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Computerised interventions designed to reduce potentially inappropriate prescribing in hospitalised older adults: a systematic review and meta-analysis

Abstract

Background: Computerised interventions have been suggested as an effective strategy to reduce potentially inappropriate prescribing (PIP) for hospitalised older adults. This systematic review and meta-analysis examined the evidence for efficacy of computerised interventions designed to reduce PIP in this patient group.

Methods: An electronic literature search was conducted using 8 databases up to October 2017. Included studies were controlled trials of computerised interventions aiming to reduce PIP in hospitalised older adults (≥65 years). Risk of bias was assessed using Cochrane's Effective Practice and Organisation of Care criteria.

Results: Of 653 records identified, eight studies were included - two randomised controlled trials, two interrupted time series analysis studies, and four controlled before-after studies. Included studies were mostly at a low risk of bias. Overall, seven studies showed either a statistically significant reduction in the proportion of patients prescribed a potentially inappropriate medicine (PIM) (absolute risk reduction {ARR} 1.3% - 30.1%), or in PIMs ordered (ARR 2% - 5.9%). However, there is insufficient evidence thus far to suggest that these interventions can routinely improve patient-related outcomes. It was only possible to include three studies in the meta-analysis – which demonstrated that intervention patients were less likely to be prescribed a PIM (odds ratio 0.6; 95% CI 0.38, 0.93). No computerised intervention targeting potential prescribing omissions (PPOs) was identified.

Conclusions: This systematic review concludes that computerised interventions are capable of statistically significantly reducing PIMs in hospitalised older adults. Future interventions should strive to target both PIMs and PPOs, ideally demonstrating both cost-effectiveness data and clinically significant improvements in patient-related outcomes.

Introduction

Prescribing medicines for multi-morbid older adults is a challenging process, and thus potentially inappropriate prescribing (PIP) remains to be a significant problem in this patient group [1]. Across the literature, there appears to be a higher prevalence of PIP amongst hospitalised older adults compared to those who are community-dwelling [2-4]; this is often due to medicines reconciliation issues at transitions of care, and because acutely ill older adults are usually exposed to new medicines under the care of multiple prescribers in hospital [5]. Computerised interventions have been suggested as an effective strategy to improve the appropriateness of prescribing for hospitalised older adults [4]. In the hospital setting, electronic prescribing and computerised physician order entry (CPOE) systems have been shown to reduce prescribing errors, and aid in the prevention of adverse drug events (ADEs) [6, 7].

However, no review has yet summarised the evidence regarding the impact of computerised interventions to reduce PIP in older adults specifically in the hospital setting. The primary aim of this paper was to collect all currently available evidence of prospective controlled studies that have utilised computerised interventions capable of independently identifying PIP, and which aimed to improve the appropriateness of prescribing in hospitalised older adults (≥65 years). Secondly, we aimed to quantify the effect that these computerised interventions could have on reducing PIP in hospitalised older adults by conducting a parallel meta-analysis.

Methods

This systematic review and meta-analysis was reported in compliance with PRISMA guidelines [8]. The inclusion criteria, exclusion criteria, and methods for the analysis were established in advance, and documented in a protocol, which was registered with the International Prospective Register of

Systematic Reviews (PROSPERO): CRD42017059795, which can be accessed from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017059795. A comprehensive electronic search of the literature was conducted using the following eight databases from inception up to and including October 2017: PubMed, EMBASE, Medline (via Ovid), Web of Science, CINAHL, Cochrane Central Register of Controlled Trials, PsycInfo, and ClinicalTrials.gov. The search strategy was developed in PubMed using a combination of key words and Medical Subject Headings, as demonstrated in the Supplementary Data. For each of the remaining databases, the search strategy was modified to suit their specific search capabilities if necessary. Additionally, our hand search involved scrutinising the bibliographies of (i) any review papers that looked at computerised interventions in reducing PIP in older adults across different healthcare settings, and (ii) all papers that were included at the full text review stage to ensure no other relevant studies were missed.

Eligibility criteria

Studies were eligible if they described a controlled intervention in which an objective was to reduce PIP in hospitalised older adults (≥65 years) using computer-generated recommendations. The primary outcomes of interest for this review were: reductions in PIP or patients with PIP. The secondary outcomes of interest were patient outcomes and acceptance rates of recommendations. As determined *a priori*, studies involving a multi-faceted intervention would be included only if the effect of the computerised intervention on reducing PIP could be clearly determined. No date or language restrictions were applied.

Study selection

For the first stage of study selection, one reviewer screened titles to eliminate papers that were clearly not relevant to the research question. Secondly, two reviewers independently screened titles and abstracts to identify potentially pertinent full texts. The last stage involved papers being read in full and their suitability for inclusion was determined independently by two reviewers. Two authors

were contacted to supply any additional information required to decide on inclusion of the full texts [9, 10]. Consensus on inclusion was reached by discussion between reviewers, with arbitration by a senior supervisor if necessary.

Data extraction

Data extraction was performed by one reviewer and verified by another. A data extraction form was piloted on two papers and adjusted thereafter where necessary. A list of the data variables extracted can be found in the Supplementary Data. All authors of the included papers were contacted to provide supplementary information where required.

Risk of bias assessments

Two review authors independently assessed risk of bias for the included studies according to Cochrane's Effective Practice and Organisation of Care (EPOC) risk of bias criteria [11]. Consensus on the assessments was reached by discussion, with advice from a senior supervisor if required. This tool was used to determine if any of the included studies were at a high risk of bias which may impact the findings from the narrative summary or meta-analysis.

Data synthesis

Quantitative analysis was conducted if at least two studies had a common comparable outcome measure, and if pooling their results was deemed appropriate. Study heterogeneity was assessed qualitatively by reviewing the differences in the interventions and study design, whereas statistical heterogeneity was assessed using the I^2 statistic. Review Manager 5.3 was employed to determine the pooled estimate of effect and 95% confidence intervals (CIs), with $p < 0.05$ considered statistically significant. When it was not possible to combine outcome data due to the variability in results reporting across studies, or simply due to lack of data available, a narrative summary was provided.

Results

Search results

A total of 653 studies were identified after duplicates were removed. After the exclusion of records based on their titles and abstracts, 20 full texts were assessed for eligibility. Eight papers were suitable for inclusion in the systematic review. A PRISMA flow diagram describes the flow of studies in the review [8] and details the reasons for exclusion of full texts reviewed (**Figure 1**).

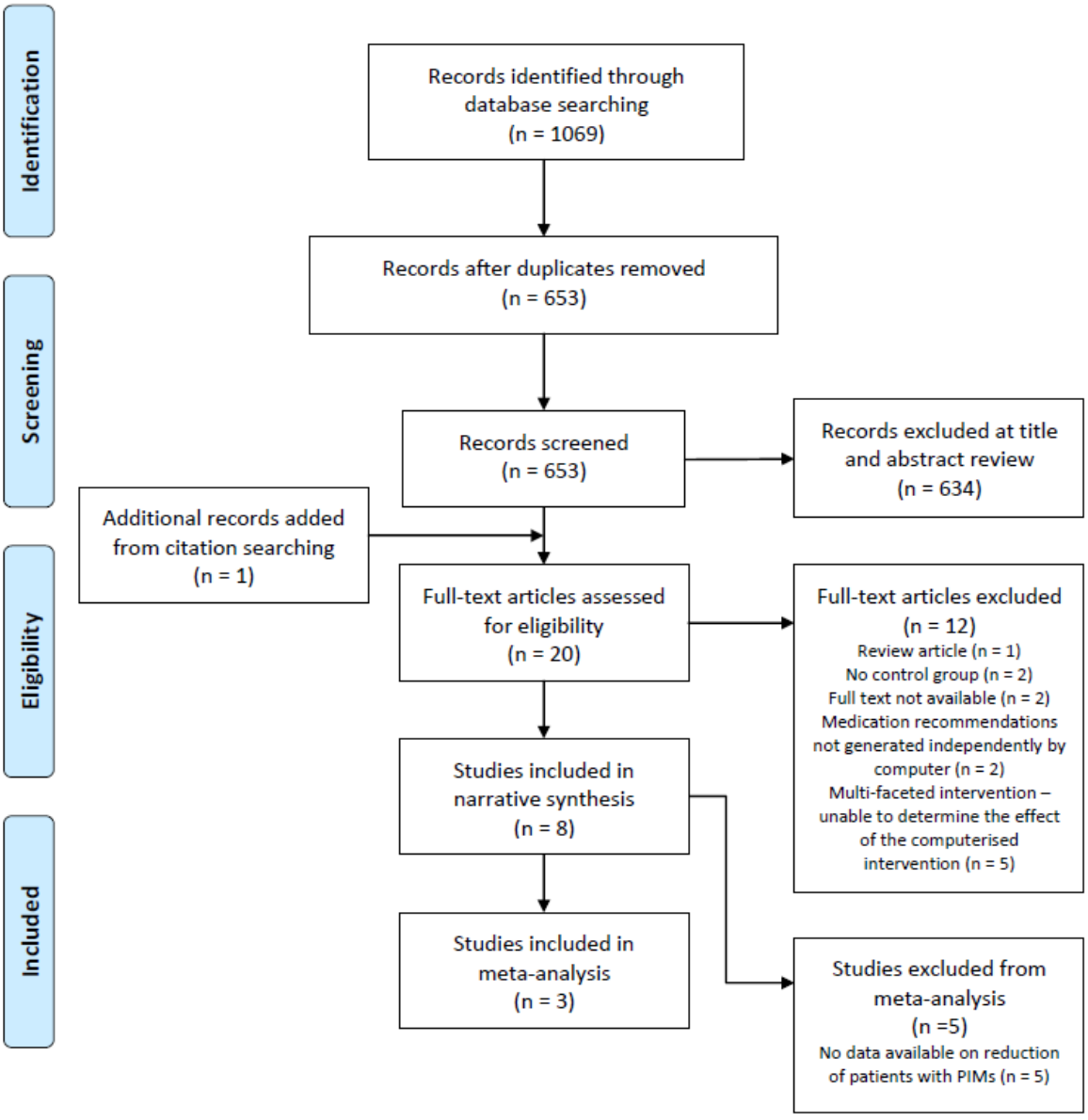

Figure 1: PRISMA flow diagram of search strategy results.

Characteristics of included studies

The included studies' characteristics and outcomes are provided in **Table 1**. A more detailed summary of each intervention is provided in the Supplementary Data. In four of the studies, the intervention utilised clinical decision support within a CPOE system [12-15]. In three other studies, the intervention comprised of alerts or reminders embedded into a CPOE system [16-18]. The remaining study involved the use of INTERcheck® software, a 'computerised prescription support system' which aimed to reduce PIMs, potentially severe drug-drug interactions, and anticholinergic burden [10]. The medicines on admission were reviewed using the computerised tool and changed according to the INTERcheck® indication. This was the only included intervention not carried out at the point of PIM prescribing. In total, there were 18,507 control patients and 24,535 intervention patients across 6 of the studies [10, 12-14, 16, 18]. One study did not report the total number of patients [17], and the remaining study reported patient visits only [15].

Six of the eight included studies utilised computerised alerts or reminders incorporated into a CPOE system, which appeared in various forms to notify healthcare professionals of PIP instances at the time a PIM was ordered [12, 14-18]. While some alerts simply provided information to the healthcare professional to guide prescribing [15, 17], other alerts provided recommendations that required acceptance or rejection at the time a medication was ordered [12]. Five of the six studies that utilised alerts or reminders suggested an alternative to PIM use [12, 14, 15, 17, 18]. The study by Lester *et al.* was the exception to this; they stated that the suggested alternative may also be inappropriate for certain older patients, thus forcing the prescriber to think for themselves regarding treatment options and the health status of individual patients [16].

Table 1: Study design, characteristics, and outcomes of the included studies.

Author	Country	Setting	Study Design	Aim of study	No. of patients	Mean age in years (± SD)	% Female	Reduction in % of patients with PIMs	Reduction in % of PIMs	% Acceptance rate of recommendations	Patient-related outcomes
Agostini *et al. [18]*	USA	Adult inpatient service in a teaching hospital.	Controlled before-after study	To develop a feasible, inexpensive, point-of-care computerized reminder to improve sedative-hypnotic prescribing in hospitalised older people.	C: 12,356 I: 12,153 Total: 24,509	Total: 76 (±7)	Not stated.	Prescribing of diphenhydramine and diazepam decreased from 18% in pre-intervention patients to 15% post-intervention*.	Not stated.	95% - 95% of patients were successfully directed to a nonpharmacological sleep protocol, or to a safer sedative-hypnotic drug.	Not assessed.
Boustani *et al. [12]*	USA	Medical ward at a university-affiliated, public hospital.	Randomised controlled trial	To evaluate the efficacy of a CDSS to improve the quality of care for patients with cognitive impairment.	C: 225 I: 199 Total: 424	C: 77.6 (± 8.3) I: 76.8 (± 7.9)	C: 71.1 I: 60.3	Not stated.	More anticholinergic orders were discontinued in the intervention arm (48.9%) vs the control arm (31.2%)†.	Not applicable.	Control vs Intervention: - Mean hospital LOS (6.8 vs 7.7 days)†. - % Patient death within 30 days of hospitalisation (5.8 vs 6)†. - % Patients discharged home (36.9 vs 43.2)†. - % Patients re-admitted within 30 days of discharge (16.4 vs 18.6)†. - % Patients with ≥ 1 hospital complication (44.9 vs 47.2)†.
Ghibelli *et al. [10]*	Italy	Acute geriatric ward in an academic urban hospital.	Controlled before-after study	To evaluate the applicability of INTERcheck® as a means of reviewing older patients' medicines. To evaluate the effectiveness of INTERcheck® in reducing PIMs, potentially severe DDIs and anticholinergic burden.	C: 74 I: 60 Total: 134	C: 81.3 I: 81.1	C: 64.8 I: 58.3	Between admission and discharge, the intervention resulted in a reduction in patients with PIMs (41.7% vs 11.6%)*.	Between admission and discharge, the intervention resulted in a reduction in the prevalence of PIMs out of total medicines (7.6% vs 1.7%)*.	Not applicable.	Not assessed.
Griffey *et al. [13]*	USA	Urban, academic, tertiary care emergency department.	Interrupted time series	To evaluate the impact of a CDS tool on physician ordering behaviour and ADEs.	C: 668 I: 739 Total: 1,407	C: 75 (± 7.2) I: 74 (± 7.4)	C: 60 I: 61	Not stated.	During intervention periods, 69% of initial orders were not consistent with recommendations (potentially inappropriate) vs 77% during control periods*.	- Of initial medicine orders: 31% were consistent with computerised recommendations for medication dosage/frequency. - 7.5% of suggestions for alternatives were accepted (4/53).	The rate of ADEs was lower for intervention patients compared with control patients (3.4% vs 7.1%)*. No significant differences were observed (intervention vs control) in: - % admission rate (53 vs 50)†. - reversal drug administration (10 vs 11)†. - number of 10-fold orders (17 vs 21)†. - emergency department LOS (5.6 vs 5.8 days)†.
Lester *et al. [16]*	USA	University-affiliated hospital.	Controlled before-after study	To evaluate the impact of "geriatric alerts" in the CPOE on ordering patterns of diphenhydramine, metoclopramide, and antipsychotics.	C: 3,259 I: 9,591 Total: 12,850	Not stated.	Not stated.	Pre-alert vs post-alert: patients prescribed diphenhydramine (26.9% vs 20%)* and metoclopramide (16.7% vs 12.5%)*. There was no decrease in patients prescribed antipsychotics (8.8% vs 9.2%)†.	Not stated.	Not applicable.	Not assessed.

Mattison *et al. [17]*	USA	Urban teaching hospital.	Controlled before-after study	To determine whether a CPOE drug warning system can decrease orders for PIMs in hospitalised older patients.	Not stated.	Not stated.	Not stated.	The authors state " a decline in the number of patients exposed to a subset of potentially problematic medications". Specific figures are not reported to reflect this, but the authors do state a reduction in the number of PIMs ordered per patient per day (0.07 vs 0.054)*.	The mean rate of non-recommended medicines (PIMs) ordered decreased from 11.56 to 9.94 orders per day post-intervention*.	Not applicable.	Not assessed.
Peterson *et al. [15]*	USA	Medical, surgical, neurology, and gynaecology services in a tertiary care hospital.	Interrupted time series	To encourage more conservative initial dosing and better psychotropic drug selection among hospitalised older patients.	C: 2,515 patient visits I: 2,647 patient visits Total: 5,162	C: 74.6 (± 6.8) I: 74.8 (± 6.9)	C: 52.7 I: 52.9	Not stated.	The intervention reduced the prescription of non-recommended drugs (10.8% vs 7.6% of total orders)*.	29.3% - 29.3% of prescriptions for psychotropics agreed with system recommendations.	Patients in the intervention cohort had a lower in-hospital fall rate (0.28 vs 0.64 falls per 100 patient-days*. No difference in LOS was detected between control and intervention periods, with identical median and interquartile range at 4 days and 2 to 6 days.
Terrell *et al. [14]*	USA	Emergency department in a university-affiliated, urban, public hospital.	Randomised controlled trial	To evaluate the effectiveness of CDS in reducing PIP in older adults	C: 1,925 I: 1,793 Total: 3,718	C: 73.7 (± 6.9) I: 73.5 (± 6.8)	C: 65.0 I: 64.9	There were significantly fewer patients prescribed PIMs by the intervention physicians compared with the control physicians (2.6% vs 3.9%)*.	Lower proportion of inappropriate medications in the intervention group (3.4% vs 5.4%)*.	43% - Decision support was provided 114 times to physicians, who accepted 49 (43%) of the recommendations.	Not assessed.

C: Control, I: Intervention, CDSS: Computerised decision support system, LOS: Length of stay, PIM: Potentially inappropriate medicine, DDI: Drug-drug interaction, CDS: Clinical decision support, ADE: Adverse drug event, CPOE: Computerised physician order entry, * Statistically significant difference, † No statistically significant difference.

Results of the risk of bias assessments

The results of the risk of bias assessments are provided in the Supplementary Data. All of the included studies were found to be at a low risk of bias, with one exception where the risk of bias was deemed unclear [17]. Both randomised controlled trials (RCTs) recognise that they may have been at risk of contamination [12, 14]. However, the potential for contamination in these studies, if present, would tend to bias against finding an effect of the intervention.

According to Cochrane's EPOC criteria [11], the controlled before-after studies must be deemed 'high risk' with regard to the two selection bias domains. Three of the four controlled before-after studies did not provide enough information to confirm that the baseline characteristics and outcome measurements are similar [16-18], and thus the risk of bias was deemed 'unclear'.

Reduction in patients with PIMs

Quantitative analysis

Three of the eight studies reported the exact number of patients that were prescribed PIMs as an outcome, and so were amenable to quantitative analysis [10, 14, 18]. In these three studies, there were a total of 29,791 patients/patient visits (14,860 and 14,931 in the intervention and control arms respectively). Given the heterogeneous types of intervention and considerable statistical heterogeneity between the study results (I^2 = 82%; p = 0.004), a random-effects model was performed to provide a pooled estimate of effect. Our meta-analysis found that patients in the intervention group were less likely to be prescribed PIMs post-intervention (odds ratio 0.6, 95% CI: 0.38, 0.93) (**Figure 2**). These three studies were found to be at a low risk of bias, so we can be reasonably confident in the results of this meta-analysis.

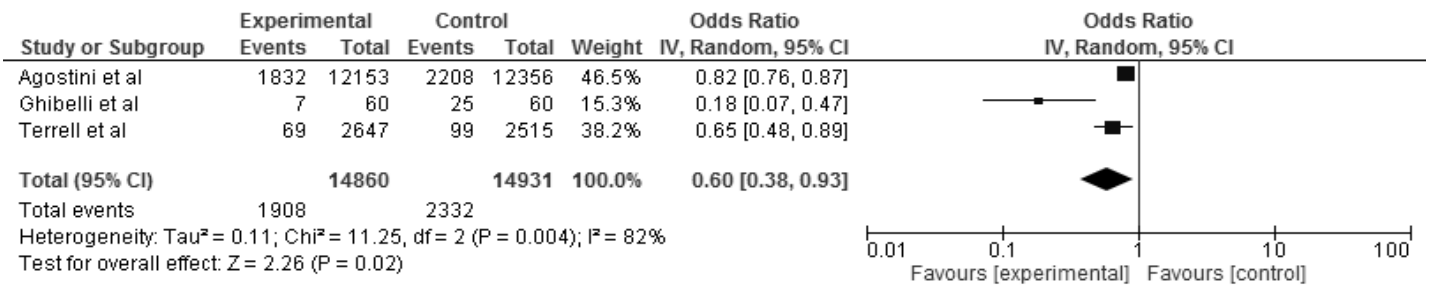

Figure 2: Forest plot for the odds ratio for the reduction in the proportion of patients prescribed PIMs post-intervention.

Narrative summary

Four of the included studies reported results on the effect the intervention had on the proportion of patients prescribed PIMs, all of which showed a statistically significant reduction ($p < 0.05$) for this outcome [10, 14, 16, 18]. Where it was possible to calculate, there was an absolute risk reduction (ARR) of 1.3% – 30.1% [10, 14, 18], and a relative risk reduction (RRR) of 16.7% - 72.2% [10, 14, 16, 18] in patients prescribed PIMs across the studies.

Reduction in PIMs prescribed

Due to the variability in which the results were reported, a meta-analysis could not be performed for this primary outcome. Where it was possible to calculate, there was an ARR of 2% – 5.9% [10, 14, 15], and a RRR of 14% - 77.6% [10, 14, 15, 17] in PIMs prescribed across the studies. Overall, six studies showed a reduction in the number of PIMs prescribed when comparing the intervention and control groups, with five studies demonstrating statistically significant reductions ($p < 0.01$) [12-15, 17]. The only exception to this was the study by Boustani *et al.*, whereby the intervention group still had a greater discontinuation rate in anticholinergic drug (PIM) orders vs the control group (48.9% vs 31.2%; $p = 0.11$) [12]. As previously mentioned, contamination may have been an issue in this study which may have reduced the difference found between the groups. Given the overall low risk of bias in these studies, we can be reasonably confident in the results provided.

Acceptance rates of computerised recommendations

Four of the included studies have data on acceptance rates or levels of agreement with the computer's recommendations (**Table 2**) [13-15, 18].

Table 2: Studies that assessed acceptance rates of the computerised interventions.

Author	Intervention type	Medications involved	% Acceptance Rates or Agreement with Recommendations (intervention arm)	
			Rate	Details
Agostini *et al. [18]*	Computerised reminder	Diazepam and diphenhydramine	95%	95% of patients were successfully directed to a nonpharmacological sleep protocol, or to a safer sedative-hypnotic drug.
Terrell *et al. [14]*	Computerised decision support	9 high-use and high impact PIMs	43%	Decision support was provided 114 times to intervention physicians, who accepted 49 (43%) of the recommendations.
Griffey *et al. [13]*	Computerised decision support	Benzodiazepines, NSAIDs, opiates, sedative-hypnotics	31%; 7.5%	Of initial medicine orders: 403/1283 (31%) were consistent with the computerised recommendations for medication dosage/frequency. 7.5% of suggestions for alternatives were accepted (4/53).
Peterson *et al.[15]*	Computerised decision support	72 medications selected by expert panel	29.3%	29.3% of prescriptions for psychotropics were in agreement with system recommendations.

Reasons for not accepting recommendations

Three studies identified reasons why prescribers did not accept or may have overridden the computerised recommendations [13, 14, 17]. A patient having previously tolerated a PIM was the most common reason for non-acceptance of recommendations in two of the studies [13, 14], while it remained the second most common in the remaining study after the reason that the prescriber felt that the regimen was clinically indicated [17]. This perhaps suggests a degree of inertia with regard to tackling PIP in the acute hospital setting.

Some of the other reasons given in these three studies included:

- On the advice of a consultant, the medicine is not to be changed [13].
- No good substitute exists for the medication [14].
- The patient insists on the medication [14].
- Interaction noted, regimen clinically indicated, will closely monitor [17].
- Warning noted, will use smaller dose and monitor for side effects [17].

Clinical Outcomes

Three of the included studies assessed clinical outcomes [12, 13, 15]. Griffey *et al.* demonstrated a statistically significant reduction in ADEs (3.4% vs 7.1%; $p = 0.02$) [13] and Peterson *et al.* showed a statistically significant reduction in inpatient falls (0.28 vs 0.64 falls per 100 patient-days; $p = 0.001$) [15]. However, there was no statistically significant difference in the remaining fifteen clinical outcomes identified, such as hospital length of stay, readmission rates, or mortality rates (see Supplementary Data).

Discussion

This systematic review and meta-analysis shows that computerised interventions can reduce PIP in hospitalised older adults. Although seven of the eight included studies showed a statistically significant reduction in PIMs ordered or the proportion of patients prescribed PIMs, it is important to note that all of these were single-centre studies. Furthermore, all the included studies in this review were conducted in the United States, except for one study conducted in Italy [10], and therefore this may impact on the generalisability of the review findings for other countries.

The acceptance rates of the computer-generated recommendations varied highly across the studies that measured this outcome (**Table 2**). These findings suggest that interventions that target a smaller number of PIP instances may have greater recommendation acceptance rates than those targeting a wider range of PIP instances. One reason for this may be that prescribers could become overwhelmed by the complexity of information provided in broader interventions [19]. It is interesting to note that Agostini *et al.* achieved a 95% success rate in switching to a safer alternative to a PIM, whereas only 4/53 (7.5%) recommendations for alternatives were accepted in Griffey *et al*. [13, 18]. Thus, providing a recommendation for an alternative doesn't necessarily mean that prescribers will accept this and discontinue the PIM in question. Further qualitative research is

required to identify factors affecting implementation of computer-generated recommendations of this kind.

Autonomy is very important when encountering computerised interventions such as these - prescribers should be capable of bypassing recommendations where clinically appropriate [18]. While overrides are often justified, they can be associated with serious adverse events (or even death) if clinically significant information is unintentionally ignored [20]. A common reason for overrides may be due to alert fatigue, whereby prescribers may pay less attention if they are encountering repeated or inappropriate alerts, or are being inundated by a large quantity of alerts [16, 20]. Customisation of alerts for individual institutions may improve their specificity, and potentially reduce the occurrence of this phenomenon [21].

The results of this systematic review are in keeping with that of previous reviews, which have shown that computerised interventions may be effective in improving the appropriateness of prescribing in older adults. One review assessed the use of electronic prescribing and other forms of technology in reducing PIP and polypharmacy in older adults [22], and an older review evaluated computer decision support to improve medication prescribing in older adults [23]; however, both studies broadly looked at interventions across different healthcare settings. This is the first systematic review to focus specifically on computerised interventions which aimed to reduce PIP for older adults in the hospital setting.

It should be noted that only two of the included studies in this review were RCTs, which are considered the most robust way of identifying if a cause-effect relationship exists between an intervention and outcome [24]. The studies included in the meta-analysis were at a low risk of bias; however, the pooled estimate of effects may have been biased as incomplete reporting in some papers meant that these were the only studies which allowed comparison of one of the primary outcomes (data retrieval bias) [25]. Even though the other studies that assessed this outcome showed a statistically significant reduction in the proportion of patients prescribed PIMs, the pooled

estimate may not accurately represent the true effect that these computerised interventions can have on reducing PIP in hospitalised older adults, especially when you consider that the meta-analysis contained studies that were not RCTs. Despite these limitations, this review is valuable for healthcare professionals as it shows that computerised interventions can be implemented in hospital settings to reduce instances of PIP for older patients.

This systematic review aimed to identify computerised interventions targeting PIMs and potential prescribing omissions (PPOs). However, the included studies in this review only targeted PIMs, and did not identify medication underuse, i.e. PPOs which older patients may benefit from. Despite our comprehensive search strategy, it is still possible that all relevant papers may not have been identified. A systematic review by Meid *et al*. recommended that future interventions targeting PIP should utilise explicit criteria, such as Screening Tool to Alert doctors to Right Treatment (START), alone or in combination with implicit reasoning, to screen for medication underuse in older people [26]. Thus, perhaps future computerised interventions should strive to target PPOs, and not just PIMs. The SENATOR (https://www.senator-project.eu/) and OPERAM (http://operam-2020.eu/index.php?id=1488) projects are ongoing multi-centre RCTs taking place in sites across Europe, which have computerised the Screening Tool of Older Persons' Prescriptions (STOPP) and START criteria as part of their intervention [27]. These trials aim to reduce PIMs and PPOs, prevent in-hospital ADRs, and reduce medication-related hospital admissions.

With the increasing prevalence of electronic prescribing and CPOE worldwide, it should be noted that implementing these systems does not always result in positive patient outcomes [28]. Hospital managers and other key stakeholders will have to devise strategies to allow for successful integration with clinical workflows and with other technologies already in place. All but one of the interventions in this review were conducted at the point of prescribing, which may be a key feature for designing future studies. The advantage of this is that prescribers are prompted in real-time to address medication appropriateness issues to reduce the risk of ADE at the earliest possible point.

Hospital managers will also have important roles in assigning funding to these computerised systems. It has been demonstrated that the extra costs associated with the implementation of CPOE with a CDSS are acceptable in the prevention of medication errors and preventable ADEs [29]. Further research should aim to identify how best to integrate these new computerised systems into routine clinical practice, and to identify methods to increase the acceptance of computer-generated recommendations, where appropriate.

Conclusions

Overall, our findings demonstrate that computerised interventions can be effective in reducing PIP in hospitalised older adults. Larger scale multi-centre RCTs, at national and international levels, will be required to further demonstrate the benefit of these interventions across different institutions, ideally showing both cost-effectiveness data and clinically significant improvements in patient outcomes.

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SUPPLEMENTARY DATA

PubMed Search Strategy

Inappropriate prescribing OR potentially inappropriate prescribing OR inappropriate prescription* OR overprescribing OR underprescribing OR inappropriate polypharmacy OR inappropriate medicine* OR inappropriate medication* OR inappropriate drug* OR optimize prescribing OR improve appropriateness of prescribing

AND

aged OR elder* OR geriatric OR older person* OR older patient* OR older adult*

AND

Computer* OR software OR software intervention OR clinical decision support OR CDSS OR CDS

Note: For each of the remaining databases, the search strategy was modified to suit their specific search capabilities if necessary.

Table 3: Supplementary details about the intervention in the included studies.

Author Year (Country)	Study Design	Duration of study	Number of patients	Target Medicines	Intervention aimed at	Prescriber involved with intervention	Intervention
Agostini *et al.* 2007 (USA) [18]	Controlled before-after study	Pre- and post-intervention periods were both 12 months	C: 12,356 I: 12,153 Total: 24,509	The sedative hypnotics diazepam and diphenhydramine.	Patients aged ≥65 years admitted to the adult inpatient service.	Physician	Computerised reminder in a CPOE system aiming to minimise use of diphenhydramine and diazepam, and directing physicians to either a nonpharmacological sleep protocol or to an alternative medication, such as trazodone or lorazepam.
Boustani *et al.* 2012 (USA) [12]	RCT	21 months	C: 225 I: 199 Total: 424	18 medications with moderate to severe centrally acting anticholinergic properties, selected by an interdisciplinary team (which included a geriatrician, a geriatric nurse practitioner, a pharmacist, a social worker, a physical therapist, an occupational therapist, and an administrative assistant).	English-speaking patients ≥65 years hospitalised on a medical ward, with cognitive impairment at the time of hospital admission. Patients excluded if they had previously been enrolled in the study, were aphasic, or unresponsive at the time of screening.	Physician	If a physician ordered any one of 18 inappropriate anticholinergic medications in a CPOE system, a CDSS interruptive alert recommended to discontinue the medicine, dose modification, or suggested an alternative.
Ghibelli *et al.* 2013 (Italy) [10]	Controlled before-after study	2 months for both phases	C: 74 I: 60 Total: 134	PIMs according to the 2003 Beers criteria, as these were the explicit criteria in INTERcheck®.	Inpatients ≥65 years – only exclusion criteria were severe malignancy (life expectancy less than 6 months) or terminal illness.	Physician	The physician utilised a computerised prescription support system (INTERcheck®) to identify PIMs and potential drug-drug interactions, as well as aiming to reduce anticholinergic load and adjust doses in patients with renal impairment.
Griffey *et al.* 2011 (USA) [13]	Interrupted time series	Alternated OFF, ON, OFF, ON. First two blocks were 6 weeks long and last two blocks were 7 weeks long.	C: 668 I: 739 Total 1,407	Benzodiazepines, NSAIDs, opiates, sedative-hypnotics. These were selected by an expert panel including a geriatrician, a general psychiatrist, a pharmacist, two general internists, and an anaesthesiologist specialising in pain management, as had previously been done in Peterson *et al* [18].	All persons aged ≥65 years who had an order for a medication in one of the targeted drug classes during the study period. The study excluded patient orders in which qualifying medication orders were subsequently cancelled and any orders with missing data.	Physician	When one of the study medications was ordered in a CPOE system for patients ≥65 years, a clinical decision support tool modified one or more of the following parameters: medication selection, default dosage, or default frequency. The physician could then choose to accept or override the recommendation. The tool was alternated 'OFF' and 'ON' in consecutive blocks during the study period.

Lester *et al.* 2015 (USA) [16]	Controlled before-after study	4 years: 2010 to 2013. Results are from the second quarters of each year.	C: 3,259 I: 9,591 Total: 12,850	Diphenhydramine, metoclopramide, and all antipsychotics.	Patients aged ≥65 years.	Prescribers – doesn't specify.	Informational alerts popped up when a PIM was ordered in the CPOE system. The physician was required to acknowledge the alert, before deciding on whether to cancel their order or continue prescribing the medication.
Mattison *et al.* 2010 (USA) [17]	Controlled before-after study	Pre-alert: 6 months Post-alert: 37 months	Number of patients is not stated	A list of Beers 2003 criteria medications selected by a geriatrician and pharmacist, and then revised by the hospital's Pharmacy and Therapeutics Committee.	All hospitalised inpatients aged ≥65 years.	Physicians	The CPOE system alerted prescribers when a PIM was ordered by providing a medication-specific warning that advised alternative medication or dose reduction.
Peterson *et al.* 2005 (USA) [15]	Interrupted time series	4 consecutive 6-week study periods. 1st and 3rd were control periods (usual CPOE). 2nd and 4th periods were intervention periods	C: 2,515 patient visits I: 2,647 patient visits Total: 5,162	72 psychotropic medications decided on by a panel of experts, including a geriatrician, a geriatric psychiatrist, a pharmacist, 2 internists, and an anaesthesiologist specialising in pain management.	All patients ≥65 years prescribed one of the targeted medication and admitted to any of the medical, surgical, neurology, and gynaecology services were evaluated. General ward and intensive care patients were eligible for analysis. Only those patients whose admission was entirely contained within 1 of the 6-week study periods were included.	Physicians	A decision support tool altered the default dose and frequency for psychotropic medications for patients ≥65 years, and suggested an alternative medication when prescribers ordered one of 12 psychotropic medications known to be poorly tolerated in older patients. The support tool was activated for 2 of 4 six-week study periods in an off-on-off-on pattern.
Terrell *et al.* 2009 (USA) [14]	RCT	30 months	C: 1,925 I: 1,793 Total: 3,718	9 high-use and high impact PIMs, selected by an expert panel consisting of two doctors of pharmacy, two physician information technology experts, three geriatricians, and three emergency physicians.	The intervention was aimed at emergency department physicians. I: 32 physicians C: 31 physicians	Physicians	Physicians in the intervention group were provided decision support when they attempted to prescribe a PIM for patients ≥65 years who were being discharged from the emergency department. The computerised reminder provided recommendations for alternatives which the physician could accept or reject.

C: Control group; I: Intervention group; CI: Confidence interval; RCT: Randomised controlled trial; CPOE: Computerised physician order entry; CDSS: Clinical decision support system;
CO: Clinical outcomes; PIM: Potentially inappropriate medicine; ADE: Adverse drug event

Table 4: Risk of bias assessments. Review authors' judgements are categorised as 'Low Risk' of bias (+), 'High Risk' of bias (-) or 'Unclear Risk' of bias (?).

Author (RCTs* and controlled before-after studies)	Selection Bias					Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Overall Risk of Bias
	Random sequence generation	Allocation concealment	Baseline outcome measurements similar	Baseline characteristics similar	Free of contamination	Outcome assessment	Incomplete data outcomes addressed			
Agostini *et al. [18]*	-	-	?	?	+	+	+	+	+	+
Boustani *et al. [12]**	+	+	?	+	-	+	+	+	+	+
Ghibelli *et al. [10]*	-	-	+	+	+	+	+	+	+	+
Lester *et al. [16]*	-	-	?	+	+	+	+	+	+	+
Mattison *et al. [17]*	-	-	?	?	+	+	+	+	+	?
Terrell *et al. [14]**	+	?	?	+	?	+	+	+	+	+

Author (Intermittent time series analysis studies)	Was the intervention independent of other changes?	Was the shape of the intervention effect pre-specified?	Was the intervention unlikely to affect data collection?	Was the knowledge of the allocated interventions adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Was the study free from selective reporting?	Other risks of bias	Overall risk of bias
Griffey *et al. [13]*	+	+	+	+	+	+	+	+
Peterson *et al. [15]*	+	+	+	+	+	+	+	+

* RCT: Randomised controlled trial

Table 5: Studies which assessed clinical outcomes.

Author	Description of Clinical Outcomes
Boustani *et al. [12]*	All clinical outcomes with no statistically significant difference (0/9). No statistically significant effects on health outcomes including: • the mean days of hospital stay (intervention: 7.7 days vs usual care: 6.8, $p = 0.12$), • 30-day mortality rate (intervention: 6% vs usual care: 5.8%, $p = 0.69$), • home discharge (intervention: 43.2% vs usual care: 36.9%, $p = 0.13$), • 30-day readmission rates (intervention: 18.6% vs usual care: 16.4%, $p = 0.53$), • hospital-acquired complications (intervention: 47.2% vs usual care: 44.9%, $p = 0.94$). The hospital-acquired complications included: • incidence of delirium (intervention: 33.7% vs usual care: 31.1%, $p = 0.78$), • the presence of ICD-9 codes of pressure ulcer at discharge (intervention: 12.1% vs usual care: 11.1%, $p = 0.77$), • the presence of ICD-9 code for fall or injury at discharge (intervention: 4.5% vs usual care: 4.9%, $p = 0.88$), • orders for physical restraints or patients observed to be physically restrained (intervention: 11.1% vs usual care: 7.6%, $p = 0.54$).
Griffey *et al. [13]*	One clinical outcome with statistically significant difference* (1/5). No significant differences were observed in: admission rate, reversal drug administration, number of 10-fold orders, or emergency department length of stay. *ADEs: There were 39 ADEs identified, distributed as 8/237 patients (3%; 95% CI 1% to 6%) during ON periods and 31/436 patients (7%; 95% CI 5% to 9%) during OFF periods ($p = 0.02$).
Peterson *et al. [15]*	One clinical outcome with statistically significant difference† (1/3). No difference between control and intervention for length of stay or altered mental status. †The rate of falls continued to be significantly less (0.28 vs 0.64 falls per 100 patient-days; $p = 0.001$).

ICD: International Classification of Diseases; ADE: adverse drug event; CI: Confidence Interval.