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

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Keywords:	Medical Informatics Applications, Deprescriptions, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, GENERAL MEDICINE (see Internal Medicine), PRIMARY CARE

Title

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

Registration: PROSPERO, nr. CRD42017067021.

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Competing Interests Statement:

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Correspondence:

Dr. Luís Monteiro; Email: luismonteiro.net@gmail.com; Postal Address: Av. Infante D. Henrique, 6200-506 Covilhã.

Contributions:

LM had the original idea for the systematic review. LM, TM, and ISS wrote the protocol and reviewed the search strategy. LM, TM, ISS, MM-S, and CM reviewed the protocol.

Abstract

Introduction: Life expectancy continues to increase in developed countries. Elderly peopleare more likely to consume more medications and become vulnerable due to age-related changes in drugs' pharmacokinetics and pharmacodynamics. Recent studies have identified opportunities and barriers for deprescribing potentially inappropriate medications. Some computer decision support systems may improve prescribing, while improved software can reduce unnecessary prescription of tests; however, there is lack of evidence about their efficacy on deprescribing. We will systematically review the available literature to understand if computerized decision support is effective in the use of potentially inappropriate medications, thus having an impact on health outcomes.

Methods and analysis: A systematic review will be conducted using PubMed, CENTRAL, Web of Science and EMBASE databases, as well as the grey literature assessing the effectiveness of computer decison support interventions in deprescribing inappropriate medication, with an impact on health outcomes in the elderly. Two reviewers will conduct the 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 selected articleswill be categorised based on the studies'participants, design and setting, methodological quality, biasandanyother potential sources of heterogeneity. This review will be conducted and reported in adherence with the PRISMA statement of quality for reporting systematic reviews and meta-analyses.

Ethics and Dissemination: As a systematic review, this research is exemptfrom ethical approval. We intend to publish the full article in a related peer-reviewed journal and report on it at international conferences.

Keywords: Medical Informatics Applications, Deprescriptions.

Registration: PROSPERO,nr. CRD42017067021.

Introduction

In developed countries, the aging population is increasing (1). Caring for older adults is a challenge for healthcare providers,because older patients are more likely to have multimorbidities(2, 3)and to consume more medication. Polypharmacy has a negative impact on senior health (4, 5) due to an increased risk of drug interactions and prescriptions for potentially inappropriate medications(6).Prescribing medication for elderly patients should be evidence-based; cautiousness is mandatory because seniors have changes in pharmacokinetics and pharmacodynamics, and research often excludespatients who are more than 65-years-old.

Deprescribing is defined as the "the process of withdrawal of inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes"(7).

In the community setting, primary care physicians/family doctors, nurses, pharmacists, and other professionals must manage the continuity of senior care. Recent studies have identified both opportunities and barriers for deprescribing.

Some computerized decision supportsystems may improve prescribing and software to reduce unnecessary tests (8),but there is lack of evidence regarding their efficacy on deprescribing. This systematic review aims to determine if computerized decision support is effective in eliminating potentially inappropriate prescriptions, and establish the efficacy of these interventions in the elderly in terms of health outcomes.

Methods and Analysis

Eligibility criteria

This systematic review will include interventional studies, such as experimental study designs [randomized controlled studies (RCTs), non-randomized controlled studies, and quasi-randomized controlled studies]. Observational studies (such as case reports, case series, cross-sectional analyses, case–controls, cohorts,etc.) will not be selected.

Only studies including participants aged 65 years and older, who were prescribed one or more regular medication, will be selected. On the other hand, studies including only

moribund, terminal, or palliative participants will be excluded. Studies published or in press will be included independently of the language, year of publication, and setting in which it was conducted (hospitals, nursing centres, communities, etc.).

Information sources

Our sources of information will include electronic databases (namely PubMed, CENTRAL, EMBASE),trial registries, different types of grey literature, and contact with specialists in the field. If further data is needed, authors of the selected articles will be contacted.

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.#1 or #2

6.#3 or #4

7.#5 and #6

For MEDLINE, the query will be "Medical Informatics Applications"[Mesh] AND ("Deprescriptions"[Mesh] OR "Inappropriate Prescribing"[Mesh]); and for EMBASE('medical informatics'/exp OR 'mobile application'/exp) AND ('deprescription'/exp OR 'inappropriate prescribing'/exp).

Study selection process

Two authors will independently, and blinded to each other, perform the primary article screening. First, they will review the title and abstract, and categorise the articles into three groups: relevant, irrelevant, and unsure. Articles categorised as irrelevant by both reviewers will be eliminated from the study. Then, each reviewer will review the full text of the remaining articles and make a list of those to be included. The two lists will be compared

and non-conformities will be discussed. When an agreement cannot be reached, the whole team of researchers will make the final decision.

Data management

Once the articles to be included are selected, data will be extracted and entered into data sheets independently by the two reviewers.

These two sheets, including their differences, will be checked by a third reviewer.

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 be sent to the authors.

Data items

The following information will be extracted from each article:1) study characteristics, intervention type; type of study; country, setting, duration of follow-up;2) participants, number, age;3) outcomes, effect of intervention on withdrawal of potentially inappropriate medication, clinical outcomes such as mortality, any reported adverse drug withdrawal effects, physical health, cognitive function, psychological health parameters, quality of life measurement, and value.

Risk of bias

Two reviewers will assess, independently and blinded to each other, the risk of bias.

The Cochrane Collaboration Risk of Bias tool will be used to assess this for each study(9).

Data synthesis

The final report will present the range of clinical decision support, as well as efficiency regarding health outcomes. If studies are sufficiently homogeneous in terms of design and comparisons, we will conduct regression-analyses using a random-effects model.

Each outcome will be combined and calculated using the statistical software RevMan 5.1(10), according to statistical guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions(11). The Mantel-Haenszel method will be used for the fixed effect model if tests for heterogeneity are not significant. If statistical

heterogeneity is observed (I2 ≥50% or p<0.1), the random effects model will be chosen. If heterogeneity is substantial, we will not perform a meta-analysis; a narrative, qualitative summary will be done instead.

Subgroups will be presented according to the setting, intervention and medication. The final paper will be prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(12, 13).

Subgroup analyses will be used to explore possible sources of heterogeneity, based on the following: medications and type of software.

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.

In order to determine whether reporting bias is present, we will determine whether the protocol of the RCT was published before recruitment of patients was initiated.

Data from RCTs will not be combined with data from other study designs. We will evaluate whether selective reporting of outcomes is obvious. The quality of evidence for all outcomes will be judged with the Grading of Recommendations Assessment, and the Development and Evaluation working group methodology(14).We further separated comparative studies with and without concurrent control groups. 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 (ATC) codes.

Randomized studies

If heterogeneity is detected, we will select the random effects model. If one or more of the original studies use a cluster-randomization method, we will use generic inverse variance.

Dichotomous data

Effect sizes and 95% confidence intervals (CIs)were expressed as odds ratios (OR). When a study reports zero events in both arms, it would be excluded from the meta-analysis.

Discussion

Although electronic health records are common in clinical practice, there is a lack of evidence of computer decision support 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 best decision support available, as well as its limitations. Therefore, this systematic review will be relevant for patients, health professionals, and policy makers.

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1

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐X	☐	2,3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐X	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐X	☐	5; 81
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐X	☐	8-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐X	☐	50-52
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐X	☐	39-46
Sponsor	5b	Provide name for the review funder and/or sponsor	☐X	☐	39
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐	☐	87-103
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐	☐	103-105 110-118

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	114-118
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐	☐	121-123
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐	☐	121-123
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐	☐	150-155
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐	☐	150-155
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐	☐	150-155
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐	☐	150-155
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐	☐	149-152
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐	☐	166-167
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☐	170-197
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☐	175
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☐	172
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☐	182

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☐	172
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☐	192

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Health informatics, Patient-centred medicine, Geriatric medicine
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Title

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Contributions:

LM had the original idea for the systematic review. LM, TM, and ISS wrote the protocol and reviewed the search strategy. LM, TM, ISS, MM-S, and CM reviewed the protocol.

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 is already been demonstrated that computerized decision support systems can reduce physician orders for unnecessary tests. We will systematically review the available literature to understand if computerized decision support is effective in 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, and EMBASE databases, as well as the grey literature assessing the effectiveness of computer decison 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 the 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 selected articles will be categorised based on the studies' participants, design and setting, methodological quality, bias and any other potential sources of heterogeneity. This review will be conducted and reported in adherence with the PRISMA 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 report on it at international conferences.

Keywords: Medical informatics applications, deprescriptions, potentially inappropriate medicines.

Registration: PROSPERO,nr. CRD42017067021.

Strengths and limitations of this study

- This study will include the first meta-analysis on this clinical topic.
- This protocol was written following the recently published PRISMA-P guidelines.
- We aim to clarify whether newer technologies, such as computerized decisions, help to improve clinical outcomes.
- Studies with high heterogeneity and varying quality may limit the quality of evidence for this systematic review.

Introduction

In developed countries, the aging population is increasing (1). Caring for older adults is a challenge for healthcare providers, as older patients are more likely to have multimorbidities (2, 3) and to consume more medication (4). Polypharmacy has a negative impact on senior health (5, 6) due to an increased risk of drug interactions and prescriptions for potentially inappropriate medications (4).Prescribing medication for elderly patients should be evidence-based; cautiousness is mandatory, since seniors have changes in pharmacokinetics and pharmacodynamics, and research often excludes patients who are more than 65-years-old (7).

Deprescribing is defined as the "the process of withdrawal of inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" (8).

In the community setting, primary care physicians/family doctors, nurses, pharmacists, and other professionals must manage the continuity of senior care. Recent studies have identified that interventions such as pharmaceutical care appear beneficial in reducing inappropriate prescribing (9). Although family doctors want to learn more through mobile technologies (10), the doctors´ perspective is that there is insufficient emphasis on geriatric pharmacotherapy training (11)

It has already been shown that computerized decision support systems can reduce physicians' orders of unnecessary tests (12). This systematic review aims to determine if computerized decision support is effective in reducing potentially inappropriate medicines. This should better establish the efficacy of these interventions in the elderly in terms of health outcomes.

Other studies have addressed this issue(9, 13). Our study will include a meta-analysis, which has not previously been done.

Methods and Analysis

Eligibility criteria

This systematic review will include interventional studies, such as experimental study designs [randomized controlled studies (RCTs), non-randomized controlled studies, and quasi-randomized controlled studies]. Observational studies (such as case reports, case series, cross-sectional analyses, case–controls, and cohorts, etc.) will not be selected.We will include trials in the general population and studies with older adults with particular diseases.

Only studies including participants aged 65 years and older, who were prescribed one or more regular medications, will be selected. On the other hand, studies including only moribund, terminal, or palliative participants will be excluded. Studies published or in press will be included independently of the language, year of publication, and setting in which it was conducted (hospitals, nursing centres, communities, etc.). Potentially inappropriate medications will be defined using the Beers Criteria (14) and STOPP/START Criteria (15)

Information sources

Our sources of information will include electronic databases (namely MEDLINE, CENTRAL, EMBASE, ISI Web of science), trial registries, different types of grey literature, and contact with specialists in the field. If further data is 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. 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 computerized 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.#1 or #2

6.#3 or #4

7.#5 and #6

For MEDLINE, the query will be "Medical Informatics Applications"[Mesh] AND ("Deprescriptions"[Mesh] OR "Inappropriate Prescribing"[Mesh]) "decision support systems, clinical"[MeSH Terms] OR clinical decision support systems [Text Word] / "decision making, computer-assisted"[MeSH Terms] OR computer assisted decision making[Text Word] / "medical order entry systems"[MeSH Terms] / "medication errors"[MeSH Terms]; and for EMBASE ('medical informatics'/exp OR 'mobile application'/exp) AND ('deprescription'/exp OR 'inappropriate prescribing'/exp).
Reference lists will be checked to identify additional relevant studies in the systematic review. For ISI Web of science the query will be "Medical Informatics Applications"[Mesh] AND ("Deprescriptions"[Mesh] OR "Inappropriate Prescribing"[Mesh]) "decision support systems, clinical"[MeSH Terms] OR clinical decision support systems[Text Word] / "decision making, computer-assisted"[MeSH Terms] OR computer assisted decision making [Text Word] / "medical order entry systems"[MeSH Terms] / "medication errors"[MeSH Terms]."

Study selection process

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Data 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. These sheets will also include the study reference,

intervention type, study design, country, setting, follow-up, number of participants, age, effect of intervention on reducing potential inappropriate medications, and clinical outcomes.

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.

Data items

The following information will be extracted from each article:1) study characteristics, intervention type; type of study; country, setting, duration of follow-up; 2) participants, number, age; 3) outcomes: The primary outcome is 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, hospitalization, any reported adverse drug withdrawal effects, and quality of life measurements.

Risk of bias

Two reviewers will assess, independently and blinded to each other, the risk of bias.

The Cochrane Collaboration Risk of Bias tool will be used to assess this for each study (16).

Data synthesis

The final report will present the available data of the computer decision to support or reduce inappropriate medications in older adults.

Each outcome will be combined and calculated using the statistical software RevMan 5.1 (17), according to statistical guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions(18). If heterogeneity is substantial, we will not perform a meta-analysis; thus, a narrative, qualitative summary will be done instead.

Subgroups will be presented according to the setting, intervention, and medication. The final paper will be prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (19, 20).

Subgroup analyses will be used to explore possible sources of heterogeneity, based on the following: medications and type of software.

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. Subgroup. We will also conduct meta-regression to evaluate whether the covariates have significant influence on heterogeneity.

The studies rated as having a high risk of bias will be included and then analysed in a sub-group analysis. They will be included for the discussion topic.

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.

In order to determine whether reporting bias is present, we will include funnel plot and statistical tests in the assessment. We will determine whether the protocol of the RCT was published before recruitment of patients was initiated.

Data from RCTs will not be combined with data from other study designs. We will evaluate whether selective reporting of outcomes is obvious. The quality of evidence for all outcomes will be judged with the Grading of Recommendations Assessment, and the Development and Evaluation working group methodology (21).We further separated comparative studies with and without concurrent control groups. 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 (ATC) codes.

Randomized studies:

If heterogeneity is detected, we will select the random effects model.

Dichotomous data:

Effect sizes and 95% confidence intervals (CIs)were expressed as odds ratios (OR). When a study reports zero events in both arms, we will consider using zero-cell correction methods.

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 report on it at international conferences.

Discussion

Although electronic health records are common in clinical practice, there is a lack of evidence of computer decision support 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 computerized decision support to reduce inappropriate medication. Therefore, this review will be relevant for patients, health professionals, and policy makers. One potential limitation of this study will be if we find a limited number of studies with clinical outcomes measured.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2,3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	5; 81
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	8-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	50-52
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	39-46
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	39
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	92-113
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	117-127 187-188

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	124-127
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	138-161
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	138-161
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	172-180
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	163-170
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	191-192
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	183-188
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	186-188
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	191-192 210-211
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	195-229
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	195-229 199-200
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	204-205 208-209

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	212-214
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	215-216
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	219-221

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018988.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Nov-2017
Complete List of Authors:	Monteiro, Luís; Universidade da Beira Interior Faculdade de Ciencias da Saude; USF Esgueira + Maricoto, Tiago; Universidade da Beira Interior Faculdade de Ciencias da Saude; USF Aveiro Aradas Solha, Isabel; USF Terras de Souza Monteiro-Soares, Matilde; Oporto University Faculty of Medicine, MEDCIDS – Department of Community Medicine, Information and Health Decision Sciences; Oporto University Faculty of Medicine, CINTESIS - Center for Health Technology and Services Research Martins, Carlos; Oporto University Faculty of Medicine, CINTESIS - Center for Health Technology and Services Research; Oporto University Faculty of Medicine, MEDCIDS – Department of Community Medicine, Information and Health Decision Sciences
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Health informatics, Patient-centred medicine, Geriatric medicine
Keywords:	Medical Informatics Applications, Deprescriptions, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, GENERAL MEDICINE (see Internal Medicine), PRIMARY CARE

Title

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

Registration: PROSPERO, nr. CRD42017067021.

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Competing Interests Statement:

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Contributions:

LM had the original idea for the systematic review. LM, TM, and ISS wrote the protocol and reviewed the search strategy. LM, TM, ISS, MM-S, and CM reviewed the protocol.

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 is already been demonstrated that computerized decision support systems can reduce physician orders for unnecessary tests. We will systematically review the available literature to understand if computerized 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 decison 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 with the PRISMA 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.

Keywords: Medical informatics applications, deprescriptions, potentially inappropriate medicines.

Registration: PROSPERO, nr. CRD42017067021.

Strengths and limitations of this study

- We aim to clarify whether new technologies, namely computerized decision systems, can help reducing inappropriate medication in the elderly.
- This protocol was written following the recently published PRISMA-P 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, aging population is increasing (1). Caring for older adults is a challenge for healthcare providers, as they are more likely to have multi-morbidities (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 generalization of clinical research results due to common exclusion of subjects with 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 they refer an insufficient emphasis on geriatric pharmacotherapy training (14).

It has already been shown that computerized decision support systems can reduce physicians' orders of unnecessary tests (15). This systematic review aims to determine if

computerized 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 8 randomized controlled trials (RCTs), 2 clusters RCTs and 2 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 computerized 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-randomized controlled studies, and quasi-randomized controlled studies; 2) that include participants with 65 years or more, to whom one or more regular medications were prescribed and 3) assess the impact of computerized 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 independently of the language, year of publication, and setting in which it was conducted (hospitals, nursing centres, communities, etc.). 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 is 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 is 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 computerized 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) #1 or #2; 6) #3 or #4; 7) #5 and #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

Two authors will independently, and blinded to each other, perform the primary article screening. First, they will review the title and abstract, and categorise the articles into three groups: relevant, irrelevant, and unsure. Articles categorised as irrelevant by both reviewers will be eliminated from the study. Then, each reviewer will review the full text of the remaining articles and make a list of those to be included. For both stages, the two lists will be compared and disagreements will be discussed. When an agreement cannot be reached, the whole team of researchers will come to 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, hospitalization, 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 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 effect 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% confidence intervals (CIs) will be expressed as odds ratios (OR). When a study reports zero events 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 meta-regression 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 (ATC) 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.

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

We will also ascertain if each RCT had their 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 (PRISMA) 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 computerized decision support to reduce inappropriate medication prescription. Therefore, this review will be relevant for patients, health professionals, and policy makers. 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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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2,3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	5; 81
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	8-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	50-52
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	39-46
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	39
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	92-113
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	117-127 187-188

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	124-127
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	138-161
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	138-161
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	172-180
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	163-170
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	191-192
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	183-188
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	186-188
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	191-192 210-211
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	195-229
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	195-229 199-200
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	204-205 208-209

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	212-214
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	215-216
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	219-221