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Review Article

Impact of Artificial Intelligence Assisted Drug Therapy Optimization on Drug Related Problems Amongst Older Adult Patients: A Systematic Review

Jehath Syed[1,2], Christy Thomas[3], Bavneet Kaur[1], Prathibha Pereira[4], Tejaswini Chittanahalli Jayaram[4], Krishna Undela[3], Ramesh Madhan[1], Pramod Kumar Teggina Math[5], Vikarm Patil[6], Shilpa Avarebeel[4], Kshama Ramesh[4], Sri Harsha Chalasani[1,*]

[1]Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Karnataka, INDIA.
[2]Department of Pharmaceutical Sciences, School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, Maharashtra, INDIA.
[3]Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research (NIPER), Guwahati, Assam, INDIA.
[4]Department of Geriatrics, JSS Medical College and Hospital, JSS Academy of Higher Education & Research, Mysuru, Karnataka, INDIA.
[5]Faculty of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Karnataka, INDIA.
[6]Department of Radiology, JSS Medical College and Hospital, JSS Academy of Higher Education & Research, Mysuru, Karnataka, INDIA.

ABSTRACT

Drug-Related Problems (DRPs) are common among hospitalized older adult patients and can lead longer hospital stays, worsening clinical conditions, increased healthcare costs, and even death. Artificial Intelligence (AI)-assisted interventions may aid in the optimization of medications and prevention of DRPs in this population. This review elucidates the impact of AI-assisted interventions on drug therapy optimization and identifies and prevents DRPs in hospitalized older adult patients. A comprehensive literature search was conducted in PubMed, Scopus, and Google Scholar for studies published between January 2012 to December 2022, pertaining to AI in drug therapy optimization in older adult care. The quality of the included studies was also assessed. A total of 567 relevant studies were identified, with 194 records excluded as duplicates. Following screening and eligibility determination, 13 studies were included in the review (five randomized controlled trials, two non-randomized trials, and six cohort studies). The quality ratings ranged from 79 to 100%. The studies examined clinical decision support systems and their impact on outcomes such as potentially inappropriate medications, medication appropriateness, adverse drug events, and AI recommendation acceptance rates ranging from 18 to 54%. Overall, AI tools aided in the improvement of prescribing practices; however, definitive effects on key outcomes were lacking. Alert fatigue and disobeying AI advice were significant barriers. AI interventions have the potential to improve medication safety and optimize treatment regimens for older adult patients in hospitals. However, more research is necessary to determine the true clinical significance of the CDSS and other technological interventions, especially in terms of critical clinical outcomes, such as adverse drug reaction identification and prevention, healthcare utilization, patient morbidity, and mortality.

Keywords: Artificial intelligence, Drug related problems, Clinical pharmacist, CDSS, Older Adults.

Correspondence:
Dr. Sri Harsha Chalasani
Associate Professor, Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru-570015, Karnataka, INDIA.
Email: sriharshachalasani@jssuni.edu.in

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INTRODUCTION

By 2030, one in every six people in the world will be aged 60 years or older (World Health Organization, n.d.). The rise in life expectancy has drawn attention to issues concerning longevity, primary and secondary health, social care, and policy planning for the older adults. This group accounts for approximately 23% of the global disease burden, with the highest expenditure on chronic and noncommunicable disease management. The burden of disease per person among older people is higher in low- and middle-income regions (827 DALYs per 1000) than in high-income regions (590 DALYs per 1000), which is due to the higher per capita burden of cardiovascular disease, chronic respiratory disease, and infectious diseases in low- and middle-income regions (Prince *et al.*, 2015). Chronic disease burden has emerged as a public health concern in low- and middle-income countries, with serious severe implications for primary and secondary care providers (Marengoni *et al.*, 2011). This issue is exacerbated by the rising prevalence of multimorbidity, leading to a decline in physical and mental functioning as well as a reduction in quality of life (Wei *et al.*, 2016).

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Owing to age-related pharmacokinetic and pharmacodynamic changes, the geriatric population is at a high risk of Drug-Related Problems (DRPs) (Mangoni and Jackson, 2004). In the United States, drug-related problems are the fourth to sixth leading cause of death, and adverse effects account for 3-6% of hospitalizations (700,000 patients/year). Furthermore, a higher incidence of drug-related problems, ranging from 14.1% reports from the US to 95.9% reported in the Netherlands, may result from the increased prevalence of multiple chronic diseases associated with age, necessitating the use of complex therapeutic regimens (Silva *et al*., 2015). DRPs are also associated with higher healthcare costs and hospital admissions, extended hospital stays, lower quality of life, and higher mortality (Naples *et al*., 2016; Salvi *et al*., 2012). As a result, drug prescription and use in older patients require special considerations, such as avoiding inappropriate drugs, rationally using indicated medications, monitoring side effects, preventing drug-drug interactions, and assessing adherence and patient involvement (Spinewine *et al*., 2007).

In recent years, there has been growing interest in using Clinical Decision Support Systems (CDSS) to assist with prescribing (Marasinghe, 2015; O'Mahony *et al*., 2016). These automated systems can notify physicians when medications have potential problems, such as drug allergies or other medication errors, drug-drug interactions, allergies, and potentially inappropriate medication. By providing real-time medication information to doctors, CDSS enables them to make appropriate prescription changes (Alagiakrishnan *et al*., 2016; Clark *et al*., 2016; Clyne *et al*., 2012; Reis *et al*., 2017). Studies have reported that such computerized interventions are more effective than traditional educational interventions delivered by prescribers or those that included a pharmacist reviewing the medication, highlighting the potential of CDSS to enhance patient safety and improve the quality of care in prescribing practices (Pinar Manzanet *et al*., 2023).

This review aimed to elucidate the effectiveness of computer-assisted interventions in identifying DRPs in hospitalized older patients, as well as the frequency, nature, and acceptance rate of computer-assisted recommendations.

MATERIALS AND METHODS

Data sources and search strategy

The preferred reporting items for systematic reviews and meta-analysis guidelines were used to guide the preparation of the protocol for this systematic review (Page *et al*., 2021). The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023387586. An extensive systematic literature search was conducted in the following scientific databases: PubMed, Scopus, and Google Scholar for peer-reviewed, full-text articles published in English between January 2012 and December 2022. A comprehensive search strategy was constructed by employing relevant MeSH terms, entry terms, and relevant keywords. References of the included studies were also searched using a snowball search approach. Supplementary file 1 contains the corresponding details of the database search strategies used.

Study selection and Data extraction

Randomized controlled trials, non-randomized controlled studies, and prospective cohort studies were included. Literature reviews, letters to editor, pilot studies, and short communications were excluded.

The retrieved studies were imported into Rayyan software (Ouzzani *et al*., 2016), which was used to remove duplicates and review studies based on inclusion and exclusion criteria. Three reviewers (JS, CT, and BK) independently screened the title and abstract of each article. Potentially eligible full texts of relevant abstracts were obtained and screened by three reviewers (JS, CT, and BK) to identify articles of interest based on the study's inclusion criteria, including studies evaluating computerized interventions, such as electronic prescribing, computerized physician order entry systems, and clinical decision support systems involved in improving the appropriateness of care. Duplicate publications, literature reviews, conference abstracts, and editorials/letters to the editor were excluded. Disagreements on study inclusion were resolved through discussions among the reviewers, with arbitration by a senior reviewer (CSH) when necessary.

The following information was extracted from each included study: author, publication year, country, study design, sample size, mean age (in years), intervention, primary outcome, secondary outcome, primary and secondary outcome results, type of DRPs, and acceptance rate.

Risk of bias and quality assessment

Two independent reviewers (JS and BK) assessed the risk of bias and methodological quality of each included study using the standard quality assessment criteria for evaluating primary research papers from various fields (Kmet *et al*., 2004) and a 14-item measurement tool used to assess the methodological quality of studies in a systematic review. Each item/question received a score of 2 (if the response was 'yes'), 1 (if the response was 'partial'), or 0 (if the response was 'no'). Questions that did not apply to a specific study were labelled 'NA' and excluded from the calculation of the summary score, which was calculated for each paper by adding the total score obtained for all items and dividing it by the total possible score. A higher summary score indicated less bias and higher study quality. Disagreements were resolved by discussion or by the addition of a third reviewer (CT).

Outcome assessment

To assess the effectiveness of computerized interventions in identifying DRPs among older adult patients in hospital settings

and the frequency, type, and acceptance rate of computerized recommendations.

RESULTS

A total of 567 relevant studies were retrieved from PubMed, Google Scholar, and Scopus, of which 194 records were excluded as duplicates. After screening 373 records, we excluded 341 for reasons such as incorrect study design, lack of outcome of interest, systematic reviews, and incorrect study setting. Thirty-two full-text articles were screened for eligibility, of which 13 were included in the final quantitative synthesis. Detailed information regarding the literature search, screening, eligibility, and study selection process is presented in the PRISMA flow diagram in Figure 1.

Included study characteristics

According to the inclusion criteria, all included studies were Randomized Controlled Trials (RCTs) (Cossette *et al.*, 2017; McDonald *et al.*, 2022; O'Mahony *et al.*, 2020; D. O'Sullivan *et al.*, 2016; Sallevelt *et al.*, 2022), non-randomized controlled trials (Griffey *et al.*, 2012; McDonald *et al.*, 2019), and cohort studies (de Wit *et al.*, 2016; Linkens *et al.*, 2023; Mattison, 2010; D. O'Sullivan *et al.*, 2014; Peterson *et al.*, 2014; Van den Hanenberg *et al.*, 2022) evaluating the use of CDSS in the inpatient care of older patients.

The study duration ranged from 2 months (Peterson *et al.*, 2014) to 4 years (McDonald *et al.*, 2022). Eight included studies had treatment as usual as a comparison group (Cossette *et al.*, 2017; de Wit *et al.*, 2016; Griffey *et al.*, 2012; McDonald *et al.*, 2019, 2022; O'Mahony *et al.*, 2020; D. O'Sullivan *et al.*, 2016; Van den Hanenberg *et al.*, 2022), and five had no comparison group (Linkens *et al.*, 2023; Mattison, 2010; D. O'Sullivan *et al.*, 2014; Peterson *et al.*, 2014; Sallevelt *et al.*, 2022). The most commonly used criteria for medication review in older adult patients were the STOPP criteria, which were used in eight studies, followed by the Beers criteria, which were used in six studies. Table 1 summarizes the key findings of the studies, while Table 2 presents the characteristics of the 13 included studies.

Tools employed in the studies included

O'Mahony *et al.*, (2020) employed the SENATOR program, whilst McDonald *et al.*, (2019, 2022) utilized the MedSafer software. Cossette *et al.*, (2017) evaluated the efficacy of a Clinical Alert System, Peterson *et al.*, (2014) explored the utilization of a PIMs dashboard. Mattison *et al.*, (2010) examined institution specific Computerized Physician Order Entry system. O'Sullivan *et al.*, (2016) assessed the effectiveness of structured pharmacist review of medication (SPRM)/CDSS.

Effectiveness of CDSS Interventions

Reduction in Potentially Inappropriate Prescribing (PIP)

Van den Hanenberg *et al.*, (2022) observed a noteworthy enhancement in Medication Appropriateness Index (MAI) ratings in the intervention group (At admission, the MAI score (Mean±SD) 14.56±11.39; at discharge: 7.26±5.07) as compared to the standard care group (At admission, the MAI score (mean±SD) 13.98±9.29; at discharge: 9.95±6.70). McDonald *et al.*, (2019) reported an increase in PIM deprescribing from 46.9% in the control period to 54.7% in the intervention phase (adjusted OR 1.4, 95% CI 1.1-1.8). Similarly, Mattison *et al.*, (2010) reported a significant drop of 20-30% in the rate of prescription drugs that are considered "not recommended". These findings indicate that treatments using the CDSS can significantly enhance prescription appropriateness and decrease the prescription of potentially inappropriate drugs in older persons.

Adverse Drug Events and Reactions

O'Sullivan *et al.*, (2016) found that there was a notable decrease in Adverse Drug Reactions (ADRs), with a 7.3% absolute reduction in risk and a number required to treat (NNT) of 14 (95% CI 8-68). This indicates a significant clinical advantage. However, other studies have shown fewer prominent effects. McDonald *et al.*, (2022) discovered no notable difference in Adverse Drug Events (ADEs) between the control group (5.0%) and the intervention group (4.9%). The adjusted risk difference was -0.8% (95% CI: 2.9 to 1.4) (McDonald *et al.*, 2022). O'Mahony *et al.*, 2020 found that there was no statistically significant variation in the frequencies of ADRs between the control group (24.7%) and the intervention group (24.8%).

Drug-Related Problems (DRPs)

PIMs emerged as the most frequently addressed DRP in eight of the 13 studies. Two studies specifically focused on ADRs (O'Mahony *et al.*, 2020; D. O'Sullivan *et al.*, 2016), whereas McDonald *et al.*, 2022 and Griffey *et al.*, 2012 investigated ADEs. Several studies have simultaneously addressed multiple types of DRPs. For example, drug-drug interactions were examined in two studies (D. O'Sullivan *et al.*, 2014; Van den Hanenberg *et al.*, 2022), while two other studies focused on inappropriate dosing (Griffey *et al.*, 2012; D. O'Sullivan *et al.*, 2014). Medication appropriateness was a key consideration in studies by Van den Hanenberg *et al.*, (2022) and D. O'Sullivan *et al.*, (2014). De Wit *et al.*, (2016) specifically categorized DRPs as untreated indications, drug use without indication, contraindications/interactions/side effects, drug duplication, and wrong medication.

Acceptance of CDSS Recommendations

The acceptance rates of the CDSS recommendations demonstrated considerable variability across studies. O'Mahony *et al.*, (2020) reported a 15% adherence rate to SENATOR software

recommendations, while Van den Hanenberg *et al.*, (2022) observed 31.6% of CDSS recommendations being accepted. Sallevelt *et al.*, (2022) noted a 39.1% acceptance rate for STOPP/START signals. Higher rates were reported by D. O'Sullivan *et al.*, (2016); Sallevelt *et al.*, (2022) with 54.8% implementation of overall interventions, and Peterson *et al.*, (2014) reported a 78% acceptance of pharmacist recommendations. Linkens *et al.*, (2023) provided a temporal perspective, reporting that pharmacist actions resulted in 36% and 62% of alerts being resolved on day 1 and day 3, respectively.

Quality assessment criteria

The quality of the included studies was assessed using the standard quality assessment criteria developed by Kmet *et al.* for evaluating primary papers from a variety of fields (Kmet *et al.*, 2004). The quality rating of the studies ranged from 79% to 100%, with five studies receiving 100% (Cossette *et al.*, 2017; Linkens *et al.*, 2023; McDonald *et al.*, 2019; D. O'Sullivan *et al.*, 2016; Van den Hanenberg *et al.*, 2022) and one study receiving the lowest rating of 79% (Peterson *et al.*, 2014). Overall, the quality of the included studies is satisfactory. The quality ratings of individual studies are listed in Table 3.

DISCUSSION

This systematic review investigated the efficacy of CDSS in enhancing medication management for geriatric patients in diverse healthcare environments. The data present an intricate depiction of the implementation and influence of CDSS, with varied outcomes seen in different settings.

Van den Hanenberg *et al.*, (2022) were the first to investigate the use of the CDSS in a hospital setting with older patients on polypharmacy. They found that using the CDSS alone had a minor, non-clinically significant effect on MAI scores, which were lower than those of standard care. On the other hand, the

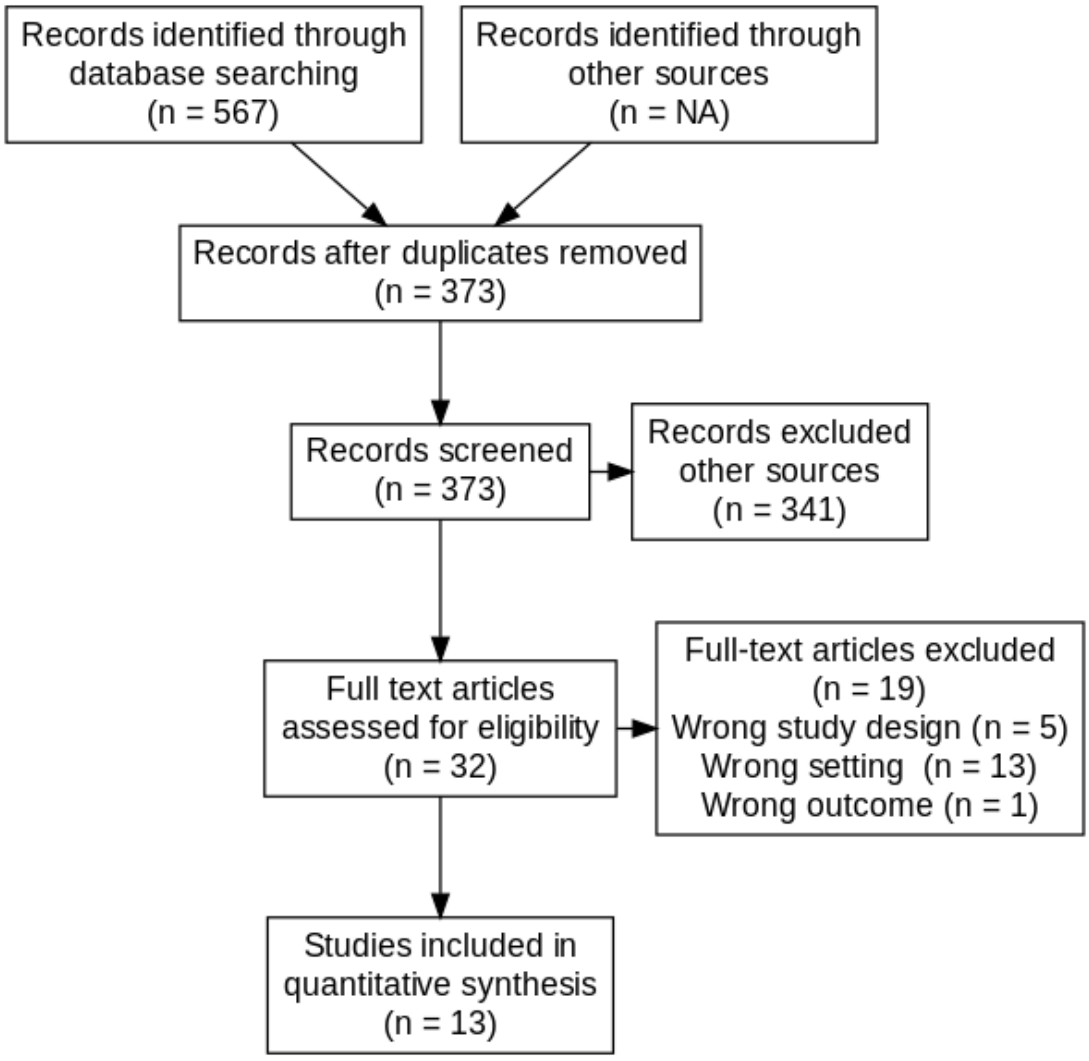

Figure 1: PRISMA Flow Diagram for Study Selection. Flowchart illustrating the number of records identified, screened, excluded, and included in the systematic review following PRISMA guidelines.

Table 1: Summary of Key Findings.

Outcome	Studies reporting	Key findings
CDSS Recommendation Acceptance	8 studies (Cossette *et al.*, 2017; de Wit *et al.*, 2016; Griffey *et al.*, 2012; O'Mahony *et al.*, 2020; D. O'Sullivan *et al.*, 2014, 2016; Sallevelt *et al.*, 2022; Van den Hanenberg *et al.*, 2022).	Acceptance rates varied widely (15% to 78%).
Reduction in PIMs	5 studies (Cossette *et al.*, 2017; Mattison, 2010; McDonald *et al.*, 2019, 2022; O'Mahony *et al.*, 2020).	20-30% reduction in PIM prescribing in most studies.
Adverse Drug Events/Reactions	4 studies (Griffey *et al.*, 2012; McDonald *et al.*, 2022; O'Mahony *et al.*, 2020; D. O'Sullivan *et al.*, 2016).	Mixed results: 1 study showed significant reduction, 3 showed no significant difference.
Medication Appropriateness	2 studies (D. O'Sullivan *et al.*, 2014; Van den Hanenberg *et al.*, 2022).	Both studies showed improvement in MAI scores.
Length of Hospital Stay	2 studies (Cossette *et al.*, 2017; D. O'Sullivan *et al.*, 2016).	No significant difference observed.
Mortality	2 studies (McDonald *et al.*, 2022; D. O'Sullivan *et al.*, 2016).	No significant difference observed.

CDSS demonstrated its role as a support system for clinicians and could not replace physician prescribing competency.

Similarly, SENATOR was the first large-scale multinational clinical trial to examine the impact of a tailored CDSS medication optimization intervention on adverse drug events in acutely ill hospitalized older adults. However, the study produced negative results, most likely because clinicians in the intervention arm did not implement the medication recommendations generated by the SENATOR software. McDonald *et al.*, (2022) also found that, despite clinically and statistically significant increases in deprescribing, communication of medication changes to community physicians and pharmacists, and sustained deprescribing 30 days after discharge, they were unable to demonstrate a significant impact of deprescribing decision support on short-term ADEs.

With the help of the Pharmacy and Therapeutics Committee of the hospital, Mattison *et al.*, (2010) created a CPOE system for drug-specific alerts. After the introduction of this alert system, the prescription rate of targeted drugs, a subset of drugs from the beer's criteria, decreased in the study population. Similarly, Linkens *et al.*, (2023) showed the pattern and natural course of clinical alerts from a hospital-implemented CDSS in a real-world clinical setting involving hospitalized older adult patients. They reported that many warnings could be resolved without specific intervention by pharmacists. This may provide important insights into the null effect of the CDSS in the OPERAM and SENATOR studies, as warnings resolved without intervention are also treated in the usual care setting and are, therefore, unlikely to improve clinical outcomes.

McDonald *et al.*, (2019) used an electronic decision support tool for deprescribing and found that the proportion of patients who had one or more PIMs deprescribed increased from 46.9 to 54.7%. This was higher than the rates of deprescribing reported in the literature, which ranged from a complete lack of deprescribing to one in every five patients having a PIM stopped or tapered at discharge. This high rate was due to the study sites' strong baseline culture of deprescribing and increased sensitivity to issues of polypharmacy and ADEs. Similarly, according to the Cossette *et al.*, (2017) study, a pharmacist-physician intervention model targeting explicit geriatric criteria identified by a computerized alert system resulted in significant drug cessation and dosage decrease compared to usual care.

When considering the mean of 7.0 (SD 2.2) DRP strategies identified during gerontopharmacology meetings, de Wit *et al.*, (2016) demonstrated that performing medication reviews in a hospitalized geriatric patient group can be beneficial. This study also revealed that the CDSS identified 20% of the DRP strategies. Furthermore, the CDSS identified 26 DRPs that were missed during the manual medication review, such as medication error types (c) 'contraindications/interactions/side effects' and error

Table 2: Characteristics of Included Studies.

Author, Publication year, Country	Study Design	Sample size	Mean age (In years)	Intervention	Primary outcome	Secondary outcome	Primary outcome results	Secondary outcome results	Type of DPRs	Acceptance rate
D.O'Mahony, 2020; Ireland, Scotland, Spain, Italy, Belgium, and Iceland.	Pragmatic prospective randomized open label, blinded endpoint (PROBE) controlled trial.	1,537	78	CDSS-generated medication advice report.	Patients with ≥1 adjudicated probable/certain ADR within 14 days.	All-cause mortality, rehospitalization, healthcare utilization, quality of life.	In the control group (*n*=765), 379 participants (24.7%) successfully attained the desired outcome as determined by the primary endpoint. Similarly, in the SENATOR group (*n*=772), 190 participants (24.8%) achieved the desired outcome based on the primary endpoint.	In both the control group (*n*=765) and the SENATOR group (*n*=772), there were no significant differences in the achievement of the primary endpoint, with 24.7% and 24.8% success rates, respectively. Additionally, the event rates for the first (S1) and second (S2) endpoints in the control group were 35.2% and 22.1%, while in the SENATOR group, they were 36.7% and 22.9%, respectively. Special population analyses (SPC, S1C, S2C) revealed no events in both groups, with calculated risk ratios ranging from 0.88 to 0.93, indicating no statistically significant differences between the groups for these endpoints.	ADR	15% adherence to CDSS recommendations.
McDonald E, 2022; Canada.	Cluster randomized trial.	6633	median age: 78	MedSafer deprescribing reports.	Any adverse drug event within 30-days of hospital discharge. ADEs could include adverse drug withdrawal events.	PIM deprescribing, medication number, ADEs, falls, ED visits, hospitalizations, mortality.	Among the control participants, 138 (5.0%) of 2742 had an ADE vs 111 (4.9%) of 2247 of intervention patients.	The number of intervention participants with 1 or more PIMs deprescribed increased substantially, from 795 (29.8%) to 1249; 92.8% of the deprescribed medications remained stopped at 30 days post discharge (vs 89.4% in the control). In the control group, 879 (32.1%) participants had an adverse event within 30 days compared with 684 (30.4%) in the intervention; The incidence of post discharge falls decreased insignificantly (odds ratio,0.76; 95% CI, 0.57 to 1.05).	PIMs; ADE; AWDEs	Not reported
Sallevelt B, 2021; Switzerland, Belgium, Ireland, and Netherland.	Cluster- randomised controlled trial.	826	Median age: 78	CDSS with STOPP/ START criteria.	The frequency and acceptance of CDSS-generated STOPP/START signals by the pharmacotherapy team.	None	In total, 5080 STOPP/START signals were generated in 826 patients. The median was 6 (IQR 4-8) generated signals per patient. No signals were generated in 0.8% (*n*=7) of the patients, whereas 1-3, 4-6, and > 6 signals were generated in 39%, 38%, and 22% of the patients, respectively.	NA	PIMs	Overall, the pharmacotherapy team accepted 39.1% (n = 1990) of all 5080 generated STOPP/ START signals, which corresponds to a median of 2 (IQR 1-3) per patient. The team accepted 40.1% (n = 1390) STOPP signals. The median number of accepted STOPP signals was 1 (IQR 0-2) per patient. The team accepted 37.2% (*n*=600) START signals resulting in a recommendation to initiate a drug (median 0; IQR 0-1).

Author, Publication year, Country	Study Design	Sample size	Mean age (In years)	Intervention	Primary outcome	Secondary outcome	Primary outcome results	Secondary outcome results	Type of DPRs	Acceptance rate
Cossette B, 2017; Canada.	Pragmatic single-site randomized controlled trial.	231	80	Pharmacist-physician intervention alerts from a CAS.	A drug cessation or dosage decrease.	Length of stay, in-hospital death, and emergency room visits and readmissions within 30 days of hospital discharge.	Significant drug cessation and dosage decreases in the intervention compared to the controlgroup at 48 h post-alert (+30.0%) and hospital discharge(+20.8%).	6% decrease (22 vs 16%) in 30-day readmissions and 4% decrease (9 vs 5%) in in-hospital deaths in the intervention group compared to the control group.These differences were not statistically different.	PIMs	Clinical relevance of 21.3% alerts in control group, 4.7% in intervention group.
McDonald E, 2019; Canada.	Non-randomized controlled before and-after study.	800	median age: Control 79; intervention: 81.	MedSafer deprescribing tool.	The proportion of patients with one or more home medications identified as a PIM and deprescribed at hospital discharge.	The occurrence of adverse events and ADEs within 30 days of hospital discharge.	The proportion of patients with one or more PIMs intervened on at discharge increased from 46.9% in the control period to 54.7% in the intervention phase. The intervention adjusted odds ratio was 1.4 (95% CI = 1.1-1.8) with an adjusted absolute risk difference of 8.3% (95% CI = 2.9-13.9) implying that for every 12 patients who received a report, one additional patient had a PIM deprescribed compared with usual care.	A total of 595 patients consented to the telephone interview, of whom 550 (92.4%) survived to discharge. An additional 29 died within 30 days before being interviewed (5.8% overall). Of the remaining 521, we were able to complete interviews with 410 (78.7%). Among interviewed patients, 293 individual PIMs were stopped (*n*=230 [78.5%]) or decreased (*n*=63 [21.5%]) at discharge. Of these, 287 (97.9%) remained deprescribed at the time of the 30-day interview.	PIMs	Not reported
Griffey R, 2012; United States of America.	Prospective controlled trial.	1407	Control: 75 (7.2); Intervention: 74 (7.4).	The status of the decision support tool alternated ON in consecutive blocks during the study period.	(i) agreement with suggested recommendations for medication substitutions, and (ii) agreement with recommended dosage substitutions for drug selection and initial dosing, broken down by drug class.	ED length of stay, admission rate, 10-fold dosing orders, the number of 'rescue' antidote drugs administered in the study periods (naloxone and flumazenil), and the relative proportion of ADEs detected during ON and OFF periods.	Among the orders for non-recommended medications during the ON periods, physicians declined the recommendation in 92.5% (49/53) of suggestions. diazepam (67%), clonazepam (10%) and indomethacin (7%). In 28 cases (51%). A greater number of initial orders during the ON periods were consistent with recommendations (403/1283; 31%) than during the OFF periods (256/1115; 23%) periods (p ≤0.001).	No significant differences were observed in admission rate, reversal drug administration, number of 10-fold orders, or ED length of stay among non-admitted patients.	ADE	overall agreement with recommendations was low for ON periods: 403/1283 (31%; 95% CI 29% to 34%) versus OFF periods: 256/1115 (23%; 95% CI 21% to 26%).
Hanenberg F, 2022; Netherland.	Prospective study.	130	83	CDSS providing prescribing advice + usual care.	Medication Appropriateness Index (MAI) score to assess the appropriateness of prescribing.	Acceptance rate of CDSS recommendations.	At admission, the MAI score (mea±SD) of the usual care group was 13.98±9.29 and that of the intervention group was 14.56±11.39; at discharge, these scores were 9.95±6.70 and 7.26±5.07, respectively.	The CDSS generated 193 recommendations. Overall, 61 recommendations (31.6%) were considered clinically relevant and accepted, which was an average of one accepted advice per patient. The scores of most MAI criteria were significantly better at discharge, except for the practicality of advice.	Improper drug selection/ PIM, Untreated indication, drug-drug interaction.	31.6% of CDSS recommendations were accepted.

Author, Publication year, Country	Study Design	Sample size	Mean age (In years)	Intervention	Primary outcome	Secondary outcome	Primary outcome results	Secondary outcome results	Type of DPRs	Acceptance rate
Mattison M, 2010; United States of America.	quasi-experimental study.	Not reported	Not reported	Institution specific CPOE system with medication-specific alerts.	Medication ordering patterns before and after CPOE implementation.	None	The rate of prescribing of the group of not recommended medications dropped by 20-30% (p<0.001). There was a modest decrease in use of unflagged medications, and no change in medications in which only a dose reduction was advised.	NA	PIMs	Not reported
Linkens A, 2023; Netherland.	Retrospective, observational study.	3574	76.7	CDSS with Clinical Rule Reporter.	(i) the total number of alerts, (ii) the number of alerts 'handled' by the pharmacist, (iii) the number of alerts resulting in an action of the pharmacist and (iv) the outcome of the alert—resolved, unresolved, and 'unknown.'	None	36% and 62% of the generated alerts were resolved on day 1 and 3 when an action by the pharmacist was performed. when the pharmacist did not perform an action, 27% and 48% of the generated alerts are resolved after 1 and 3 days, respectively.	NA	Renal function, potassium, antibiotics (intravenous to oral), antibiotics (long use), opioids/ laxatives, anticoagulant therapy and unknown lab value.	In 4083 (51.6%) of the handled alerts, an action was performed by the pharmacist, resulting in 1297 (36.1% after excluding 'unknown') resolved alerts after day 1; For the day 3 evaluation, 5750 handled alerts were analysed. In 3025 (52.6%) alerts, an action by the pharmacist was performed, resulting in 1242 (62.4% after excluding 'unknown') resolved alerts after day 3.
de Wit H, 2016; Netherland.	Prospective interventional study.	33	83	CDSS	DRP notifications from CDSS vs. medication review.	None	The CDSS generated 574 DRP notifications. (516/574: non-relevant; 58/574: relevant); 26 DRP notifications from the CDSS had not been identified in the medication review and were assessed as clinically relevant. A total of 221 DRP suggestions based on the 33 medication reviews; additional 57 DRP remarks were presented during the meeting and accepted as DRP strategies.	NA	Untreated indication, drug use without indication, contraindications/ interactions/ side effects, drug duplication, and wrong medication.	Of the confirmed relevant CDSS DRP notifications, 63% (44) DRP notifications were also noted and accepted as DRP strategies in the medication reviews.
Peterson J, 2015; United States of America.	Prospective interventional study.	797	72	PIM dashboard to flag patients with at least one PIM for pharmacist review.	Find patient or drug characteristics that increased risk including overlapping sedating medications, cumulative dosing of opiates, or interacting medications.	None	The pharmacist issued 37 recommendations to revise prescriptions and/or change the clinical monitoring strategy. The most common recommendations were to discontinue medication (n=11), change dose or frequency (n=13), substitute with an alternative (n=6), or increase clinical monitoring (n=2).	NA	PIMs	78% of recommendations accepted.

Author, Publication year, Country	Study Design	Sample size	Mean age (In years)	Intervention	Primary outcome	Secondary outcome	Primary outcome results	Secondary outcome results	Type of DPRs	Acceptance rate
O'Sullivan D, 2014; Ireland.	Prospective interventional study.	361	Median age: 77	CDSS-supported pharmacist intervention.	Appropriateness of prescribing as defined by the Medication Appropriateness Index (MAI) and a modified subset of the ACOVE criteria at follow-up (7-10 days) or discharge, whichever came first.	The prevalence of PIP and PPO at admission and follow-up and recommendation acceptance.	MAI score: Median at admission was 15 (IQR 7-21) and median at follow-up was 12 (IQR 6-18). The difference was statistically significant (p<0.001). ACOVE criteria: 28.3% of patients had at least one inappropriately rated criteria at admission compared to 26.9% at follow-up. The difference was not statistically significant (p=0.739).	Intervention acceptance: 548 out of 1000 (54.8%) interventions were implemented by physicians. PIP based on combined criteria: Median PIP instances per patient was 1 (IQR 1-3) at admission versus 1 (IQR 1-3) at follow-up (p<0.001). PIP based on STOPP criteria: Median was 1 (IQR 0-2) at admission versus 1 (IQR 0-1) at follow-up (p<0.001). PPO based on START criteria: Median was 0 (IQR 0-1) at admission versus 0 (IQR 0-1) at follow-up (p=0.512).	PIMs, appropriateness issues, reconciliation issues, drug-drug interactions, renal dosage adjustment.	54.8% recommendations were implemented.
O'Sullivan D, 2016; Ireland.	Prospective RCT.	737	Median age: 78	CDSS-supported pharmacist intervention.	The proportion of patients in either group who experienced a non-trivial ADR during their hospital stay.	Median length of hospital stay in days; Hospital all-cause mortality rate.	overall rate of ADR incidence in the control and intervention groups of 24.2 and 16.9%, respectively, the ARR for ADR occurrence was 7.3%, i.e., the total number of patients needed to treat to avoid one ADR (as distinct from one patient experiencing one ADR) was 14 (95% CI 8-68).	Median Length of Hospital Stay: The median (IQR) LOS in the control group was 9 days (5-16); in the intervention group it was 8 days (5-13.5); this difference was non-significant (p= 0.444). The median LOS in patients from either group who experienced an ADR was 11 days (7-18), significantly longer than that in patients who did not experience an ADR, i.e., 8 days (5-13) (p< 0.001) Hospital Mortality Rate: There was no significant difference found in the all-cause mortality rate between thetwo groups; 17 patients from both the intervention (4.7%) and control (4.5%) groups died during their index hospital stay.	PIMs, ADRs	54.8% recommendations were implemented.

ACOVE: assessment of care of vulnerable elders; **ADE:** Adverse Drug Event; **ADR:** Adverse Drug Reaction; **AWDEs:** Adverse Drug Withdrawal Events; **CAS:** Computerized Alert System; **CDSS:** Clinical Decision Support System; **CI:** Confidence Interval; **CPOE:** Computerized Physician Order Entry; **DRP:** Drug Related Problem; **ED:** Emergency Department, **IQR:** Interquartile Range; **LOS:** Length of stay; **MAI:** Medication Appropriate Index; **NA:** Not Applicable; **PIM:** Potentially Inappropriate Medication; **PIP:** Potentially inappropriate prescribing; **PPO:** potential prescribing omissions; S1: ≥1 adjudicated possible, probable, or certain, non-trivial, hospital-acquired ADRs occurring within 14 days of randomization during the index hospitalization; S1C: total number of adjudicated possible, probable, or certain, non-trivial, hospital-acquired ADRs occurring within 14 days of randomization during the index hospitalization; S2: ≥1 adjudicated probable or certain, non-trivial, hospital-acquired, pre-specified ADRs occurring within 14 days of randomization during the index hospitalization; **S2C:** total number of adjudicated probable or certain, non-trivial, hospital-acquired, pre-specified ADRs occurring within 14 days of randomization during the index hospitalization; **SD:** Standard Deviation; **SPC:** total number of adjudicated probable or certain, non-trivial hospital-acquired ADRs occurring within 14 days of randomization during the index hospitalization; **START:** Screening Tool to Alert doctors to Right Treatment; **STOPP:** Screening Tool of Older Person's Prescriptions

type (a) 'indication without medication,' demonstrating that the CDSS adds value to the manual medication review.

A prospective RCT conducted by D. O'Sullivan *et al.*, (2016) demonstrated that SPRM/CDSS intervention significantly reduced hospital-acquired ADRs in older people with acute illness compared to standard pharmaceutical care; this is the first study to report that an SPRM supported by appropriate CDSS significantly reduces ADRs in older acutely ill hospitalized patients. However, this SPRM/CDSS intervention did not affect median hospital length of stay or all-cause hospital mortality.

Peterson *et al.*, (2014) created an electronic PIM dashboard that identifies hospitalized patients 65 and older who have been prescribed at least one PIM in real time. PIMs were defined as medications that met the Beers criteria, were on the STOPP lists, were on a published anticholinergic risk scale, and were cross-referenced with medicines in the pilot institution's hospital formulary. Pharmacists could use this dashboard to quickly identify patient or drug characteristics that increase risk, such as overlapping sedating medications, cumulative opiate dosing, or interacting medications. An utterly manual approach requires data abstraction or review from a significantly larger set of charts. This dashboard provides a quick way for clinical pharmacists to review the medication regimens of hospitalized older adult patients.

Table 3: Quality assessment score.

Criteria	Study												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Question / objective sufficiently described?	2	2	2	2	2	2	2	2	2	2	2	2	2
Study design evident and appropriate?	2	2	2	2	2	2	2	2	2	2	2	2	2
Method of subject/comparison group selection or source of information/input variables described and appropriate?	2	2	2	2	2	2	2	2	2	2	2	2	2
Subject (and comparison group, if applicable) characteristics sufficiently described?	2	2	2	2	2	2	2	2	2	2	1	2	2
If interventional and random allocation was possible, was it described?	NA	2	2	NA	2	1	2	2	2	2	2	2	2
If interventional and blinding of investigators was possible, was it reported?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
If interventional and blinding of subjects was possible, was it reported?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	2	2	2	2	2	2	2	2	2	2	2	2	2
Sample size appropriate?	2	1	0	2	1	2	2	2	1	2	2	2	2
Analytic methods described/justified and appropriate?	2	2	2	2	2	2	2	2	2	2	2	2	2
Some estimate of variance is reported for the main results?	2	2	2	2	2	2	2	2	0	2	0	0	0
Controlled for confounding?	2	2	0	NA	2	2	2	2	NA	2	0	0	0
Results reported in sufficient detail?	2	2	2	2	2	2	2	2	2	2	2	2	2
Conclusions supported by the results?	2	2	2	2	2	2	2	2	2	2	2	2	2
Total Points	22	23	20	20	23	23	24	24	19	24	19	20	20
Maximum Points	22	24	24	20	24	24	24	24	22	24	24	24	24
Summary score (%)	100	96	83	100	96	96	100	100	86	100	79	83	83

1: Hanenberg *et al.*; 2: D.O'Mahony *et al.*; 3: Mattison *et al.*; 4: Linkens *et al.*; 5: McDonald et al.; 6: Sallevelt et al.; 7: McDonald et al.; 8: Cossette et al.; 9: de Wit H et al.; 10: O'Sullivan D *et al.*; 11: Peterson J *et al.*; 12: O'Sullivan D *et al.*; 13: Griffey R *et al.*

Similarly, an Irish study using SPRM intervention supported by a CDSS to improve prescribing appropriateness in older hospitalized individuals found a statistically significant difference in the median summated MAI at admission (15, IQR:7-21) and follow-up (12, IQR:6-18); $p<0.001$). The CDSS was created to structure the medication reconciliation process by prompting research pharmacists to ask questions to ensure that all relevant information was obtained from each patient. It not only helped with data collection but also provided the research pharmacist access to additional information about each medication. Although there was a statistically significant improvement in the MAI score, the actual clinical significance of this improvement is yet to be demonstrated. Similarly, while several studies have shown improvements in the MAI due to various intervention strategies, only a few have shown how these improvements can impact vital clinical outcomes, such as healthcare utilization, morbidity, and mortality (D. O'Sullivan *et al*., 2014).

In a prospective controlled trial conducted in the emergency department to assess the impact of a real-time computerized decision support tool that guides medication dosing for the older adults on physician ordering behaviour and ADEs, the proportion of medication orders consistent with the recommendations increased. Furthermore, although several secondary outcomes remained unchanged, the ADE rate was lower in the intervention group. According to these findings, opioids account for roughly two-thirds of all potentially inappropriate orders. Other medication categories yielded mixed results, with some showing a potential learning effect (benzodiazepines and sedative-hypnotics) and one showing an inter-period possible reversal effect (sedative-hypnotic) (Griffey *et al*., 2012).

CDSSs have been reported to be effective tools for assisting with pharmaceutical care delivery (Hellström *et al*., 2012; Mueller *et al*., 2012; Schnipper *et al*., 2009), improving prescription appropriateness (Kaur *et al*., 2009; O'Connor *et al*., 2012; Schnipper *et al*., 2009), and reducing ADRs (Cherubini *et al*., 2011; Schnipper *et al*., 2009). Although CDSSs enable users to conduct a thorough review promptly, they are only as good as the information entered into them, and they are intended to supplement, rather than replace, the clinical judgement of the healthcare professional using them (Gallagher and O'Mahony, 2008; D. P. O'Sullivan *et al*., 2013; O'Connor *et al*., 2012).

Numerous examples of CDSS success stories have been published over the past decade. Still, notable setbacks have also demonstrated that CDSS has limitations, such as fragmented workflow (Sutton *et al*., 2020). According to previous studies, up to 95% of CDSS alerts are insignificant and physicians frequently disagree with or distrust alerts. Sometimes, they do not read them (Ash *et al*., 2007). Alert fatigue can occur when physicians are bombarded by too many or insignificant alerts (Khalifa and Zabani, 2016).

The limitations of the included studies in terms of the CDSS used were that the recommendations were reported verbally and flagged by the electronic prescribing system. However, these alerts were frequently ignored because prescribers stopped reading and scrolled through them (Van den Hanenberg *et al*., 2022). Multiple STOPP and START criteria could be generated, recommending medication changes for the same drug; however, the CDSS only allowed the pharmacotherapy team to accept one recommendation per patient for each drug. It also had a signal overload; therefore, the involvement of an expert team in translating population-based CDSS signals to individual patients is critical to avoiding low implementation rates in usual care, as demonstrated in the SENATOR trial (Sallevelt *et al*., 2022).

Similarly, in the MedSafer study, which generated deprescribing opportunities for potentially inappropriate medications, the treatment team had to address many reports. Some PIMs were most likely not discontinued because (a) the drug was appropriate, or (b) the timing of deprescribing in the acute care setting was inappropriate (McDonald *et al*., 2019). These CDSSs help with medication reviews; however, they can be more efficient in terms of time. Developing algorithms capable of distinguishing between patients initiating 'deprescribing' or specifically not initiating pharmacotherapy treatment will be complex (de Wit *et al*., 2016).

Furthermore, the single-time-point nature of the SPRM/CDSS review may have underestimated the total potential value of the intervention. Deploying the intervention at additional time points during hospitalizations of older patients would further reduce ADR incidence (D. O'Sullivan *et al*., 2016).

CONCLUSION

As healthcare systems struggle with the complexity of medication management in an increasingly ageing population, refinement of the CDSS will be of paramount importance. Future research should prioritise longitudinal studies to determine the sustained impact of CDSS on clinical outcomes, investigate strategies to optimise the integration of CDSS into clinical workflows, conduct cost-effectiveness analyses to justify widespread adoption of CDSS, and examine the impact of CDSS on patient-centred outcomes, including quality of life and functional status.

ABBREVIATIONS

ADE: Adverse Drug Event; **ADR:** Adverse Drug Reaction; **CDSS:** Clinical Decision Support System**; DALYs:** Disability-Adjusted Life Years; **DRP:** Drug-Related Problem; **MAI:** Medication Appropriateness Index; **NNT:** Number Needed to Treat; **OR:** Odds Ratio; **PIMs:** Potentially Inappropriate Medications; **PIP:** Potentially Inappropriate Prescribing; **SPRM/CDSS:** Structured Pharmacist Review of Medication/Clinical Decision Support System; **START:** Screening Tool to Alert Doctors to Right Treatment; **STOPP:** Screening Tool of Older Persons' Prescriptions.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Jehath Syed: Conceptualization; Data curation; Formal analysis; Investigation; Roles/Writing - original draft. Christy Thomas: Data curation; Formal analysis; Investigation; Roles/Writing - original draft. Bavneet Kaur: Data curation; Formal analysis; Investigation; Roles/Writing - original draft. Krishna Undela: Formal analysis; Project administration; Supervision; Validation; Writing - review and editing. Sri Harsha Chalasani: Conceptualization; Formal analysis; Investigation; Project administration; Resources; Supervision; Validation; Writing - review and editing. Madhan Ramesh: Project administration; Supervision; Validation; Writing - review and editing. Prathibha Pereira: Project administration; Supervision; Validation; Writing - review and editing. Pramod Kumar T M: Project administration; Resources; Supervision; Validation; Writing - review and editing. Vikram Patil: Project administration; Resources; Supervision; Validation; Writing - review and editing. Tejaswini C J: Supervision; Validation; Writing - review and editing. Shilpa Avarebeel: Supervision; Validation; Writing - review and editing. Kshama Ramesh: Supervision; Validation; Writing - review and editing

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