptation of the STOPP/START screening tool to the Portuguese language, followed

by patient data collection (phase II). Phase III consisted of an intra-rater reliability and agreement study, and phase IV consisted of an inter-rater reliability and agreement study. Preregistration on the 'Open Registries Network' was conducted (DOI10.17605/OSF.IO/SK2RJ (accessed on 31 March 2021), and the translation and adaptation of the STOPP/START screening tool to Portuguese has been described elsewhere [18].

2.1. Phase I: Translation and Adaptation of the STOPP/START Screening Tool to the Portuguese Language

The translation and adaptation of the STOPP/START screening tool followed the Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes Measures [30]. The adaptation and translation were carried out based on the 2014 O'Mahony et al., version of STOPP/START [20]. Permission from the STOPP/START's authors to translate, adapt, and validate this tool for use in Portuguese was obtained by email. The final version was distributed to 15 general practitioners to verify if there were any interpretation issues and improve clarity. The research team analyzed the results obtained from applying the STOPP/START tool and prepared the final version. As a translation was needed, the chance for possible disagreements between raters was reduced by validating these translations before studying the intra-rater and inter-rater agreements. The detailed procedure was published previously in the protocol [18].

2.2. Phase II: Data Collection of Patient Data

Patients were randomly selected from a list of patients aged > 65 years old from a primary care center in the Centre Region of Portugal, following which a total of 8165 patients were followed, with 1625 aged over 65 years old. The sample size was calculated in the published protocol, and 334 subjects were randomly selected to participate in the study [26,54]. Exclusion criteria included incapacity or unwillingness to provide written informed consent, diagnosis of psychotic disorder, institutionalization, and the presence of terminal illness. Patients were interviewed during previously scheduled medical appointments. Every participant signed a written consent form (Supplementary Materials File S1). The identity of all participants was protected throughout the study.

Sociodemographic data such as age, sex, and educational level were collected and are shown in Table 1. Clinical data were collected by consulting health record registries and conducting interviews of clinical patients, including the identification of the total number of medications used for chronic diseases, any prescribed drugs, dosage, pharmaceutical dosage, pharmaceutical form and route of administration, reason for taking medication, allergies, drug-related conditions, history of adverse drug reactions, and current or past conditions/diseases. Other clinical information was also collected and described in the protocol but not used in the adaptation of the STOPP/START tool [18]. The information collected was input into a database, each patient was numbered from 1 to 334 by the main investigator, and the record of the coding was stored offline in an Excel 2016® spreadsheet. All data recorded during this study will be stored for 5 years after the closure of the investigation, following the Portuguese Clinical Research Law. After this period, data containing participant codes will be destroyed.

2.3. Phase III: Intra-Rater Reliability and Agreement Study

As previously proposed by Kottner et al. [55], reliability may be defined as the ability of a measurement to differentiate among subjects or objects, comprising the ratio of variability between subjects or objects to the total variability of all measurements in the sample [56,57]. Intra-rater agreement assesses the extent to which the two responses from the same rater are concordant [58]. By definition, intra-rater reliability refers to the consistency of data recorded by the same rater, using the same scale, classification, instrument, or procedure, to assess the same subjects or objects at different times one rater over several trials. It is best determined when multiple trials are administered over a short period [55]. An independent researcher physician (named investigator/rater 'A') applied the Portuguese version of the STOPP/START criteria to all patient data collected in phase II. The investigator/rater 'A'

was a family doctor with more than 10 years of experience in primary care, which included caring for and making daily prescriptions for older adults. To ensure intra-rater reliability and agreement, two weeks later, investigator A re-administered the tool. Both assessments of rater 'A' were used to study the intra-rater reliability.

Table 1. Characteristics of patients (n = 334).

Variable	*n* (%)
Age, years mean (SD); min–max	74.2 (6.9); 65–99
65–69 years	105 (31.4%)
70–74 years	71 (21.3%)
75–79 years	78 (23.4%)
80–84 years	50 (15.0%)
85+ years	30 (9.0%)
Sex	
Women	159 (47.6%)
Men	175 (52.4%)
Education level	
Early childhood, primary and lower secondary education (level 0–2)	316 (94.6%)
Upper secondary and post-secondary non-tertiary education (levels 3–4)	17 (5.1%)
Short-cycle tertiary education, Bachelor's, Master's, or Doctorate (levels 5–8)	1 (0.3%)
Number of medicines used	
0–1	57 (17.1%)
2 to 4 (Minor polypharmacy)	66 (19.8%)
5 to 9 (Major polypharmacy)	210 (62.8%)
10+ (Severe polypharmacy)	1 (0.3%)

Discrepancies in totals are due to rounding.

2.4. Phase IV: Inter-Rater Reliability and Agreement Study

Inter-rater reliability refers to the consistency of data recorded by different raters, using the same scale, classification, instrument, or procedure, to assess the same subjects or objects. Inter-rater agreement assess the extent to which the responses of two or more independent raters are concordant [58]. In this specific study, intra-rater and inter-rater reliability assist in determining if the measurement tool produces results that can be used by a clinician to make decisions confidently [55]. Three independent researchers (named investigators/raters 'B', 'C', and 'D') independently applied the Portuguese version of STOPP/START using the data collected in phase II. The investigators/raters 'B', 'C', and 'D' were family doctors with more than 10 years of experience in primary care. For the total of 334 subjects who participated in the intra-rater study, 205 patients were randomly selected for the inter-rater assessment [59]. These three physicians were independent investigators and only had contact with the authors to access the collected data. These investigators independently assessed the STOPP/START criteria in each of the 205 patients and were invited to provide written comments if necessary. Inter-rater agreement was assessed by comparing the results of the three raters. Between raters 'B', 'C', and 'D', an inter-rater reliability test was performed. Inter-rater reliability assessment is useful because observers will not necessarily interpret answers (or tools) in the same way and may disagree on how the constructed tool is used [60,61].

2.5. Statistical Analysis

Data were stored with Microsoft Excel 2016® software (Microsoft Corporation, Redmond, WA, USA). Data analyses were conducted using SPSS® V.27.0 (SPSS Inc, Chicago, IL, USA) and R Studio® V 1.3.1093 (Integrated Development for R. RStudio, PBC, Boston, MA, USA). Categorical variables were described using absolute and relative frequencies, n (%). Quantitative variables were summarized by means and their respective standard deviations (SDs), along with minimum and maximum values (min–max). According to the 'Guidelines for reporting reliability and agreement studies', reliability analyses and agreement analyses (intra- and inter-rater) were performed using Kappa statistics and the proportions of a

specific agreement, respectively [62–64]. The Kappa statistics were interpreted as poor if the score was ≤0.2, fair if it was 0.21–0.40, moderate if it was 0.51–0.6, substantial if it was 0.61–0.8, and good if it was 0.81–1.00. The proportion of specific agreement distinguishes agreement on positive (PPos) or negative (Pneg) proportions, which might have different implications in clinical practice [65]. The 95% confidence intervals (95% CI) were presented for Kappa statistics and agreement proportions [55].

Kappa statistics were used for the calculation of both inter- and intra-rater reliability [66]. The Kappa statistic is a coefficient of reliability for categorical data [67]. As the Kappa coefficient is known to be affected by rare observations, it may not always reflect the true agreement rates and will provide an underestimation of the actual agreement [68]. A simple solution for this problem is calculating the proportions of agreement and separating the agreement rates into positive and negative agreements, thus making it easier for readers to interpret the results [63,69].

3. Results

A total of 334 patients were enrolled in this study. The patients' characteristics (age, sex, educational level, and number of medicines used) are described in Table 1.

Educational level was grouped according to the International Standard Classification of Education (ISCED 2011) [70]. The number of medicines used was grouped according to the definition of polypharmacy, grouping the number of medicines [23,71–73].

Intra-rater reliability and agreement involved the analysis of Rater A's evaluation of 334 patients' records and re-evaluation after a 2-week interval. Results are reported in Table 2 (STOPP) and 3 (START). Inter-rater reliability and agreement analyses were performed by three different raters ('B', 'C', and 'D') who evaluated 205 randomized patients from the database. Each rater evaluated the same patients to allow for their comparison. The results obtained for the inter-rater reliability and agreement using the STOPP and START tools are shown in Tables 2 and 3, respectively.

Table 2. Intra- and inter-rater reliability and agreement based on the analysis of the STOPP criteria.

STOPP Criteria	Rater Combination	Agreement (%)		Reliability
		Ppos † (95% CI)	Pneg + (95% CI)	Kappa (95% CI)
Intra-rater	Rater A Rater A	94.2 (93.1–95.1)	75.2 (70.9–79.1)	0.70 (0.65–0.74)
Inter-rater	Rater B Rater C	99.8 (99.4–99.9)	98.9 (97.1–99.7)	0.99 (0.97–1.00)
	Rater B Rater D	99.6 (99.1–99.8)	97.8 (95.5–99.1)	0.97 (0.95–0.99)
	Rater C Rater D	99.5 (99.1–99.8)	97.5 (95.0–98.8)	0.97 (0.95–0.99)
	Rater B Rater C Rater D	99.6 (99.3–99.8)	98.1 (96.6–99.2)	0.98 (0.94–1.00)

† Ppos, agreement on positive proportions. + Pneg, agreement on positive negative proportions.

Table 3. Intra- and Inter-rater reliability and agreement from the analysis of the START criteria.

START Criteria	Rater Combination	Agreement (%)		Reliability
		PPos † (95% CI)	PNeg + (95% CI)	Kappa (95% CI)
Intra-rater	Rater A Rater A	88.2 (85.4–90.6)	71.1 (64.5–76.8)	0.60 (0.52–0.68)
Inter-rater	Rater B Rater C	98.7 (97.3–99.4)	94.4 (88.6–97.7)	0.93 (0.87–0.99)
	Rater B Rater D	98.7 (97.3–99.4)	94.4 (88.6–97.7)	0.93 (0.87–0.99)
	Rater C Rater D	99.1 (97.9–99.7)	96.1 (90.1–98.7)	0.95 (0.91–1.00)
	Rater B Rater C Rater D	98.8 (97.9–99.6)	94.9 (90.8–98.2)	0.94 (0.87–1.00)

† PPos, agreement on positive proportions. + Pneg, agreement on positive negative proportions.

For the STOPP criteria, the intra-rater reliability showed a Kappa coefficient of 0.70 [95% CI 0.65–0.74], considered substantial; the positive and negative proportions of agreement obtained were 94.2% [95% CI 93.1–95.1] and 75.2% [95% CI 70.9–79.1], respectively. The results obtained for the inter-rater reliability were almost perfect, with κ near to

one in all possible combinations of raters. Inter-rater agreement determines the agreement between pairs of raters and all raters' judgments regarding the STOPP criteria.

For the START criteria, the intra-rater reliability showed a Kappa coefficient of 0.60 [0.52–0.68], considered a moderate value; the positive and negative proportions of agreement obtained were, respectively, 88.2% [85.4–90.6] and 71.1% [64.5–76.8]. The inter-rater reliability results were almost perfect, with κ near to one in all possible combinations of raters. Inter-rater agreement determines the agreement between pairs of raters and all raters' judgments regarding the START criteria.

The final version of the Portuguese adaptation of STOPP/START is presented in Supplementary Material File S2.

4. Discussion

This is to the best of our knowledge, the first study to translate and adapt the STOPP/START screening tool to Portuguese. The intra-rater reliability and inter-rater reliability scores obtained were not inferior to those obtained in previous studies conducted in other languages [28–33].

When testing reliability, several approaches are taken to determine consistency [74,75]. However, according to Innes et al., test–retest reliability, intra-rater reliability, and inter-rater reliability are the most common measures used among work-related assessments [74,75].

The first source of intra-rater inconsistency could be explained by various factors related to the assessment process. Rater A presented a high disagreement between two STOPP and START criteria evaluations. A major explanation was based on the analysis of the discrepancies. From 129 discrepancies seen between the first and second evaluation, 94 were related to proton pump inhibitors (F2 or A1 criteria without further investigation). In the second evaluation, with a better knowledge of the tool, the drug was properly assessed. Out of 119 discrepancies found in the evaluation on the START criteria, 51 were related to the introduction of vaccines in the second evaluation (I1 or I2 criteria were used). According to previous studies, a high level of familiarity is required to efficiently apply the STOPP/START criteria in clinical practice [49]. Additionally, raters could differ concerning their experience, specialties, and professional skills and have different perceptions regarding the knowledge required to use a particular item of the assessment tool. It is therefore important to highlight that the professionals that perform medication reviews with the STOPP/START tool should receive adequate training in order to use the tool appropriately [76,77].

One strength of this study is its innovation, with it representing the first development of a Portuguese version of the STOPP/START criteria. Our research was not merely a translation, but also an adaptation carried out by independent general practitioners that will hopefully increase the use of this version in the primary care setting. To ensure intra-rater reliability and agreement, the same doctor re-evaluated patients' records by applying the same criteria 2 weeks later, avoiding recall bias. Additionally, this study provides evidence for a near-perfect inter-rater reliability, meaning that raters almost always agree on whether to exclude/include medicines, although the reasons for these decisions were not necessarily similar. Finally, this version translated into Portuguese can be used by general practitioners or any other medical practitioner and could be used in countries where Portuguese is the main language. However, the differences in healthcare systems between countries; the different ranges of medicines available; and differences in population characteristics, such as genetic or racial differences, should be considered.

One potential limitation was related to the fact that the adapted version of STOPP/START exclusively focuses on primary healthcare centers. The authors deliberately did not include patients with specific pathologies. It is important to clarify that this tool may not be appropriate for use in all population groups or in different healthcare settings, and the assessment tool should be evaluated in future studies, including in other populations with specific pathologies and in different contexts.

Furthermore, some of the randomized patients (n = 26, 8%) did not have any drugs prescribed, which would have reduced discrepancies between the raters when evaluating the STOPP criteria. Another potential limitation is the fact that the current tool was originally published in 2014, which means that there may be new medication and/or additional therapeutic indications that do not fit the current tool. Finally, the raters' decision to stop or start a drug based on this tool was a dichotomous decision and was not validated as either right or wrong from a clinical point of view. No assessment of clarity was performed, so a quality appraisal study should be conducted in the future to improve the clarity of clinical practice guidelines on a language level and enhance its clinical applicability [78].

In addition, using this tool, raters can point out different reasons for withdrawing or adding drugs without this changing the final decision. Since the criteria were applied to data from files in the absence of a clinical evaluation of patients by raters and prescriptions are subject to a certain variation in interpretation concerning the clinical heterogeneity observed in the elderly population, clinical evaluation was not performed by PPOs and the reasons for stopping and starting drugs were not compared [79].

5. Conclusions

The major research result of the current study was the adaptation of the STOPP/START (2014) criteria into Portuguese.

The objective of our research was not to test the tool in a Portuguese population. The use of this tool in this context may not lead to clinical differences for patients, or, at least, this was not the main objective for its use in this study.

The STOPP/START criteria have been proven to be a good tool for detecting potentially inappropriate prescriptions and improving prescription quality in older people in all healthcare settings, therefore leading to improved quality of life in patients, reducing the incidence of PIMs and PPOs, and improving clinical care quality. This research provides clinicians with a screening tool with which to detect potentially inappropriate prescribing in patients older than 65 years old that is easier to use for Portuguese native speakers. The tool is also useful for improving the training of medical students in managing polypharmacy [76] and can have a positive economic impact by reducing medicine expenditure in older patients [80,81]. This version in Portuguese represents a step forward in improving the management of medications in the elderly. The adaption of this tool will be useful not only for Portugal but also for other Portuguese-language countries.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/ijerph19116896/s1: Supplementary Materials File S1: Informed Consent; Supplementary Materials File S2: STOPP/START criteria—Portuguese version.

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