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Methodological Review

Decision-support systems for managing polypharmacy in the elderly: A scoping review



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ABSTRACT

Polypharmacy, the consuming of more than five drugs, is a public health problem. It can lead to many interactions and adverse drug reactions and is very expensive. Therapeutic guidelines for managing polypharmacy in the elderly have been issued, but are highly complex, limiting their use. Decision-support systems have therefore been developed to automate the execution of these guidelines, or to provide information about drugs adapted to the context of polypharmacy. These systems differ widely in terms of their technical design, knowledge sources and evaluation methods.

We present here a scoping review of electronic systems for supporting the management, by healthcare providers, of polypharmacy in elderly patients. Most existing reviews have focused mainly on evaluation results, whereas the present review also describes the technical design of these systems and the methodologies for developing and evaluating them. A systematic bibliographic search identified 19 systems differing considerably in terms of their technical design (rule-based systems, documentary approach, mixed); outputs (textual report, alerts and/or visual approaches); and evaluations (impact on clinical practices, impact on patient outcomes, efficiency and/or user satisfaction). The evaluations performed are minimal (among all the systems identified, only one system has been evaluated according to all the criteria mentioned above) and no machine learning systems and/or conflict management systems were retrieved. This review highlights the need to develop new methodologies, combining various approaches for decision support system in polypharmacy.

1. Introduction

According to a WHO report published in 2019, polypharmacy is a major and growing public health problem occurring in all healthcare settings worldwide¹. In Sweden, for example, in a study including the entire population the prevalence of polypharmacy increased from 16.9% in 2006 to 19.0 % in 2014 [1]. In Denmark, the prevalence of polypharmacy is 12% for the total population and 51% for citizens over the age of 75 years [2]. In United States, the prevalence in older adults seen in physician offices from 2009 to 2016 is 36.8% [3]. In China, in a study conducted from March to May 2021, the prevalence of polypharmacy is 50.14% among the old patients [4]. Polypharmacy is associated with an

increase of the risk of negative health effects [5] such as adverse drug events (ADEs), morbidity, hospitalization and death. In a meta-analysis of 47 studies [6], the authors reported an odds ratio for mortality of 1.08 ($p < 5\%$, [95% CI] 1.04–1.12) for each additional drug prescribed. In an observational study [7], the authors found that patients taking more than five drugs were almost four times more likely to be hospitalized for ADEs.

Polypharmacy is particularly frequent in the elderly. Elderly patients commonly suffer from multiple diseases and therefore take several drugs. In addition, the physiological changes induced by age in this population influence the pharmacodynamics and pharmacokinetics of drugs [8], potentially decreasing the benefit/risk ratio for some drugs.

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¹ <https://apps.who.int/iris/bitstream/handle/10665/325454/WHO-UHC-SDS-2019.11-eng.pdf>

Such drugs are thus classified as “Potentially Inappropriate Medications” (PIMs), a particular category of Drug Related Problems (DRPs).

Several therapeutic guidelines have been proposed for the management of polypharmacy in the elderly. These guidelines provide either a list of PIMs for this population, or more complex rules for identifying potentially inappropriate prescriptions involving drugs and other patient conditions, such as disorders or laboratory test (lab test) results. Some rules may also identify missing prescriptions, e.g. for tackling ADEs. The first such guideline to be published, which remains among the best known, was the BEERS criteria [9]. The first version of the BEERS criteria [9] was published in the United States in 1991 and focused on American practices. Another example is provided by the Screening Tool of Older People’s Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START) criteria [10], which provides rules for the detection of inappropriate and missing prescriptions.

However, these guidelines are entirely textual and difficult to use in daily clinical practice (e.g. STOPP & START V2 [10] includes 115 rules to be applied to each patient). Electronic Clinical Decision Support Systems (CDSS) have been developed to overcome this problem. These systems implement the guidelines and run the rules automatically based on patient data, either extracted from the Electronic Health Record (EHR) or manually entered by health professionals. Another approach is based on documentary systems that display drug knowledge adapted to the polypharmacy context, by summing the risks of ADEs associated with each of the drugs on the patient drug order, for example. Finally, these two approaches have been combined in a number of systems, associating automated rules with on-demand documentation. The difficulty and complexity of CDSS implementation is well known. For instance, P. Anrys et al. [11] reviewed the difficulties encountered in the implementation of STOPP & START V2: some criteria are not well-specified, some patient data are difficult to obtain from an EHR, some patient conditions are difficult to code with medical terminologies, and some rules lack “unless” conditions, generating a large number of false-positive alerts.

Several reviews of these CDSS were published from 2014 to 2019. C. Curtain et al. [12] reviewed CDSS for community pharmacies. K. Dalton et al. [13] proposed a meta-analysis of computerized interventions for polypharmacy in the hospital/inpatient setting. K. M. Marasinghe [14] reviewed CDSS to improve medication safety in long-term care homes. I. A. Scott et al. [15] proposed a narrative review of EHR-connected decision-support systems reducing PIMs prescription. L. Monteiro et al. [16] reviewed CDSS for reducing PIMs in the elderly. However, these reviews focused on the evaluation of the systems, and did not consider their design and functionalities.

We provide here a scoping review of the decision support systems created for polypharmacy management in the elderly over the last decade. This review analyzes the various approaches proposed, the technical design of the systems, and the methodologies used for their development and evaluation.

2. Methods

We aimed to select all the articles describing a decision-support system for managing polypharmacy in the elderly from the articles written in English and published from January 1, 2010 to May 31, 2021.

2.1. PubMed Requests

We followed the PRISMA-ScR guidelines for systematic reviews (Preferred Reporting Item for Systematic Review and Meta-Analysis extension for Scoping Reviews) [17]. The literature search was performed on Medline, the main database of biomedical literature, via the PubMed interface developed by the National Library of Medicine. We designed two different queries. The first was a simple query based on broad keywords, written by a PhD student (AM), and the second was more complex, making extensive use of MeSH (Medical Subject

Headings), and was written by a professional documentalist (CL).

The first query was as follows:

(((clinical decision support system) OR (electronic tool)) AND ((polypharmacy[MeSH Terms] OR (potentially inappropriate medication))) AND (“2010/01/01”[Date - Publication]: “2021/05/31”[Date - Publication])).

The second query searched for the intersection of three concepts: (1) geriatrics, (2) a list of inappropriate prescriptions or tools for identifying inappropriate prescriptions, and (3) a computer system for decision-support. Articles were excluded if a fourth concept, diagnosis support tools, was present. These concepts were translated into a PubMed query as follows:

(((“aged”[MH] OR “aged”[TIAB] OR “Elderly”[TIAB] OR “geriatrics”[MH] OR “geriatri”[TIAB] OR “older”[TIAB]) AND (“Medical Order Entry Systems”[MH] OR “Medical Order Entry System*”[TIAB] OR “CPOE”[TIAB] OR “Computerized Provider Order Entry”[TIAB] OR “Computerized Provider Order Entry System*”[TIAB] OR “Medication Alert System*”[TIAB] OR “Decision Support*”[TIAB] OR “Medical Record System*”[TIAB] OR “Decision Support Techniques”[MH] OR “Decision Making, Computer-Assisted”[MH] OR “Computer-Assisted Decision Making”[TIAB] OR “eDS-tool*”[TIAB] OR “CDSS”[TIAB] OR “electronic tool*”[TIAB]) AND (“Potentially Inappropriate Medication List”[MH] OR “Inappropriate Medication*”[TIAB] OR “PIM List*”[TIAB] OR “Medication Appropriateness*”[TIAB] OR “appropriateness of prescription*”[TIAB] OR “drug burden”[TIAB] OR “inappropriate polypharmacy”[TIAB] OR “Inappropriate Prescribing”[MH] OR “inappropriate prescri*”[TIAB] OR “Over Prescribing”[TIAB] OR “Deprescriptions”[MH] OR “Deprescri*”[-TIAB])) NOT (“Diagnosis, Computer-Assisted”[MH] OR “diagnos*”[TIAB])) AND (“2010/01/01”[Date - Publication]: “2021/05/31”[Date - Publication])).*

Finally, we computed the union of the results of the two queries.

2.2. Article selection

The papers were selected by two reviewers (AM and JBL), in five steps: (1) exclusion of irrelevant papers based on the title, (2) exclusion of irrelevant papers based on the abstract, (3) exclusion of irrelevant papers based on the full text, (4) for systems discussed in several different articles, we included only articles about their design or evaluation, (5) the two reviewers (AM and JBL) came to an agreement on the papers to be selected by consensus.

We considered the following inclusion criteria: (1) the system had to target polypharmacy in the elderly, (2) the system must be implemented as a computer software (but not necessary being used in clinical setting), and (3) the paper must be published between January 1, 2010 and May 31, 2021. We also considered the following exclusion criteria: (1) fictitious system, e.g. a description of an ideal system that has not been implemented, (2) system focusing exclusively on a particular therapeutic family or scoring system, (3) traditional alert systems based on drug-drug interactions, for example, and not specific to polypharmacy, and (4) papers describing the protocol of a clinical trial for evaluating a system, but not providing the results.

2.3. Article analysis

The systems retrieved from the literature were described according to the following criteria:

Type: We classified the systems into three categories: rule-based systems, documentary systems and mixed systems combining both rule-based and documentary systems. Each system was classified on the basis of the nature of its knowledge base: (a) in rule-based systems, the knowledge base is a set of rules or criteria used to raise alerts by implementing recommendations from clinical guidelines or PIM lists, (b) in documentary systems, the knowledge base is a computer-structured database describing drug

properties, such as adverse effects or drug-drug, drug-disease and/or drug-gene interactions. Documentary systems provide search and/or visualization tools for database access.

User: The final target user of the system, *i.e.* the healthcare professionals expected to use the system: physicians or pharmacists working in hospitals or in the community.

Intended use: Relevance of the system to the overall management of polypharmacy, targeting all DRPs, or a more specific focus on certain elements, such as ADRs (ADR adverse drug reactions).

Knowledge base/inference system: The knowledge base and inference system are the two basic components of a CDSS. The quality of the support provided to the clinicians is conditioned by both the content of the knowledge base and the reasoning capacity of the inference system. These elements provide information about the complexity of the CDSS.

Input: The type of data considered by the system, *i.e.* prescribed drugs but possibly also patient data (*e.g.* patient conditions, lab tests, *etc.*).

Output: *The type of output provided by the system, i.e. textual reports, alerts, or visual representations. By visual representation we mean information visualization methods based on Visual Analytics techniques [18]. Visual representations translate data into a visible form that highlights the relationships that exist between these data in order to access complex information more quickly.*

EHR: *Automatic or non-automatic (i.e. manual) collection of the data from the EHR.*

Evaluation: *Where possible, we extracted the following information:*

- **Design:** *The design of the evaluation study. All types of design were considered, including, but not limited to, RCT (randomized controlled trials).*
- **Measurement:** *The criteria measured during the study, e.g.: the number of PIMs detected, the time required for use of the system, usability, etc.*
- **Participants:** *The number of the study participants and their profile.*
- **Results:** *The results of the study and if available, their statistical significance.*

For each system, these items of information were extracted from the corresponding articles. We then contacted each author by e-mail, both to check the accuracy of the information extracted and to complete missing information. A second e-mail was sent to authors who failed to respond to the first message.

Classification of evaluations : *Evaluations are classified according to the criteria they measure. Three main criteria were considered: effectiveness, efficiency and user satisfaction.*

- **Effectiveness;** *two subcategories were considered:*
 - **Impact on clinical practices:** *assessment of the ability of a system to increase professional adherence to recommendations, including decreasing in PIM prescription and the number of potential DRPs.*
 - **Impact on clinical outcomes:** *assessment of the improvement in clinical outcomes. An increase in PIM prescription is associated with poor clinical outcomes [19], but the converse is not necessarily true (i.e. decrease in PIM prescription is not necessarily associated*

with an improvement in clinical outcomes).

- **Efficiency:** *assessment of the time required to use the system.*
- **User satisfaction:** *assessment of the ease of use of the system and its acceptability in practice.*

3. Results

Our search strategy identified 328 articles from MedLine for screening. Based on these articles, 19 systems were selected. Fig. 1 shows the PRISMA-ScR flow diagram.

Table 1 shows the systems selected based on the bibliographic search. They were classified into three main categories: (a) rule-based tools executing rules from a knowledge base to detect specific problems, (b) documentary tools providing drug-related information to the user, often associated with querying or visualization functions, and (c) mixed approaches. The systems in each category were sorted in chronological order (See Table 2).

3.1. Description of the selected articles

All the systems selected were developed to deal with the problems associated with polypharmacy. Sixteen systems aim to detect DRPs (*e.g.* MEDSAFER [27], PIM-CHECK [26], TRIM [30], SMART [32] and STRIPA [33]). Two systems focused on providing specific information about the different drug interactions generated by polypharmacy for Graphsaw [36], or the adverse effects caused by the simultaneous intake of several drugs for RXplore [40]. Finally, the remnant system, proposed by A. Grando *et al.* [34], involves checking the efficiency of a complex treatment.

Eleven systems were rule-based systems, associated with an ontology in some cases. Two were based on database searches. Six combined these two approaches. Three systems were intended for use by pharmacists, whereas four were intended for use by doctors and 12 systems are intended for use by both. In addition, one system targeted hospital/inpatient setting, whereas eight systems targeted primary care and 10 systems did not targeted any particular setting. Finally, systems such as Graphsaw [36] are also of potential interest to researchers.

3.2. System design

Two kinds of **resources** were used to build the CDSS knowledge bases: structured databases and clinical practice guidelines in a textual format.

Structured databases adhere to a predefined data model. These databases may be external to the system, such as DRUGBANK [37] or KEGG [38], as used in Graphsaw [36] and KALIS [42] (Graphsaw being integrated into KALIS), or they may be internally developed for the system, such as RXplore [40], for which authors developed a database for the adverse effects of each drug and their frequency.

Clinical practice guidelines provide recommendations to help healthcare professionals to optimize patient care. Many guidelines are available. In this review, we distinguish two types of guidelines: (1) disease-oriented guidelines are devoted to a particular disorder, such as those of the system developed by A. Grando *et al.* [34], which relate to hypertension and type 2 diabetes; (2) guidelines devoted to polypharmacy, including PIM lists for the elderly with a list of criteria. Each criterion is presented as either a drug potentially inappropriate in all situations in the elderly, or as a drug potentially inappropriate under certain conditions. Many PIM guidelines exist. In Fig. 2, we retrace the history of the PIM guidelines published and the existing relationships between them. In this figure, the guidelines used by at least one of the systems we selected in this review are highlighted in blue.

In addition to using databases and guidelines, some systems compute

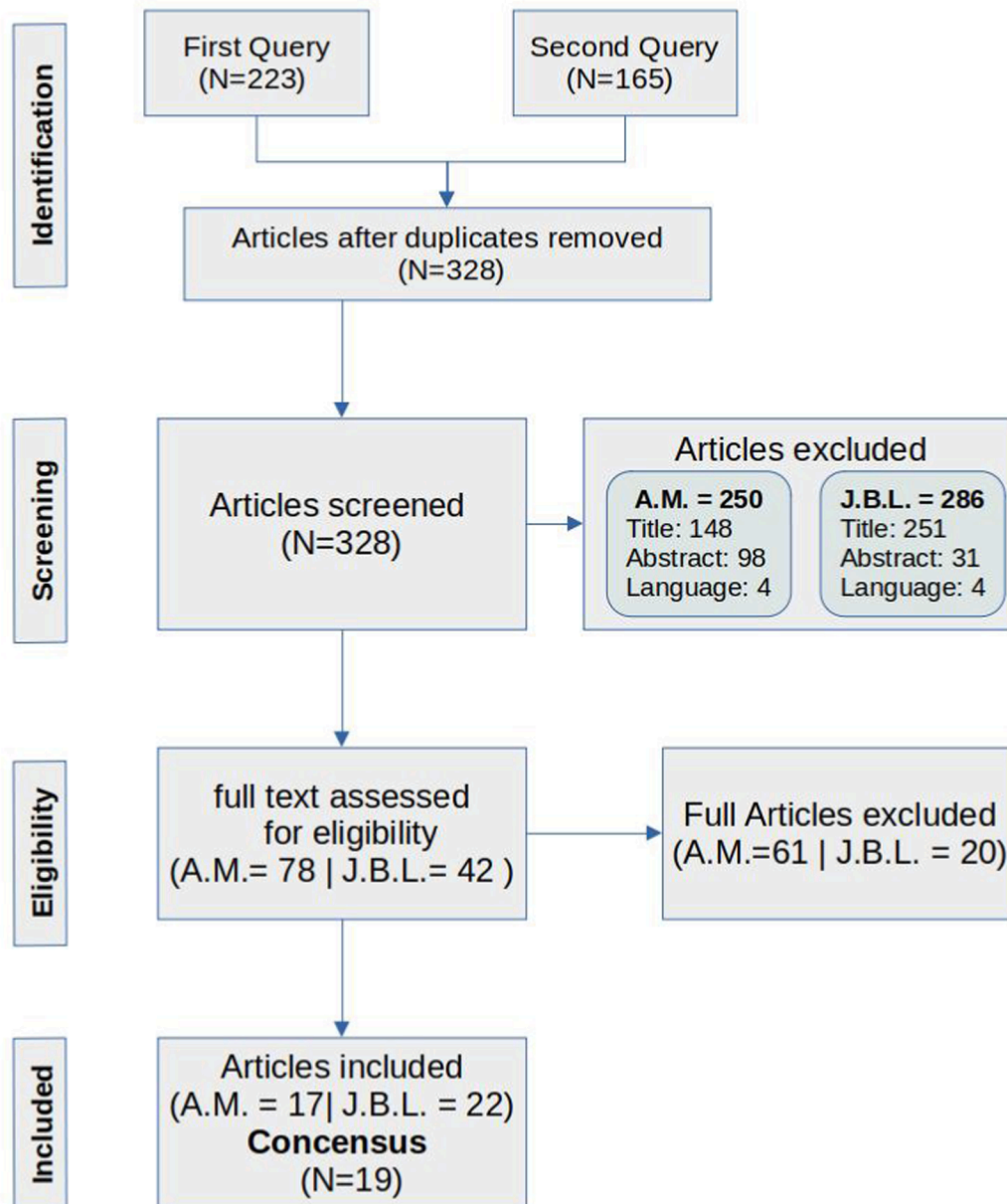


Fig. 1. Flow diagram of article search and inclusion, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-Scr).

scores. For example, the system of A. Grando *et al.* [34] uses the MRCI score [35] (Medication Regimen Complexity Index). This score is a valid tool for assessing the complexity of medication regimens. It is based on the number of drugs prescribed, the dosage form, the frequency of intake, and additional information about the mode of intake.

The list of drugs taken by the patient is the principal **input data** required for the running of these systems. However, some systems also consider patient diagnoses (*i.e.* patient conditions), lab test results (N. A. Zwietering *et al.* [23]) or pharmacogenetic data (K. Kim *et al.* [24]). These data are either entered manually, *e.g.* in PIM-CHECK [26] and INTERCHECK® [51], or captured automatically from the EHR, *e.g.* in STRIPA [33], SMART [32], TRIM [30] and Medsafer [27].

The **output** is displayed in three formats:

- **Textual reports:** The system displays all of the detected DRPs in a textual format. For example, Medsafer [27] displays an online text and proposes a downloadable PDF report.

- **Alerts:** The system interrupts the process of prescription or drug delivery when a PIM is encountered, by displaying an alert message. This is the case for SMART [32].
- **Visual approaches:** The system synthesizes rich complex information into a visually accessible, easily exploitable and interpretative approach (synthetic visual representation). This is the case for RXplore [40], which provides a visual synthesis of the information concerning the adverse effects of polypharmacy. This system represents all the adverse effects of all drugs on a single graphical interface, with an involvement score for each drug for each adverse effect. Another system, Graphsaw [36], provides a synthetic summary of the various interactions of a given drug. This system presents the interactions between drugs and the various entities with they interact (molecules, diseases, pathways, etc.), as a network.

Some systems combine several types of output. This is the case for KALIS [42], which integrates Graphsaw [36] into its system in addition to its textual report. Similarly the PRIMA-EDS system [44] proposes both

Table 1
Technical description of the CDSS developed for polypharmacy in the elderly

Type	System	Country/ Year	User	Intended use	Knowledge base	Inference system	Input	Output	EHR	
Rule-based systems	E. R-Blanco <i>et al.</i> [20].	Spain/2020	- Physicians	Checking for PIMs	- STOPP [21] - BEERS [22]	NA	- Drugs - Patient conditions	Textual report	No	
	N. A. Zwietering [23]	Netherlands/2019	- Clinicians	Checking for DRPs	- STOPP & START [10]	If/Then rules	- Drugs - Laboratory tests	Alerts	Yes	
	K. Kim <i>et al.</i> [24]	USA/2018	NA	Checking for DRPs	- NA	NA	- Drugs - Pharmacogenetic test results	NA	NA	
	T. M. G-Caballero <i>et al.</i> [25]	Spain/2018	- Physicians	Checking for PIMs	- STOPP [10]	DB querying with VBA	- Drugs	Alerts	NA	
	PIM-Check [26]	Switzerland/2017	- Junior hospital physician - Junior hospital pharmacist	Checking for PIMs	- Internally developed PIM list	If/Then rules	- Drugs - Patient conditions	Textual report	No	
	Medsafer [27]	Canada/2017	- Physicians - Pharmacists - Nurse practitioners	Checking for PIMs	- BEERS [22] - STOPP [10] - Choosing Wisely ² - Scientific literature on deprescribing	Ontology based system	- Drugs - Patient conditions - Measure of frailty [28]	Textual report	Yes	
	S. Verdoon <i>et al.</i> [29]	Netherlands/2017	- Pharmacists	Checking for DRPs	- BEERS [22] - STOPP & START [10]	NA	- Drugs	Alerts	Yes	
	TRIM [30]	USA/2016	- Pharmacists at Veterans Affairs	Checking for PIMs	- MRF [31] - STOPP [10] - BEERS [22] - Inappropriate renal dosing	If/Then rules	- Drugs - Patient conditions	Textual report	Yes	
	SMART [32]	Canada/2016	- Physicians - Geriatricians	Checking for PIMs	- BEERS [22]	NA	- Drugs	Alerts	Yes	
	STRIP Assistant [33]	Switzerland & Netherlands/2015	- Physicians - Pharmacists	Checking for PIMs	- STOPP & START [10] - Drug interactions DB	Drools rule engine ³	- Drugs - Patient conditions	Textual report	Yes	
Mixed approaches	A. Grando <i>et al.</i> [34]	USA/2012	- NA	Checking the safety and effectiveness of polypharmacy	- MRCI [35] - Clinical guidelines	Ontology based system (OWL + SWRL)	- Drugs - Patient conditions	Textual report	No	
	Graphsaw [36]	Germany/2015	- Health professionals - Researchers	Checking drug interactions and ADRs	- DrugBank [37] - KEGG [38] - ABDA ⁴ - SIDER [39]	Database query	- Drugs - Patient conditions	Graph-based representation of drug interactions	No	
	RXplore [40]	USA/2010	- Clinicians	Checking ADRs	- Adverse effects developed DB	Database query	- Drugs	Visualization approach for ADRs	No	
	R-M. Johanson-P. <i>et al.</i> [41]	Sweden/2017	- Physicians and registered nurses in elderly care settings	Drug prescribing and medication reviews	- STOPP & START [10] - BEERS [22]	NA	- Drugs - Patient conditions	NA	No	
	KALIS [42]	Germany/2017	- NA	Checking for prescribing errors	- Drug molecular and pharmacological DBs - HTA guideline -Priscus list [43]	NA	- Drugs - Patient conditions	Textual report -Graphsaw [36] (visualization of interactions)	No	
	(PRIMA)-Eds-tool [44]	Finland/2016	- Physicians - Graphsaw	Checking for PIMs	- EU(7) PIMs list [45] - SPINX [46] - RISKBASE ⁵ - RENBASE ⁶	NA	- Drugs - Patient conditions	- Visualization approach for ADRs - Textual report	Yes	
	SENATOR software [47]	Europe/2016	- Clinicians	Optimization of medical and non drug therapy	- STOPP & START [10] - DDI and indications DB - CIRS-G [48] - ONTOP [49]	NA	- Drugs - Patient conditions	Bullet-point recommendations	NA	

(continued on next page)

Table 1 (continued)

Type	System	Country/ Year	User	Intended use	Knowledge base	Inference system	Input	Output	EHR
	D. O'Sullivan et al. [50]	Ireland/2015	- Pharmacists	Checking for DRPs	- STOPP & START [10] -PRISCUS list [43] - BEERS [22]-Drug interactions - Computerized SPC	DB querying	- Drugs - Patient conditions	Textual report	No
	INTERcheck® [51]	Italy/2013	- Health professionals	Checking for PIMs	- Base of drug interactions [52] - BEERS [53] - ACB scale [54]	NA	- Drugs	Textual report	No

Abbreviations: NA:Not Available; DB: Database; ADR: Adverse Drugs Reaction; PIMs: Potentially Inappropriate Medications; DRPs: Drug-Related Problems; DDI: Drug-Drug Interactions; MRCI: Medication Regimen Complexity Index; OWL: Ontology Web Language; SWRL: Semantic Web Rule Language; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; ONTOP: Optimal Evidence-Based Non-drug Therapies in Older People; VBA: Visual Basic for Applications; MRF: Medication Regimen Feasibility; SPC: Summary of Product Characteristics; ACB: Anticholinergic Cognitive Burden

² <https://www.choosingwisely.org/getting-started/lists/>

³ <https://www.drools.org/>

⁴ <https://abdata.de/>

⁵ <https://www.mebase.fi/en/professionals/riskbase>

⁶ <https://www.mebase.fi/en/professionals/renbase>

Table 2

Evaluation of the CDSS developed for polypharmacy in the elderly

System	Design	Measurement	Participants	Results
Medsafer [27]	Non-randomized controlled before/after study	- The proportion of patients with one or more PIMs deprescribed	- 1066 patients, 65 + years old with >=5 drugs	- Effectiveness: Significant increase in the proportion of patients with one or more PIMs deprescribed (54.7% vs. 46.9%)
PIM-Check [55]	Prospective interventional study	- Mean number of potential DRPs per patient	- 297 patients admitted to internal medicine departments	- Effectiveness: No significant impact on the mean number of DRPs (2.9 vs. 3.2, $p = 0.12$)
TRIM [56]	Randomized clinical trial	- Number of drugs or decrease in the number of PIMs.	- 3904 patients 75 + years old with >=8 drugs - 359 physicians	- Effectiveness: No significant impact on the number of drugs or decrease in the number of PIMs
SMART [32]	In vitro qualitative study, focus groups, and semi-structured interviews	- Workflow interruption	- 15 physicians	- Efficiency: No significant negative impact on workflow
STRIP Assistant [57]	Pre-experiment with a one-group pre-test post-test design	- Usability: SUS Score (System Usability Scale), - Effectiveness of medication reviews: appropriate decisions - Efficiency: Time taken to perform the MR	- 42 physicians	- Effectiveness: Significant increase of the appropriate decision rate from 58% to 76% ($p < 0.0001$), and decrease in the inappropriate decision rate from 42% to 24% ($p < 0.0001$). - Efficiency: Significant increase in the time spent optimizing medication (24 vs.13 min; $p < 0.0001$). - User satisfaction: SUS score = 63.25 (poor rating)
RXplore [40]	Comparative in vitro study	- Speed and accuracy of RXplore for retrieving ADR data relative to UpToDate ⁷	- 24 physicians	- Effectiveness: No significant impact - Efficiency: Significant decrease in the time required to analyze ADRs
PRIMA-EDS [58]	Cluster-randomized controlled trial	- The number of unplanned hospital admissions or deaths by 24 months. - Decrease in the number of drugs.	- 3904 patients 75 + years old with 8>= drugs - 359 physicians	- Effectiveness: Significant decrease in the number of drugs with no detrimental effect on patient outcomes ($p < 0.001$); no significant difference in the number of unplanned hospital admissions or deaths by 24 months (44.6% vs. 48.4%, $p = 0.19$)
INTERcheck® [51]	Non-randomized controlled trial	- Percentage of patients with at least one PIM	- 134 patients, 65 + years old with >=5 drugs	- Effectiveness: Significant decrease in the number of patients with at least one PIM (30.1%, $p < 0.001$)
D. O'Sullivan et al. [50]	Cluster randomized controlled trial	- The proportion of patients experiencing a non-trivial ADR during their hospital stay	- 737 patients	- Effectiveness: Significant decrease in the occurrence rate of ADRs in the intervention group (13.9% vs. 20.7)
SENATOR software [59]	Observational study	- The degree of clinical relevance of computer-generated STOPP/START(2) recommendations.	- 204 patients	- Effectiveness: 73.6% of recommendations judged clinically relevant
R-M. Johanson-P. et al. [41]	Quasi-experimental one-group pre-test/post-test design	- Comparison of the potential DRPs identified by nurses with those identified by the CDSS	- 54 patients - 11 registered nurses	- Effectiveness: The CDSS detected 205 DRPs; the nurses independently reported 54 of these DRPs
S. Verdoon et al. [29]	Before/after study	- The mean number of potential DRPs identified and resolved	- 121 pharmacies (patients, 65 + years old with >=5 drugs)	- Effectiveness: No significant impact on the mean number of DRPs resolved (1.6 vs.1.6; $p = 0.93$)

(continued on next page)

Table 2 (continued)

System	Design	Measurement	Participants	Results
K. Kim <i>et al.</i> [24]	Post-hoc analysis of a randomized, observational trial: 3 intervention arms: standard MTM (SMTM), MTM incorporating CDSS (CMTM), and CMTM further enhanced by PGx	- The mean numbers of potential DRPs identified	- 342 patients	- Effectiveness: The mean number of DRPs identified were similar in all three analytical groups. The total number of DRPs identified did not differ significantly between the three groups (ANOVA, $p = 0.77$)
N. A. Zwietering <i>et al.</i> [23]	Observational study	- The mean number of potential DRPs identified by a geriatrician, an outpatient pharmacist, and the CDSS	- 200 patients	- Effectiveness: The mean number of DRPs per patient identified by the geriatrician was 1.3 (± 1.5), vs. 2.7 (± 1.4) by the outpatient pharmacist and 4.6 (± 3.6) by the CDSS ($p < 0.05$).

ADR: adverse drug reaction, DRP: drug related problem, MR: medication review, PIM: Potentially inappropriate medication, CDSS: Clinical Decision Support System. MTM: medication therapy management, PGx: pharmacogenetics.

⁷ An Evidence-based Clinical Decision Support, <https://www.uptodate.com/>

a textual report and a visual approach (it includes PHARAO² decision-support software for adverse drug reactions) for analyzing adverse drug effects.

3.3. System evaluation

Below are the results of the evaluations for each category of the classification described in the method section.

- **Effectiveness;** two subcategories were considered:
 - **Impact on clinical practices:** A significant impact was detected for seven of the 12 systems for which this criterion was assessed. Conversely, the PIM-CHECK [26], TRIM [30], RXplore [40] and S. Verdoon [29] systems had no significant impact on practices.
 - **Impact on clinical outcomes:** This criterion was assessed for two systems: PRIMA-EDS [44] and the D. O'Sullivan *et al.* system [50]. In the evaluation of PRIMA-EDS [44], a positive impact on the level of PIM prescription was demonstrated, but the authors were unable to draw any firm conclusions about effects on clinical outcomes. By contrast, the evaluation of the D. O'Sullivan system [50] showed a significant decrease in the rate of ADRs in the intervention group (13.9 % vs. 20.7 %).
- **Efficiency:** This criterion was evaluated for three systems. RXplore [40], with its visual approach, was found to be associated with a time gain for the user. For STRIP Assistant [33], participants spent significantly more time optimizing medication with the system (24 min) than without it (13 min; $p < 0.0001$). With SMART [32], use of the system did not significantly interrupt the workflow.
- **User satisfaction:** This criterion was evaluated for only one system (STRIPA [33]), for which the results were not good.

4. Discussion

This literature review focuses on the design and evaluation of 19 CDSS for polypharmacy management in the elderly published between January 1, 2010 and May 31, 2021.

The selected systems aim to reduce DRPs via a broad diversity of approaches. We classified them into three categories: rule-based systems, documentary systems and mixed systems. Two main resources were used for the knowledge base design: (1) clinical guidelines, in text form, which had to be formalized into machine-readable rules and (2) structured drug databases, which can be queried to extract information on the drugs taken by the patient.

In terms of input data, all systems require access to the list of drugs taken by the patient. However, some systems take additional data into account: patient health conditions, disorders, laboratory test results and pharmacogenomic data. The output of the selected systems took the

form of alerts, text reports, or visual approaches.

Some systems focused on a specific problem, such as RXplore [40], which aimed to decrease ADR rates. Others such as KALIS [42], focused on polypharmacy more generally. Beyond the simple detection of DRPs, some systems suggest alternatives and monitoring strategies. This is the case for Medsafer [27], which proposes strategies for deprescribing the detected PIMs, based on published evidence, with annual updates. It is also the case for SENATOR [47] which suggests non-pharmacological alternatives. This system is currently only suitable for patients with delirium, but it could be extended to a larger population of patients in the future.

We also found that the evaluations of the presented systems were heterogeneous in terms of both design and the criteria evaluated: effectiveness, efficiency or user satisfaction.

The results were variable, but more positive results were obtained for the impact on clinical practices than for impact on clinical outcomes.

4.1. Strengths and limitations of our work

We followed a rigorous and reproducible methodology, PRISMA ScR, to review the articles indexed by PubMed. Two people were involved in the bibliographic search, and we contacted the authors of the selected papers personally to obtain more information. We limited our search to articles published between January 1, 2010 and May 31, 2021. This may appear short period and not sufficiently exhaustive, but, given the rapid evolution of technologies and recent interest in medication reviews and deprescription, this period was considered the most appropriate. In addition, the search was limited to articles indexed on PubMed. We may therefore have missed some articles not indexed by PubMed. However, PubMed remains the main bibliographic source in the medical domain. This review did not consider commercial solutions that exist on the market either. It would be have been difficult to generate an exhaustive list of the various existing commercial solutions and the publicly available technical documentation concerning the design and the evaluation of these systems is limited. Finally, this review focusing on polypharmacy was limited to elderly patients, but it is the age group in which polypharmacy is particularly prevalent.

Most published reviews on this topic have focused on system evaluations, without considering their design. By contrast, we considered here the design of the systems and we also included systems that have yet to be evaluated, provided that they are implemented and can be used. We also considered various evaluation designs, whereas previous reviews focused on controlled trials. We show that different criteria can be evaluated (effectiveness, efficiency and user satisfaction), each requiring an appropriate evaluation design. This review is, thus, the first to consider both system and evaluation design for systems for managing polypharmacy in elderly. We believe that these results will be helpful to CDSS designers, as suggested by the review by Fraccaro *et al.* [60].

² <http://www.medbase.fi/en/professionals/pharao>

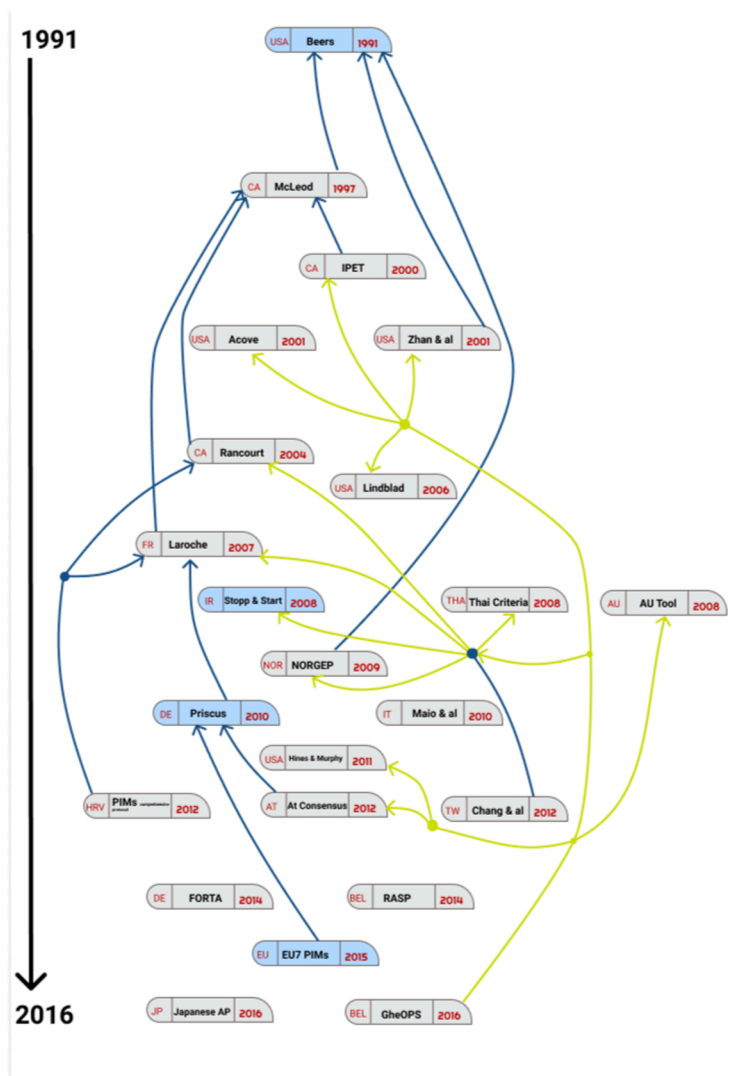


Fig. 2. Genealogical tree of PIM guidelines: PIM lists are organized chronologically from the date of first publication (vertical axis). The arrows show the inspirational relationships between these lists. If one list is linked to another, it implies that it was inspired by the other list. The lists shown here with a blue background were used in at least one of the electronic systems selected for this review.

4.2. Design limitations identified in CDSS for polypharmacy

The systems we reviewed suffered from several limitations. In terms of input data, systems considering only the drug order often resulted in an over-detection of problems, possibly leading, in turn, to “alert fatigue”. By contrast, the integration of patient conditions (e.g. diagnoses, lab test results) as input data made it possible to generate more specific alerts, possibly decreasing the risk of over-detection. Patient conditions can be entered manually or extracted from the EHR. Connection to the EHR is an important feature because it saves the healthcare professionals time, particularly as clinicians may be reluctant to enter manually data in clinical practice. However, systems destined for use by primary care pharmacists are not usually connected to the EHR, which is generally in the possession of the physician. The only exception we found in this review was TRIM, which was implemented in a very particular setting: US Veterans Affairs, which operates specific health centers with both physicians and pharmacists.

None of the systems included in this review made use of machine learning algorithms. Machine learning is a process by which the system learns predictive models from data. It has been widely applied in medicine, but more than 80% of the studies concerned targeted diagnosis decisions rather than therapy and drug prescriptions [61]. Nevertheless,

a recent study used machine learning to identify prescriptions with a high risk of medication errors [62], and this system performed better than rule-based systems. This suggests that machine learning is a promising approach for future CDSS targeting polypharmacy. In terms of the knowledge base, many lists of PIMS have been published. In a previous study [63], we used an original method to compare these lists visually. We found a considerable overlap between these lists. However, only a small number of these lists have been implemented in CDSS. Indeed, many systems use the BEERS list [64] and/or STOPP & START [10]. Other systems use molecular databases, e.g. Graphsaw [36]. These systems are of interest for researchers, but may be less relevant in routine practice because molecular drug interactions are not necessarily clinically significant.

Finally, none of the systems proposed intelligent mechanisms for managing conflicts between several rules, e.g. in STOPP & START guidelines [10], the START A2 rule recommends prescribing aspirin in the presence of chronic atrial fibrillation in cases of contraindication for antivitamin K and factor Xa inhibitors, whereas rule STOPP C2 recommends stopping aspirin in cases of a history of gastrointestinal ulcers, thus a conflict occurs if the patient has both chronic atrial fibrillation and history of gastrointestinal ulcers. Future CDSS should integrate mechanisms for solving these conflicts.

4.3. Limitations of evaluations of CDSS for polypharmacy

Very few systems have been evaluated through RCTs (4 of 19), the gold standard for evaluation [65]. This may be due to the complexity of setting up RCTs in clinical practice (multiple factors, such as patient safety and efficacy, workflow integration and financial aspects must be taken into account). RCTs should also be preceded by early-phase studies [66].

Evaluation studies should focus on the three factors identified in this review: effectiveness, efficiency and user satisfaction. In this review, we found that only one of 19 articles considered two factors (RXplore [40]), and only one considered the three factors (STRIPA [57]). In a systematic review on the usability of CDSS [67], the authors also classified the usability aspects into three factors (effectiveness, efficiency and satisfaction) as we did and the results are similar to those of this review, few systems being evaluated according to several factors. Ideally, these factors should be assessed individually, because they are known to be independent [68], but they should also be interpreted together. For instance, a poor efficiency (*i.e.* long time required for the use of the system) may be counterbalanced by a better efficacy and may be explained by the need for training time with the system. In addition, visual systems (RXplore [40] and Graphsaw [36]) have not been evaluated for user satisfaction, which is of considerable importance for the visual interface. However, each factor may be evaluated through several different measurements. For example, effectiveness can be measured through various clinical outcomes (*e.g.* the number of potential DRPs per patient (PIM-Check [55]), the number of ADRs per patient or the decrease in the rate of ADRs (PIM-Check [55])).

Table 3 summarizes the various factors evaluated by the selected systems and the results obtained (positive or negative). User satisfaction was evaluated, with the SUS score, in only one of the selected systems (STRIPA [57]), however, the SUS score is one of a consensual tools for assessing user satisfaction that has been applied to several CDSS beyond polypharmacy.

N. A. Zwietering *et al.* [23] evaluated not only the number, but also the type of DRPs. The electronic system used in this evaluation detected more DRPs than pharmacists and geriatricians. But their performance differs between the various types of DRPs. For example, the pharmacist and the geriatrician detected significantly more drugs prescribed without indication than the CDSS. However, this may be because the

Table 3

Summary of evaluation results. The “+” symbol indicates a positive result for the considered factor and the “-” symbol indicates a negative result.

System	Effectiveness		Efficiency	User satisfaction
	Impact on clinical practice	Impact on clinical outcomes		
Medsafer [27]	+			
PIM-Check [55]	-			
TRIM [56]	-			
SMART [32]			+	
STRIP Assistant [57]	+		-	-
RXplore [40]	-		+	
PRIMA-EDS [58]	+	-		
INTERcheck® [51]	+			
D. O'Sullivan <i>et al.</i> [50]		+		
SENATOR software [59]	+			
R-M. Johansson-P. <i>et al.</i> [41]	+			
S. Verdoorn <i>et al.</i> [29]	-			
K. Kim <i>et al.</i> [24]	-			
N. A. Zwietering <i>et al.</i> [23]	+			

CDSS had no access to information about patients conditions. The design of the system can, therefore, significantly modify the results of the evaluation. It is, thus, of the utmost importance to think out the design of the system well, in advance, to ensure an accurate evaluation.

There is still no standardized protocol for evaluation design or for the measurement of each factor, to provide a reliable basis for the comparison of different systems. Such standardization is urgently required and would facilitate comparisons. In addition, retrospective real-world datasets from clinical data warehouses could also be used for the assessment of efficacy and patient safety in early-phase studies [69]. This would make it possible to measure both the performance and safety of CDSS rapidly and reliably in conditions close to those of real life. This validation process would save both money and time. If a CDSS is considered sufficiently efficient and safe after such validation, then it could be tested in a RCT in real-life conditions.

4.4. Perspectives

Based on the findings of this review, we identified the main recommendations for an ideal system, which we summarize in Table 4. Several key recommendations had already been identified by J. Turgeon & V. Michaud [70], whereas others, such as a synthetic visual representation and system evaluation, are new.

In our view, the ideal system for managing polypharmacy should be connected to the EHR and destined for use by both pharmacists and physicians for better cooperation. The ideal system would allow healthcare providers to exchange structured medical information for better decision-making. Additionally, the ideal system should also combine textual reports, alerts and visual representation. In the dual-coding theory of cognition [71], it is postulated that both visual and verbal information can be used for representing information to a human user, and that both follow distinct channels in the mind. Consequently, it is expected that combining visual and verbal information yields better results for various tests, than when image or text is present alone. It should provide information about all types of DRPs, including interactions between different drugs, adverse effects and PIMs, aggregated into a global view through visual approaches to have a global vision on DRPs and the relationships that may exist between them. For example several drug interactions can contribute to the appearance of the same side effect. It should ultimately propose an optimized and simplified drug treatment with fewer DRPs, while maintaining optimal efficiency. Finally, the ideal system should also consider machine learning and conflict management, in addition to the implementation of PIM lists and the presentation of knowledge extracted from drug databases. Indeed, in the context of multi-morbidity and polypharmacy, interactions and conflicts can exist between the recommendations intended to treat each problem. It is in this context that V. Zamborlin *et al.* [72] proposed a conflict management approach and that A. Hassaine *et al.* [73] show that machine learning techniques are promising for untangling the complexity of multi-morbidity.

5. Conclusion

We presented here a scoping review of CDSS for polypharmacy, with 19 selected systems. This review provides a global overview of the different systems that currently exist for the management of polypharmacy, in terms of design approaches, and evaluation protocols and results. Regarding design, we encountered a wide range of approaches, from rule-based systems to visual knowledge representation, and none of the systems combined all these approaches. We consider there is a considerable potential in the combination of the different approaches identified, and their association with machine learning, to achieve a synergistic interaction for managing polypharmacy more effectively. Regarding system evaluation, there is still a major lack of standardization in terms of protocols and the parameters measured.

Table 4
Ideal system recommendations

System design	System evaluation
<p>The ideal system should:</p> <ul style="list-style-type: none"> be connected to the electronic health record^a be shared between healthcare professionals^b <p>integrate the following input:</p> <ul style="list-style-type: none"> drugs (prescribed and over the counter)^a patient conditions^a laboratory tests [24] pharmacogenomic data [24] <p>produce the following outputs:</p> <ul style="list-style-type: none"> alerts^a detailed textual reports^a suggestions of alternatives and deprescribing strategies [27] [47] synthetic visual representation [36] [40] [42] [44] <p>have a knowledge base providing information about:</p> <p>The following drug related problems:</p> <ul style="list-style-type: none"> drug-drug interactions^a drug-disease interactions^a adverse effects^a <p>The following molecular information:</p> <ul style="list-style-type: none"> metabolic pathways, pharmacokinetics and pharmacodynamics [70] pharmacokinetic and pharmacodynamic interactions [70] <p>implement guidelines:</p> <ul style="list-style-type: none"> potentially inappropriate medications lists (need for medical experts to develop and update these guidelines regularly)^a specific disease guidelines^a <p>integrate various inference systems</p> <ul style="list-style-type: none"> ontology/ if-then-else rules^a machine learning/deep learning^b conflict management^b 	<p>The ideal system should be evaluated simultaneously for:</p> <p>effectiveness</p> <ul style="list-style-type: none"> Impact on clinical outcomes [50,58] Impact on drug related problems detection and decreases in their rate^a <p>efficiency^a</p> <p>usersatisfaction^a</p> <p>Early-phase studies should precede randomized clinical trials Retrospective real-world datasets from clinical data warehouses [69]</p> <p>Ideally, a standard evaluation protocol should be developed.^b</p>

^a. The recommendation comes from a consensus between the articles we reviewed.

^b. The recommendation comes from authors brainstorming. Other recommendations come from the papers cited.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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