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Effectiveness, safety and implementation results of the strategies aimed at the safe prescription of medications in university hospitals in adult patients. Systematic review

Efectividad, seguridad y resultados de implementación de estrategias dirigidas al proceso de prescripción segura de medicamentos en hospitales universitarios en pacientes adultos. Revisión sistemática

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Abstract

Introduction
A broad range of practices aimed at improving the effectives and safety of this process have been documented over the past few years.

Objective
To establish the effectiveness, safety and results of the implementation of these strategies in adult patients in university hospitals.

Methodology
A review of systematic reviews was conducted, in addition to a database search in the Cochrane Library of Systematic Reviews, Embase, Epistemonikos, LILACS and gray literature. Any strategy aimed at reducing prescription-associated risks was included as intervention. This review followed the protocol registered in the International Prospective Registry of Systematic Reviews (PROSPERO): CRD42020165143.

Results
7,637 studies were identified, upon deleting duplicate references. After excluding records based on titles and abstracts, 111 full texts were assessed for eligibility. Fifteen studies were included in the review. Several interventions grouped into 5 strategies addressed to the prescription process were identified; the use of computerized medical order entry systems (CPOE), whether integrated or not with computerized decision support systems (CDSS), was the most effective approach.

Conclusions
The beneficial effects of the interventions intended to the prescription process in terms of efficacy were identified; however, safety and implementation results were not thoroughly assessed. The heterogeneity of the studies and the low quality of the reviews, preclude a meta-analysis.

Keywords
Medication errors; Drug prescriptions; Electronic prescription; Inappropriate prescribing; Medical errors.

What do we know about this issue?

- The prevalence of prescription errors was approached in a trial conducted in the United Kingdom in 2012. A prescription or follow-up error was identified in one of every 8 patients, or in one of every 20 prescriptions.

- Prescribing is of particular interest in the medication prescription process since it is one of the phases with higher risk of medication errors—quite preventable—and its intervention may significantly reduce the incidence of these errors.

What does this new study contribute?

- Several intervention strategies were identified as effective in reducing prescription errors, but the safety of the interventions was not thoroughly evaluated.

- Further studies are needed to assess the cost-effectiveness of these interventions.

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Resumen

Introducción
En los últimos años se han documentado gran variedad de prácticas dirigidas a mejorar la efectividad y la seguridad de este proceso.

Objetivo
Establecer la efectividad, seguridad y resultados de implementación de estas estrategias en pacientes adultos en hospitales universitarios.

Metodología
Se realizó una revisión de revisiones sistemáticas. Igualmente, la búsqueda en las bases de datos de la Biblioteca Cochrane de Revisiones Sistemáticas, Medline, Embase, Epistemonikos, LILACS y literatura gris. Se incluyó como intervención cualquier estrategia dirigida a reducir el riesgo asociado a un error de prescripción. Esta revisión siguió el protocolo registrado en el Registro Prospectivo Internacional de Revisiones Sistemáticas (PROSPERO): CRD42020165143.

Resultados
Se identificaron 7.637 estudios después de eliminar las referencias duplicadas. Después de la exclusión de registros basados en títulos y resúmenes, se evaluaron 111 textos completos para elegibilidad. Se incluyeron quince estudios en la revisión. Se identificaron varias intervenciones agrupadas en 5 estrategias dirigidas al proceso de prescripción, de las cuales el uso de sistemas computarizados de entrada de órdenes médicas (CPOE) integrados o no a sistemas de soporte de decisión computarizados (CDSS) la estrategia más eficaz.

Conclusiones
Se identificaron efectos benéficos de las intervenciones dirigidas al proceso de prescripción en términos de eficacia; sin embargo, la seguridad y los resultados de implementación no fueron ampliamente evaluados. La heterogeneidad de los estudios y la baja calidad de las revisiones impiden la realización de un metaanálisis.

Palabras clave
Errores de medicación; Prescripciones de medicamentos; Prescripción electrónica; Prescripción inadecuada; Errores médicos.

INTRODUCTION

A global interest about patient safety emerged over the end of the past century. Since then, different trials have focused on the incidence and nature of adverse events in different regions around the world (1-3), including Latin America (4,5). Up to 15.1% (3) of all adverse events are associated with the use of medications, which highlights the morbidity and mortality derived from errors in medication use.

There is a lack of consensus regarding the definition of "medication errors" (6); however, the most widely accepted definition in the literature is the definition by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) which defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use" (7).

A prospective study conducted in Boston in 1995 by Bates at al., evaluated the medical and surgical admissions in two hospitals over a 6-months period and found that 6.5 % of the admissions had medication errors and 5.5 %, potential medication errors; 28 % of the errors were preventable and the phase of most frequent occurrence of errors was during prescribing(56 %), followed by administration (34 %), transcription (6 %) and dispensing (4 %) (8).

Consequently, prescription is particularly interesting as part of the process of use of medications since it is one of the phases with higher risk of medication errors — with a prescription or follow-up error of one in every 8 patients, or one in every 20 prescriptions (9), that are highly preventable (8) —; hence intervention could represent a significant reduction in the incidence of such errors.

According to the United Kingdom consensus, a prescription error occurs when "as a result of a prescribing decision or a prescription writing process, there is an unintentional significant reduction in the probability of delivering timely and effective treatment, or increasing the risk of harm when compared against the generally accepted practice" (10).

Prescribing is not a simple process; on the contrary, the complexity of appropriately selecting the best pharmacological treatment, keeping in mind the interactions with other medications, their metabolism, the particular patient conditions (age, multiple morbidities, complexity), inter alia, make this a really challenging phase. Hence, any efforts aimed at optimizing medication prescribing are more than justified. In fact, over the past few years, a broad range of practices have been documented intended to improving the

effectiveness of prescribing, including: patient and staff education and training (11-14), multidisciplinary approaches encouraging deprescribing (15), active pharmacist involvement in care (11,16,17), computerized support systems for clinical decision-making (11,18), electronic prescribing (19,20) and verification and reconciliation of medications (21,22).

There are numerous studies assessing the effectiveness and safety of these interventions (11-22); however, the methodological design of the studies has hindered the possibility to ascertain the effectiveness and safety of such strategies.

Consequently, this review is intended to establish the effectiveness, safety and implementation results of the strategies aimed at securing a safe medication prescribing process in adult patients in university hospitals, through a search and synthesis of information based on systematic reviews of the literature.

METHODS

This review followed the protocol of the International Prospective Registry of Systematic Reviews (PROSPERO): CRD42020165143. Some changes to the protocol were justified since only systematic reviews were included, to avoid duplication in the evidence review; the bias ROBINS-TOOL appraisal tool was changed for AMSTAR 2 (23).

Design

Review of Systematic Reviews

Type of studies included

Systematic reviews of quantitative interventions, with or without meta-analyses and qualitative reviews were included. Narrative reviews defined as those without a clearly defined question, with unverifiable methods and lacking a systematic or reproducible search were excluded.

Type of participants

Adult patients aged 18 years old and above who received medications during their hospital stay and family members involved in medication reconciliation, as well as hospital healthcare teams that prescribe medications in teaching institutions / university hospitals.

Type of interventions

Any type of simple or multidimensional strategy addressed to reduce the risk associated with a prescription error was included.

Type of outcome measures

Primary outcomes

The effectiveness and safety of the prescription strategies measured in the target population were considered. The clinical effectiveness was defined as any measure which showed improved patient health or a reduction in the number of prescription errors. The safety outcomes were defined as any outcome that during the implementation of the strategies to improve medication prescription caused harm or undesirable results in family members, patients, or healthcare teams.

Secondary outcomes

The following implementation measures were considered as secondary outcomes (24):

- **Acceptability:** the perception among the interested parties that an intervention is acceptable.
- **Adoption:** the intention, initial decision or action to try to use a new intervention.
- **Adaptation:** the change or perceived relevance of the intervention in a particular setting or for a target audience or problem.
- **Feasibility:** the extent to which an intervention may be conducted in an organization or an environment.
- **Fidelity:** the extent to which an interventio n was implemented exactly as it was designed in an original protocol, plan or policy.
- **Cost of implementation:** the incremental cost of the strategy.
- **Coverage:** the extent to which the population is illegible to benefit from an intervention.
- **Sustainability:** the extent to which an intervention is maintained or institutionalized in a particular environment.

Effectiveness should be understood as the ability to accomplish a result, while safety is the ability to reduce the risk.

The acquisition of new knowledge or lessons learned by the users of these strategies are also considered as secondary outcomes.

A search strategy was designed using controlled Embase terms and Health Sciences Descriptors - DeCS in LILACS) and free language (synonyms, acronyms and abbreviations) related to the population (university hospital, teaching hospital) and the strategies (Drug prescription strategy, drug prescription strategy, drug prescription interventions, drug prescriptions, potentially prescription errors) in all their possible combinations. The search reviewed the Medline database, the Cochrane library of Systematic Reviews and Epistemonikos. Embase and LILACS were used to search regional data sources. Searches in the grey literature from various sources were included: SIGLE (System of Information on Grey Literature in Europe), NITS, PsycExtra, OpenGrey, Google Scholar (first 200 results) and the Joanna Briggs Institute libraries. The search deadline was January 21st, 2020.

The selection was independently conducted by two reviewers; any selection differences were settled via a third reviewer. First, they verified that the reviews met the inclusion criteria by title and summary, and then in full text. The selection process is illustrated in the PRISMA diagram (figure 1).

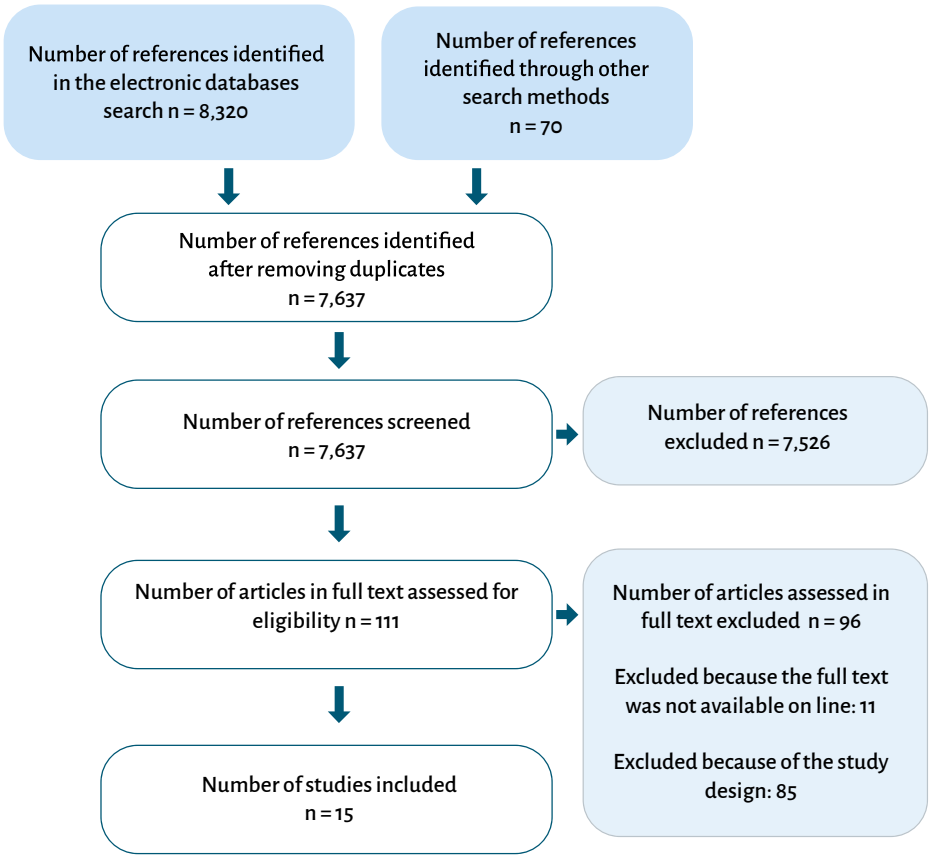
The data mining from the reviews selected was independently conducted by three investigators on a standardized table and included: complete reference of the authors and year, type of review (quantitative or qualitative), number of studies included in the review, population, context of the implementation, characteristics of the implementation strategy, effect measurements used, results obtained, sources of financing and disclosures.

The quality of the selected reviews was assessed by the investigators using the AMSTAR 2 tool (23). The consensus on quality assessments was reached through debate, with the advice of an expert investigator when needed.

The results are described using the effect estimator in the original study. The relative effect measures, the relative risk and odds ratio (RR, OR) and absolute risk are presented for the dichotomous data: risk difference and number needed to treat (RD and NNT) with their corresponding 95% CI. For the continuous data, the measures and standard deviations or the standardized mean difference are submitted.

The synthesis of the information was presented as a narrative, submitting the primary and secondary outcomes grouped by interventions. First, the effectiveness results were presented, and then safety and implementation results.

FIGURE 1. PRISMA Diagram.



SOURCE: Authors.

RESULTS

Search results

7,637 studies were identified after removing the duplicated references. After excluding the records based on titles and abstracts, 111 full texts were assessed for eligibility. 15 documents were included in the review. The PRISMA flowchart (figure 1) illustrates the flow of studies and lists the reasons for exclusion of the full texts reviewed.

Characteristics of the studies included

The summary of the characteristics of the studies are shown in Table 1.

Methodological considerations

A total of 15 systematic reviews were included, of which six included meta-analyses. The studies comprised in the reviews were mostly conducted in the United States (25,27,31,33-35,39), Australia (26,35,36,38), and the United Kingdom (28,29,32). A systematic review included studies conducted in Brazil (25); there were no reviews including studies conducted in Latin America.

Description of the population studied

Six systematic reviews included primary studies in pediatric populations (25,31-34,38,39); however, it was possible to discriminate the results corresponding to adult population in all cases.

All reviews included hospitalized patients; nevertheless, seven also included other care settings; four included outpatients (32,33,35,36), two included long-term care (30,36) and one was conducted in all the types of care settings (28).

Description of interventions

The interventions assessed were specifically

Table 1. Characteristics of the studies included.

Author and year	Publication	Number of studies. AMSTAR 2 assessment	Population	Objective	Components of the strategy
Franklin Acheamponga, 2014 (25)	*International Journal of Risk & Safety in Medicine*	42 studies Critically low	Adults and pediatric	Improve safety in the use of medications	Computerized medical order entry, clinical decision making support system, pharmacists intervention and education.
Austin, 2019 (26)	*International Journal of Medical Informatics*	27 studies. Median	Adults	Improve safety and quality in the use of anticoagulants	Computerized physician order entry, clinical decision making support system, board use and overall EMR implementation
Kieran Dalton, 2018 (27)	*Age and Ageing*	8 studies. High Includes meta-analysis	Adults over 65 years old	Improve the appropriation of the prescription in elderly hospitalized patients (65 years).	Computerized physician order entry, clinical decision making support system, and INTERcheck software.
Christina Hansen, 2018 (28)	*British Journal of Clinical Pharmacology*	25 studies. High. Includes meta-analysis	Adults aged over 65 years	Encourage deprescription or reduction of inappropriate prescription	Recommendations and suggestions to the prescriber, based on the STOPP/START criteria, education workshops, individualized feedback, medications system by multidisciplinary teams using the Beer criteria; clinical pharmacists system, computerized physician order entry and consulting.
Elizabeth Manias, 2012 (29)	*British Journal of Clinical Pharmacolgy*	24 studies. Low	Adults	Reduce medication errors in the ICU	Computerized physician order entry, changes in working hours, IV systems, modes of education, reconciliation of medications, pharmacists involvement, protocols and guidelines and clinical decision making support systems.
B. Hill-Taylor, 2016 (30)	*Journal of Clinical Pharmacol and Therapeutics*	4 studies. High. Includes meta-analysis	Adults over 65 years old	Improve prescribing quality and clinical, humanistic and economic results.	Recommendations and suggestions to the prescriber based on the STOPP/START criteria.
David C. Radley. 2013 (31)	*Journal of the American*	9 studies. Critically low. Includes meta-analysis	Adults and pediatric	Reduce medication errors (comprises prescription, transcription, dispensing, delivery and monitoring).	Computerized physician order entry
Fátima Roque, 2014 (32)	*BMC Public Health*	78 studies (31 in hospital settings). Critically low.	Adults and pediatric	Improve the prescription of antibiotics by doctors and/or dispensing of antibiotics by pharmacists.	Educational interventions.
Carolien M. J. van der Linden, 2013 (33)	*Therapeutic Advances in Drug Safety*	45 studies. Critically low	Adults and pediatric	Prevent the prescription of a medication when it had been previously removed because of an ADE.	Electronic systems (computerized physician order entry) and non-electronic systems.

Author and year	Publication	Number of studies. AMSTAR 2 assessment	Population	Objective	Components of the strategy
Walsh, 2016 (34)	*Age and Ageing*	4 studies. Low. Includes meta-analysis	Adults over 65 years old or adults of any age with dementia	Reduction of PIP in patients 65 years old or older, or patients of any age with dementia.	Pharmacist involvement in the healthcare team.
Ria Hopkins, 2019 (35)	*Pain Physician*	9 studies. High	Prescribing doctors	Reduce the prescription of opioids in hospitalized patients.	Educational interventions, development of management protocols, auditing, alert systems and computerized physician order entry.
Sukhpreet Kaur, 2009 (36)	*Drugs Aging*	24 studies. Critically low	Adults over 65 years old	Reduction of prescription errors in geriatric patients.	Educational interventions, computerized support systems, interventions based on pharmacists, multidisciplinary reviewers.
Nancy Iankowitz, 2012 (37)	*JBI Library of Systematic Reviews*	5 studies. Low. Includes meta-analysis	Adults over 65 years old	Reduction of PIM in geriatric patients at the time of hospital discharge.	Support system for electronic clinical decision making
Page, 2017 (38)	*International Journal of Medical Informatics*	23 studies. Critically low	Adults and pediatric	Improved prescription and patient safety.	Support system for clinical decision making, integrated into computerized physician order entry.
Brittin Wagner, 2014 (39)	*Infection Control and Hospital Epidemiology*	37 studies. Low	Adults and pediatric	Improved medication prescription and appropriate use of antibiotics.	Audit and feedback, implementation of guidelines and decision support.

Note: EMR: Electronic Medical Record; STOPP: Screening Tool of Older Persons' Prescriptions; START: Screening Tool to Alert to Right Treatment; ADE: Adverse Drug Events; PIP: Potentially Inappropriate Prescribing; PIM: Potentially Inappropriate Medications.

Source: Authors.

directed to the prescribing process in 10 reviews (27,28,30,33-39); however, five reviews included other stages or assessed the medication use process in general (25,26,29,31,32). Seven reviews used multifunctional strategies (25,28,29,33,35,36,39), the remaining eight used single strategies (26,27,30-32,34,37,38).

A broad range of intervention strategies assessed in the various reviews were identified, which may be classified as follows: 1. Computerized physician order entry systems (CPOE), whether integrated with computerized decision support systems (CDSS) or not (n=10 studies) (25-27,29,31,33,36-39); 2. Intervention by pharmacists and multidisciplinary teams (n=3 studies) (25,28,34); 3. Prescriber education and training (n=3 studies) (29,32,35); 4. Audit and feedback (n=2 studies) (30,39); 5. Protocols and management guidelines (n=2 studies) (29,39).

Computerized physician order entry (CPOE) systems, whether integrated with Computerized Decision Support Systems (CDSS) or not.

1. Effectiveness

The systematic review by Acheampong et al. included 42 primary studies (25) and stated that of the nine studies assessing the use of CPOE, two reported a reduction in prescribing errors (FitzHenry et al. and Boling et al.). In both cases, the estimators of the impact of the interventions were not specified.

The systematic review and meta-analysis by Dalton et al. (27), which assessed the computerized interventions to identify the potentially inappropriate prescriptions (PIP) included eight studies, of which seven showed a reduction in the proportion of patients with potentially inappropriate medications (PIM) (RAR 1.3-30.1 %) or PIMs ordered (RAR 2-5.9 %). The meta-analysis, which only included three studies with a low risk of bias, estimated that the intervention group had less probabilities of being prescribed a PIM (OR 0-6; 95 %CI [0.38-0.93]).

The review by Manías et al. (29) of 2012, evaluated the interventions to reduce medication errors in the intensive care unit. Ali et al. found a reduction in the proportion of dosing errors from 6.2 % (229/3,720 medications) to no error, 5 and 12 months

following the introduction of CPOE with clinical decision support. Colpaert et al., found a reduction in prescribing errors when comparing the intervention group (3,4 %) against the control group (27 %). Evans et al. found a reduction in errors of excessive dosing of 4.5 % to 2.1 % (p <0,01) -intervention, in a community hospital, while the reduction was from 50.4 % to 44.0 % (p <0.001) in a tertiary hospital.

Page et al. (38) included 23 studies aimed at establishing the effectiveness of the alert systems in hospitals with regards to the discontinuation of medications to change the behavior of the prescriber and improving patient safety. The largest volume of evidence is associated with three alert categories including: medication-condition interaction, drug interactions, and complementary orders. Of these interventions, the medication-condition alert reported effective results (five of six studies). Only two of the six studies that evaluated drug interaction and one of the six alerts about complementary orders reported positive benefits. The studies included investigated the impact of the alert and its effect on the prescriber, and found that more than one half of the studies reported a statistically significant beneficial effect from the alert (53 %, n=17) while 35 % (n=11) failed to report any statistically significant effect and 6 % reported a significant detrimental effect. There was no difference between the combined use of alerts, versus the implementation of just one alert category.

The systematic review conducted by Lankowitz in 2012 (37), included five randomized clinical trials assessing the impact of IT decision making tools on the prescription of PIM, the visits to the emergency department and hospital re-admissions of patients over 65 years old. Three studies indicated a statistically significant reduction in PIM prescribing. The results of two studies were grouped into a meta-analysis which showed that computerized alerts significantly reduce the frequency of PIM prescribing (RR 0.82; 95 % CI [0.76-0.88]).

Van der Linden et al. (33) included 45 articles assessing 33 different systems to prevent prescribing of recalled medications due to adverse events, of which 28 (85 %) were electronic. Bates et al. indicated a reduction in the rate of medication errors in case of known allergies from 0.65 to 0.29 per 1,000 patients-day, with an integrated computerized system (p=0.009). Park et al. found a reduction in the administration of the presumptive culprit drug from 15 % (8/54 events) to 1 % (1/100 events) with an electronic surveillance system. Finally, Mahoney found a reduction in the prescription of medications in known allergies from 833 to 109 following the implementation of an IT system for CPOE (OR 0.14, 95 % CI [0.11-0.17], p < 0.001).

Kaur et al. (36) in 2009, evaluated the interventions that could reduce inappropriate prescription in the elderly. 24 primary studies were evaluated, three of which involved the use of CPOE. A study showed that an alert system for potential prescribing problems reduced the occurrence of PIM. The second one was a clinical trial showing that the use of CPOE reduced the prescribing of inappropriate medications by 1.8 % for the intervention group, and 2.2 % in the standard care group (p = 0.002). The third one showed that this type of intervention may improve the use of suboptimal medications in the elderly. All of the interventions were heterogeneous in terms of the population, the intervention and measurements.

2. Safety

Acheampong et al. (25) reported two studies assessing the safety of the interventions. Wetterneck et al. reported an increase of 2.6 % to 8.1 % in the number of duplicate medical orders in the post-intervention group (p <0,0001). FitzHenry et al. argue that administration errors persist despite the introduction of a computerized physician order entry system without an electronic record of medication administration.

Manías et al. (29) reported two studies claiming that following the introduction of CPOE, with or without clinical decision support, there was an increase in the total number of medication errors from 0.12 % to 0.25 % per dose prescribed, and of 90 %, respectively, though they further state that there was a reduction in the number of errors leading to harm. With regards to the clinical decision support systems, one of the six studies included reported an increase in prescribing errors from 12.5 to 24.4 %, as compared to hand written prescriptions, with no effect estimators being reported.

3. Implementation

Radley et al. (31) report that for 2008 in the United States, 34 % (1,589 of 4,701) of the acute care hospitals had adopted the CPOE system. Of these, 39 % said that more than 90 % of their medication orders were processed with CPOE, while 42.4 % reported an implementation percentage of less than <50 %. The authors state an average implementation of 58.8 % and further indicate that there was no statistically significant association between the levels of implementation and the number of hospital beds.

4. Other outcomes

Two studies of the systematic review by Acheampong et al. (25) reported a reduction in medication errors. Van Doormaal et al. documented the reduction of 40.3 % (95 % CI: −45.13 %; −35.48 %) in the incidence of medication errors in the intervention rooms. Shulman et al. documented a reduction in the proportion of medication errors for CPOE (4.8 %) vs. hand written (6.7 %) p <0.04 and an improvement in the overall score of patient outcomes.

Austin et al. (26) reported that Roberts et al. assessed the impact prior to the previous and subsequent use of CPOE on the frequency of all medication errors (number of errors per 1,000 bed days) and

found a statistically significant reduction post-intervention (10.4 vs. 14.1, p <0.001); however, there was no reduction in the frequency of error for heparin per 1,000 heparin orders (5.2 vs. 6.2, p = 0.47). Due to the heterogeneity of the studies and multidimensional interventions with the implementation of the electronic medical record, it was not possible to conduct a meta-analysis.

A study included in Dalton's (27) review showed a statistically significant reduction in the number of adverse events associated with medications (3.4 % vs. 7.1 %; p = 0.02). Another one showed a reduction in falls (0.28 vs. 0.64 falls per 100 patients day; p=0.001); however, there were no differences in the length of hospital stay, the rates of readmission, or in mortality.

A study reported by Manías et al. (29) found a 30% reduction in medication errors with CPOE, with no clinical decision making support when comparing against hand-written orders. These authors reported in a pre- and post-intervention observational study by Fraenkel et al. a reduction from 85 to 55 (p <0.05) in the number of medication incidents with the use of a clinical information system in the ICU. The aggregate analysis of the studies included in the review by Radley et al. (31) indicated a 48 % lower medication error rate (95 % CI, 41 % to 55 %) following the CPOE implementation. The authors estimated that 17.4 million medication errors are avoided per year due to CPOE, representing a 12.5% reduction. However, they do highlight the lack of information about whether such reduction translates into less harm for the patient.

Van der Linden et al. (33) report that Evans et al. claim that with the use of computerized surveillance systems with alerts, none of the eight type B ADE (idiosyncratic or allergic) were due to a known allergy, as compared with 23 % of 56 type B ADE that were documented in the system with no alerts.

Wagner (39) describes three studies evaluating CPOE interventions to identify the requirement of using antimicrobials. None of the three studies found an impact on mortality, but a randomized clinical trial linking the laboratory results and the pharmacy orders found a shorter hospital length of stay in the intervention group. The readmission rates remained unchanged following the implementation of the programs. The incidence of Clostridium difficile infection decreased in a time series study. Mixed results were reported with the use of antimicrobials in two studies. A computerized decision support system aimed at reducing the use of broad spectrum antimicrobials improved the susceptibility of gram-negative isolates in the ICU.

Interventions by pharmacists and multidisciplinary teams

1. Effectiveness

Acheampong et al. (25) in 2014 included 11 primary studies assessing the intervention by pharmacists. Only Klopotowska et al. documented a reduced incidence in prescription errors (190.5 per 1,000 patients-day preintervention vs. 62.5 per 1,000 patients-day postintervention, p < 0.001).

Hansen et al. (25) assessed the behavioral change techniques of the deprescription interventions on the number of medications and inappropriate prescribing. The number of medications was significantly lower in the intervention group as compared to the control group (mean difference -0.96, 95 % CI [-1.53, -0.38], heterogeneity I 2 = 70 % and p = 0.002), while the impact on the number of inappropriate medications was relatively small, with a high level of heterogeneity when comparing the intervention group versus the control group (-0.19, 95 % CI [-0.40, 0.02], heterogeneity I 2 = 90 % and p = 0.07).

Manías et al. (29) included four studies assessing the impact of the pharmacist's intervention; however, only one study specifically examined prescription errors before and after the intervention, with a reduction of 190.5 per 1,000 patient days to 62.5 per 1,000 patient days (p <0.001).

Walsh et al. (34) assessed the effect on quality of the prescription among elderly hospitalized patients via the involvement of the pharmacist in the care team. The intervention resulted in a reduction in the MAI score (Medication Appropriateness Index) at discharge (mean difference in the MAI score -5.27, 95 % CI [-8.44, -2.11]). Similarly, the intervention resulted in a reduction of the MAI score when analyzing the changes in terms of the reference data (mean difference in the MAI score I -7.45, 95 % CI [-11.14,- 3.76]).

The study by Klopotowska et al. described in Acheampong et al. (25) systematic review, showed a reduction in the rate of reportable events with undesired outcomes (four errors in the intervention group vs. one error in the postintervention group). Leape et al. showed a 66 % reduction in adverse events in the intervention group.

Manias et al. (29) reported a reduction in preventable adverse events from 10.4 to 3.5 events per 1,000 patient days (p<0.001) with the pharmacist's intervention, as compared to the control (10.9 vs. 12.4 per 1,000 patient days, p > 0.05).

2. Safety

A study included by Manias et al. (29) found that the medication error rate with the pharmacist's intervention was 370 per 1,000 patient days versus the control which was 80.1 per 1,000 patient days p <0.0001.

3. Implementation

Acheamponga et al. (25) in 2014, described four studies with an acceptance rate above 70 % in pharmacists' intervention; one of them (Dashti-Khavidaki et al.) reported a 32% reduction in pharmacotherapy costs.

Hansen et al. (28) described four studies reporting rates of implementation of the recommendations to discontinue or switch medications above 15.4 %.

Prescriber education and training

1. Effectiveness

Manías et al. (29) approaches the interventions in education, but just one of the studies focuses specifically on prescription. Educating the prescriber and feedback resulted in a reduction in prescribing errors from 22.6 % to 15.9 % in postintervention, and to 5.6 % in the next six weeks (p <0.0005).

2. Safety

Was not assessed in any of the studies.

3. Implementation

Not assessed in any of the studies.

4. Other outcomes

Acheampong et al. (25) reported that Freeman et al. showed a reduction to 28 medication errors after the intervention, as compared to 41 during the same period of the previous year.

Roque et al. (32) assessed the educational interventions to improve prescribing and dispensing of antibiotics, both in the hospital and in primary care. Of the 78 studies included, 31 were identified in the hospital setting, of which 24 (78 %) reported positive effects in all outcomes: compliance with the guidelines, total number of antibiotics prescribed and behaviors associated with the prescription of those medications.

Hopkins et al. (35) assessed the impact of educational interventions on opioid prescribers. Several studies showed a reduction in the use of meperidine from 10.4 % to 6 % (p = 0.03), reduction in the percentage of patients in the ER receiving parenteral meperidine 6.3 % vs. 1.5 % (p < 0,001), 3.6 % reduction in the use of intramuscular opioids (p < 0.001), 5.2 % reduction in high doses of hydromorphone over 2 mg (p = 0.017), 4.9 % reduction in the use of morphine at doses above 4 mg (p < 0.001), after four years of a multidimensional intervention. A study reported a decrease in the use of long-acting opioids following intervention (35.3 vs. 16.5 %; p < 0.0001) or patient-controlled intravenous analgesia (PCA; 39.4 vs. 17.9 %; p < 0.0001). All the studies that assessed the use of opioids in hospitalized patients reported significant changes, including decreased use of meperidine, reduction in the high doses of morphine, use of hydromorphone and intramuscular opioids, as well as decreased use of long-acting opioids or patient-controlled analgesia after the intervention.

Auditing and feedback

1. Effectiveness

Hill Taylor et al. (30) included two randomized clinical trials in the hospital setting. The first one reported that after the recommendations given to the prescriber, based on the STOPP/START criteria, the prevalence or the incidence of at least one PIP was 82 at admission (43.2 %) and 7 (3.7 %) at discharge, versus the control group which was 85 (44.3 %) at admission and 93 (48-4 %) at discharge. The second study reported an incidence of at least one PIM, which in this case was 39 (52.7%) after the intervention at admission and 30 (40.5 %) at discharge, as compared against the control group, which was 37 (51.4 %) at admission and 31 (41.9 %) at discharge. Furthermore, the study reported that the discontinuation of MPO from the time of admission until discharge was 19.3% in the control group vs. 39.7% with the intervention, OR 2.75 (95 % CI [1.22-6.24]), p = 0.013.

2. Safety

Was not assessed in any of the studies.

3. Implementation

Was not assessed in any of the studies.

4. Other outcomes

Wagner et al. (39), assessed 37 randomized, controlled, clinical trials, 14 of which included auditing and feedback as an intervention strategy. Ten studies reported mortality but only one showed a significant reduction in the probability of death adjusted for risk in the intervention group, as compared to the control. The length of stay was no different between the intervention and the control groups. One RCT reported a significant reduction in the readmission of patients with recurrent infection at 60 days, in favor of the intervention group (intervention 3.4 %, control 7.9 %). The audit and feedback programs reduced the use of specific antimicrobials and overuse.

Protocols and management guidelines

1. Effectiveness

Manías et al. (29) described a prospective trial assessing the effect of a medical order format for prescribing antibiotics in the ICU, reporting a reduction from 16.8% to 8.9 % in the control group and of 29.5 to 0.6 % (p <0.001) in the intervention group.

2. Safety

Was not assessed in any of the studies.

3. Implementation

Was not assessed in any of the studies.

4. Other outcomes

Manias et al. (29) included a retrospective trial reporting a reduction in the incidence

of incompatible medications from 5.8 % to 2.4 % (p <0.003) with the implementation of a standard operating system to identify incompatibilities in a 12-bed ICU. Another study described a reduction in the proportion of days with missed heparin prophylaxis from 20.0 % (135/674) to 0 % (0/2,819) with the implementation of a thromboprophylaxis evidence based guideline and to 0 % (0/1,206) in the 10-month follow-up.

Wagner et al. (39) included eight studies assessing the implementation of protocols in clinically stable adults with community acquired pneumonia. Such implementation reduced the hospital stay and the duration of IV treatment (a reduction of 2 days with 95% CI [-2.0 to -1.0]).

Quality assessment

Four high quality reviews were identified (27,28,30,35), one of medium quality (26), four were low quality (29,34,37,39) and six were critically low quality (25,31-33,36,38). Table 2 illustrates the assessment of the overall confidence in the results according to the AMSTAR 2 tool.

DISCUSSION

This review of reviews assessed the effects of the interventions addressing the medication prescription process in terms of efficacy, safety and implementation results.

The use of CPOE associated with CDSS represents the most frequently assessed intervention strategy. Different reviews indicated the benefits of CPOE in reducing the number of medication errors, prescription errors, reduction in the prescription of potentially inappropriate medications, as well as PIM-associated adverse events (25,26,29,31), particularly when using CDSS (25-27,38). While there are studies independently assessing the use of CPOE and CDSS, most primary studies do a combined assessment, resulting in efficacy synergism, particularly for difficult to manage medications such as heparins. Our results are consistent with a

Table 2. Quality rating according to AMSTAR 2.

Author	Item																Confidence evaluation
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Franklin Acheampong (25)	1	2	1	1	1	1	1	1	2	2	4	4	2	1	4	1	Critically low
Austin (26)	1	1	1	1	1	1	2	1	1	2	4	4	1	1	4	1	Medium
Kieran Dalton (27)	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	High
Christina Hansen (28)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	High
Elizabeth Manias (29)	1	2	1	3	1	1	3	1	1	2	4	4	1	1	4	1	Low
B. Hill-Taylor (30)	1	3	1	3	1	1	1	1	1	1	1	1	1	1	1	1	High
David C. Radley (31)	1	2	1	2	1	1	2	3	2	2	1	2	2	1	1	1	Critically low
Fátima Roque (32)	1	2	1	1	2	2	2	1	2	2	4	4	2	1	4	1	Critically low
Carolien M.J. van der Linden (33)	1	2	1	1	1	1	1	1	3	2	4	4	2	1	4	1	Critically low
Walsh (34)	1	2	1	1	1	1	3	1	1	2	1	1	1	1	1	1	Low
Ria Hopkins (35)	1	1	1	1	1	1	1	1	1	2	4	4	1	1	4	1	High
Sukhpreet Kaur (36)	1	2	1	1	2	2	1	1	2	2	4	4	2	1	4	1	Critically low
Nancy Iankowitz (37)	1	2	1	1	1	1	1	1	1	2	1	1	1	1	1	1	Low
Page (38)	1	2	1	1	1	1	1	1	2	2	4	4	2	1	4	1	Critically low
Brittin Wagner (39)	1	2	1	3	1	1	3	3	1	2	4	4	1	1	4	1	Low

Rating: 1: yes, 2: no, 3: partially yes, 4: not applicable.

Source: Authors.

review of reviews published in 2006 (40) which assessed the CDSS impact on the use of medications in the care process. These results evidenced quality improvement in physicians prescribing (14/30-46.6 %) and a reduction in the number of prescription errors (5/30-16.6 %). However, the quality of the studies was poor.

A decrease in prescription errors and in the rate of reportable events with undesirable results associated with the intervention of pharmacists was documented (25). Moreover, the prescription intervention by multidisciplinary teams was effective in reducing the number of medications, inappropriate prescription and the MAI score. However, the effects were highly heterogeneous (27,34).

With regards to the prescriber education and training strategy, a review documented a reduction in prescription errors in the critical care setting (29). Additionally, changes in the opioid and analgesics prescription practices were evidenced, with a reduction in the use of these drugs and improved compliance with the institutional protocols (25,32).

Other strategies such as auditing and feedback have been used in the context of infection committees, decreasing the use of specific antimicrobials and the excessive use thereof; however, changes in hospital length of stay or mortality were not consistently reported (39). The management guidelines and protocols indicated a reduction in the prescription of incompatible medications, fewer omission errors and ambiguity of the prescription (29). With regards to the use of antimicrobials, the implementation of protocols and guidelines significantly reduced inappropriate antimicrobial use, while appropriate prescribing, selection and time of administration of antibiotics improved (39).

In terms of applicability of the results, it should be highlighted that the interventions assessed in the systematic review generate significant healthcare costs, limiting their implementation in developing countries (25), particularly the IT systems. Moreover, implementing these strategies involves training the healthcare staff and generating an institutional organizational culture around an electronic system (25). However, the implementation of these measures could reduce the number of prescription error-associated adverse events, with a subsequent decrease in care costs. Further studies are needed to ascertain the cost-effectiveness of each strategy. In contrast, pharmaceutical interventions showed adequate acceptability by the treating service (25).

Whilst the various reviews report benefits derived from the use of strategies addressed to the medication prescription process in terms of efficacy, safety and the results of the implementation were not thoroughly assessed.

It is important to emphasize that the interventions assessed in this review generate additional costs for the healthcare system, limiting their implementation in developing countries (25), especially of IT systems. Moreover, implementing such strategies involves training the healthcare staff and creating an institutional organization culture around an electronic system (25). In contrast, the pharmaceutical interventions showed adequate acceptability by the treating service (25), which could facilitate their implementation.

The low quality of the reviews (only four of the 15 studies are high quality), the clinical and methodological heterogeneity resulting from the intervention, the population involved, the measurement methods selected, as well as the use of multidimensional strategies, makes it difficult to identify the individual effects of the interventions and the generalization of the results. This paper may be the starting point for conducting interventional studies in our region, to address the previously identified methodological difficulties, in order to ascertain the cost-effectiveness of each strategy in our setting, since the implementation of these measures could reduce the adverse events associated with prescription errors, with a subsequent reduction in care costs .

Changes were made to the protocol initially published, including systematic reviews only, in order to avoid duplication of the evidence. Additionally, the AMSTAR 2 bias assessment tool was modified and these changes may result in losing some potentially relevant primary studies.

This review fully summarizes the available evidence with regards to implementation strategies aimed at assessing medication prescription safety. This is a novel topic not yet thoroughly assessed in the literature, despite its high impact on patients' health and healthcare costs. This paper is intended to encourage new studies in the field, particularly cost-effectiveness and feasibility studies for the implementation of these strategies in Latin America.

CONCLUSION

The systematic reviews assessed herein, point to beneficial effects of the interventions aimed at the medication prescription process in terms of efficacy; however, further studies are needed for an in-depth evaluation of safety and the results of the interventions, especially in terms of cost-effectiveness. The heterogeneity of the studies and the low quality of the reviews hinder the possibility to reach firmer conclusions and to conduct a meta-analysis.

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Authors' contributions

-JDNC, MCAN and MPBV: contributed to the planning, methodological development, literature search and selection of articles, extraction of information, interpretation of the results and drafting of the manuscript.
- KEO: suggested the study subject and contributed to planning, methodological development, interpretation of the results and drafting of the manuscript.

- HGD: contributed to the methodological development, interpretation of the results and drafting of the manuscript.

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Conflicts of interest

No disclosures.

Presentations

None disclosed.

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SUPPLEMENTARY CONTENT
Electronic search report

Electronic search report N° 1			
Type of search	Systematic		
Database	Embase		
Platform	Embase		
Search date	January 21st, 2020		
Range of search dates	Unlimited		
Language restrictions	Spanish and English		
Other limitations	Humans, clinical trial, cohort analysis, controlled clinical trial, longitudinal study, meta-analysis, randomized controlled trial, systematic review		
Search strategy (results)	ID	Search	Hits
	#1	hospital* AND ('university'/exp OR university OR 'teaching'/exp OR teaching OR 'education department') AND ('drug'/exp OR drug) AND (prescribing OR prescription* OR 'electronic prescribing'/exp OR 'electronic prescribing') AND (strateg* OR intervention* OR 'therapy management' OR 'potentially inappropriate prescription'/exp OR 'potentially inappropriate prescription')	12471
	#2	hospital* AND ('university'/exp OR university OR 'teaching'/exp OR teaching OR 'education department') AND ('drug'/exp OR drug) AND (prescribing OR prescription* OR 'electronic prescribing'/exp OR 'electronic prescribing') AND (strateg* OR intervention* OR 'therapy management' OR 'potentially inappropriate prescription'/exp OR 'potentially inappropriate prescription') AND ([english]/lim OR [spanish]/lim) AND [humans]/lim	11636
	#2	#2 AND ('clinical trial'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'longitudinal study'/de OR 'meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de)	3148
References identified	3148		

Source: Authors.

Electronic search report N° 2			
Type of search	Systematic		
Database	Medline		
Platform	Pubmed		
Search date	January 23rd, 2020		
Range of search dates	No time limit		
Language restrictions	Spanish and English		
Other limitations	Humans, systematic reviews, review, meta-analysis, clinical trials, clinical trials protocols, clinical trials phase I, clinical trials phase II, clinical trials phase III, clinical trials phase IV		
Search strategy (results)	ID	Search	Hits
	#1	((hospital* AND (teaching OR university))) AND ((medication OR drug*) AND (prescribing* OR prescription OR "E prescription*" OR "E-prescription*" OR (Electronic AND (prescribing OR prescription* OR "transmission of prescriptions")) AND (strateg* OR intervention* OR "Therapy management" OR potentially inappropriate prescription)) Sort by: Best Match	8529
	#2	((hospital* AND (teaching OR university))) AND ((medication OR drug*) AND (prescribing* OR prescription OR "E prescription*" OR "E-prescription*" OR (Electronic AND (prescribing OR prescription* OR "transmission of prescriptions")) AND (strateg* OR intervention* OR "Therapy management" OR potentially inappropriate prescription)) Sort by: Best Match Filters: Systematic Reviews; Review; Meta-Analysis; Clinical Trial, Phase IV; Clinical Trial, Phase III; Clinical Trial, Phase II; Clinical Trial, Phase I; Clinical Trial Protocol; Clinical Trial; Humans	3000
References identified	3000		

Source: Authors.

Electronic search report N° 3			
Type of search	Systematic		
Database	BVS		
Platform	LILACS		
Fecha de búsqueda	January 23rd, 2020		
Range of search dates	None		
Restricciones de lenguaje	Spanish and English		
Other limitations	None		
Search strategy (results)	ID	Search	Hits
	#1	Hospital AND prescripción de medicamentos	330
References identified	330		

Source: Authors.

Electronic search report N° 4			
Type of search	Systematic		
Database	Cochrane CENTRAL		
Platform	OVID		
Fecha de búsqueda	January 23rd, 2020		
Range of search dates	To this date		
Restricciones de lenguaje	None		
Other limitations	Clinical trial, Clinical trial phase I, Clinical trial phase II, Randomized clinical trial		
Search strategy (results)	ID	Search	Hits
	#1	hospital* AND (teaching OR university) AND (medication OR drug*) AND (prescribing* OR prescription OR E prescription* OR E-prescription* OR (Electronic AND (prescribing OR prescription* OR transmission of prescriptions))) AND (strategies OR intervention OR Therapy management OR potentially inappropriate prescription) {Incluyendo términos relacionados}	10096
	#2	1 and "Randomized Controlled Trial" (Publication Type)	1544
	#3	1 and "Clinical Trial" (Publication Type)	506
	#4	1 and "Clinical Trial, Phase I" (Publication Type)	16
	#5	1 and "Clinical Trial, Phase II" (Publication Type)	50
	#6	2 or 3 or 4 or 5	1601
References identified	1601		

Source: Authors.

Electronic search report N° 5			
Type of search	Systematic		
Database	Epistemonikos		
Platform	Epistemonikos		
Fecha de búsqueda	January 21st, 2020		
Range of search dates	To this date		
Restricciones de lenguaje	None		
Other limitations	None		
Search strategy (results)	ID	Search	Hits
	#1	(title:((title:(Hospital AND drug prescription) OR abstract:(Hospital AND drug prescription))) OR abstract:((title:(Hospital AND drug prescription) OR abstract:(Hospital AND drug prescription))))	241
References identified	241		

Source: Authors.

Electronic search report N° 6			
Type of search	Systematic		
Database	Joanna Briggs Database		
Plataforma	Joanna Briggs Evidence Synthesis		
Fecha de búsqueda	January 23rd, 2020		
Range of search dates	To this date		
Restricciones de lenguaje	None		
Other limitations	None		
Search strategy (results)	ID	Search	Hits
	#1	Hospital AND drug prescription	70
References identified	70		

Source: Authors.