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Original Research

Protocol for systematic review and meta-analysis of randomized controlled trials, cost-benefit analysis and interrupted time-series interventions on pharmacist's prescribing

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Abstract

Background: Shortening the process of prescribing via permitting the pharmacist to select the most appropriate pharmaceuticals for each particular patient may provide great opportunities for pharmacists to develop suitable pharmaceutical care plan, monitor and follow up prescribed medications, communicate and consult physicians for more confirmations. **Objective:** The objective of the current protocol for the systematic review and meta-analysis of pharmacists prescribing interventions was to explore, investigate the evidence, assess and compare PICO in patients with medical conditions (population), receiving pharmacist's prescribing care services (interventions) versus non-pharmacist's prescribing (comparators), and identify how it will impact the clinical, humanistic, and economic patient's outcomes (outcomes). **Methods:** The necessary elements of PRISMA will be strictly followed to report the systematic review. The meta-analysis will be reported in line with the Cochrane guidelines for synthesis of trials and all forms will be based on quality measures as per the validated Cochrane templates. We will present the results of the systematic review and the meta-analysis based on PICO comparison between the included trials. **Results:** We have identified four models of pharmacist prescribing interventions (independent, dependent [collaborative], supplementary, and emergency prescribing). The results will contain a systematic critical evaluation of the included trials in terms of the sample number of the population (characteristics), the type of interventions and the comparators, and the main outcome measures. **Conclusion:** This protocol will report the evidence and explore the magnitude of impact of pharmacist prescribing interventions, on clinical, humanistic, and economic outcomes. .

Keywords: collaborative prescribing; cost-benefit analysis; dependent prescribing; emergency pharmacist-prescribing; independent prescribing; interrupted time-series interventions; randomized controlled trials

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INTRODUCTION

The growing concerns of medication errors, time spent by physician prescribing (computerized physician order entry), and drug budget constrain are crucial to healthcare businesses.[1] All these factors taken together, may affect the physician's main objective in focusing on diagnosing the patient and placing laboratory tests and documenting patient clinical details. Dependent pharmacist prescribing (based on protocol, formulary, and/or referral) is when the pharmacist and physician will have an agreement, where pharmacist, can write prescription for certain patients and on specific drugs.[2] The dependent pharmacist's prescribing, usually well-known as collaborative prescribing also.[2] There are three forms of dependent pharmacist prescribing based on literature review which are: i. Firstly, dependent prescribing based on the explicit and detailed protocol is the most common type of it; ii. Secondly, prescribing according to formulary, which based on a formal agreement physician will delegates prescribing authority to the pharmacist on specific medications; iii. Thirdly, the patient's referral, in which the physician will refer the patient to the pharmacist to get specific drug therapy and treatment based on the pharmacist's knowledge. Pharmacists with this type of dependent prescription are most typically seen in health-care institutions' ambulatory care settings.[3] The challenges to implementation of this model are relevant to building a favorable socio-political environment and prescriber competency to ensure the smooth integration of pharmacist prescribers into inter-professional clinical teams.[4] Independent prescribing refers to the pharmacist's own decision regarding what to prescribe, to whom it should be prescribed, however it does not need any sort of agreement with other practitioners, not permission.[2]

This model is exemplified by prescribing statin,[5] many benefits that arise from independent pharmacist's prescribing, such as improve patient clinical outcomes, maximizes pharmacists' knowledge and skills to better use, decreases the physician's workload, and improves pharmacists' job satisfaction.[6] Patients who have been prescribed statin medications expressed positive attitudes towards pharmacist services.[6] Some barriers were reported in the United Kingdom, New Zealand, Canada, and Australia[4] e.g., for instance, lack of funding or reimbursement for pharmacists prescribing, insufficient support from health authorities, pharmacists, public, and even healthcare professionals.[4]

The major benefit of pharmacist prescribing in emergency departments is the possibility of filling in gaps among doctors or nurses. In addition, they can also provide pharmaceutical care which may be missing in emergency departments, like verifying prescriptions for clinical appropriateness.[7] Due to many factors, medication errors are very common in the emergency department. The pharmacist can identify and intervene to reduce such errors.[8]

The concept of emergency pharmacist prescribing can pose some challenges due to some operational and clinical variables. It is not always viable to have an emergency medicine pharmacist 24/7 or to have sufficient staffing to provide both direct and indirect patient care services. Due to the varying needs of the emergency department, level of pharmacist training and expertise, and allocation of resources, the gamut of pharmacists involved in this department differs between institutions.[9] The pharmacist's essential duty is to shift away from dispensing drugs toward having greater responsibility for and promoting optimal medication usage through collaboration.[10]

Research questions?

Our specific research questions will be: 1) Does pharmacist prescribing decrease prescribing errors, medication errors, and medication-related adverse effects? 2) Does it improve patients' physical functioning, cost-benefit and quality of life?

Rationale

The advanced patient centered approach dictates that doctors spent much time in diagnosis and planning the treatment options. The prescribing phase can be collaboratively or independently undertaken by the pharmacist with strict protocols and granted competencies. The rationale for the current protocol relies on exploring evidence for the magnitude of impact of pharmacist prescribing on clinical, humanistic, and economic patient outcomes.

Objective

The objective was to explore, investigate the evidence, assess, and compare the population/intervention/comparator/outcomes (PICO) in patients with medical

conditions (population), any setting (community pharmacy, hospital pharmacy, emergency department, nursing homes, ambulatory setting, etc.), receiving pharmacist's prescribing services (interventions) versus non-pharmacist's prescribing (comparators), and identify how it will impact the clinical, humanistic, and economic patient's outcomes (outcomes). We will objectively, test if the effect sizes (effect of interventions of pharmacist prescribing on humanistic, clinical and economic outcomes) are consistent across studies (precise estimate of the effect), estimate a pooled effect size and identify potential moderators (report if it is robust across population).

METHODS

The current systematic review and meta-analysis was registered with PROSPERO (CRD42022314492), an international database of prospectively registered systematic reviews in health and social care. The protocol has been developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol (PRISMA-P) checklist. We will search CINAHL (via EBESCO), EBESCO, EMBASE, Google Scholar, Medline (via EBESCO) PubMed, the Cochrane Central Register and the Web-of-Science for any pharmacist's prescribing type of interventions (randomized controlled trials, interrupted time-series and cost-benefit analysis) using specific Medical Subheadings (MeSH) terms published between January 2000 and March 2022, since pharmacist prescribing was initiated after the millennium. We will search for RCT-s published in English language (full article) and indexed in Scopus journals data-base.

We will use the predefined Cochrane-approved structured modified forms specific for systematic review and meta-analysis. The relevant data-sets will be collated using the predefined Cochrane library-approved structured modified forms. The draft of the search strategy to be used for one electronic database including planned limits was shown in, [diagram flow chart, Figure 1]. The setting for the systematic review and meta-analysis will be the research lab at the Al Ain University (Abu Dhabi Campus-United Arab Emirates) and will commence from inception date to September 2022.

Study selection

In order to decide which studies to include in our analyses, we will conduct an extensive literature search for relevant papers. We will search by index terms for articles containing the following MeSH, (subject indexing assigned by Center for Reviews and Dissemination [CRD]): -

"ambulatory pharmacist's prescribing, clinical pharmacist's prescribing, collaborative prescribing, consultant pharmacist's prescribing, clinical outcomes, dependent prescribing, independent prescribing, economic outcomes, emergency prescribing, humanistic outcomes, interrupted time-series interventions, pharmacist's prescribing, pharmacist's prescribing in nursing homes, randomized controlled trials, supplementary prescribing".

The titles and the abstracts of the identified articles will be checked against pre-determined criteria for eligibility and relevance (peer review method). Each included study will be assigned an objective assessment of methodological quality, preferably using a method conforming to PRISMA-P (the

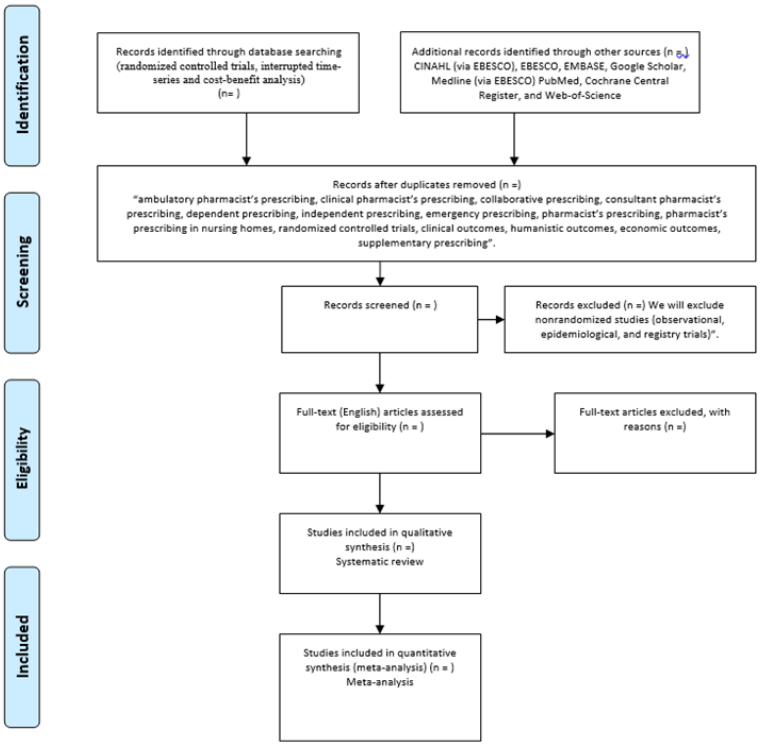

Figure 1. PRISMA flow diagram

current guideline) "PRISMA-P". [Equator: Appendix 1]. The PRISMA-P statement[11a] suggests a standardized way to ensure transparent and complete reporting of systematic reviews, and is now required for this kind of research by more than 170 medical journals worldwide. Endorsing PRISMA. http://www.prisma-statement.org/endorsers.htm.[11b]

Inclusion and exclusion criteria for studies

The PICO items were subjects (population) who have received medications (chronic or acute) prescribed by the pharmacist (intervention) with any acute/chronic diseases at any setting (hospitals, community pharmacy, emergency department, ambulatory care, nursing home, and family medicine) will be considered for inclusion. Studies included pharmacists prescribing as main study question and only studies published in English throughout the searched databases (as full text and/or abstract). Studies involving pharmacist prescribing versus all other forms of prescribing, and care services (comparators) will be eligible for inclusion into the datasets. Only trials with the outlined study design (randomized controlled trials, interrupted time-series, and cost-benefit analysis)) with primary clinical, humanistic and economic outcomes (outcomes) will be considered for inclusion. We will exclude nonrandomized studies (observational, epidemiological, and registry trials)".[12] Waiting list controls, usual care, attention only, and any other active controls will be accepted as appropriate controls (comparators). We will state the number of excluded articles, giving reasons for exclusion, and present this using a PRISMA diagram.[13] The corresponding authors of all the included studies will be contacted to obtain additional information where necessary and to identify any other unpublished studies.

Data extraction (selection and coding)

Data will be extracted by each author and checked by another author interchangeably using standardized data collection form. The data collection form will be piloted prior to commencing real-time reporting with independent verification followed by duplicate removal. Disagreements will be resolved through author discussions and if consensus is not reached an expert not within the authors will be invited to judge the dispute. Where appropriate authors of selected trials will be contacted (to confirm materials/data/unclear items) and electronic supplementary materials of selected trials will be obtained.

The pre-planned data assumptions and simplifications

We will extract the type of pharmacist's prescribing model (interventions), the type of control used, medications dosage, frequency and duration of treatment, subject characteristics (mean age, gender, mean duration of symptoms, type of disease), related to primary and secondary outcome, sample size, randomization, random allocation, duration of follow-up, trial reported outcomes type, and source of financial support. The means and measures of dispersion will be approximated from figures in the reports. We will use results from an intention-to-treat analysis. If effect sizes cannot be calculated, we will contact the authors for additional data. In order to avoid the possibility of introducing bias caused by multiple statistical comparisons (individual studies consist of multiple treatment groups, such as different types of interventions) with one control group, we will combine the groups from multiple arm studies into a single group. Extraction forms will include definitions of variables, with particular details about the study design, planned outcomes (clinical, economic and humanistic outcomes), and their measurement duration and frequency (coding studies for their distinctive characteristics). Specific trials with humanistic and/or cost-benefit analysis will be reported with relevant data variables.

Primary outcome(s)

The evidence of pharmacist prescribing and care services will be the primary outcome measured. This will include clinical outcomes such as treatment failure, therapeutic benefit, adverse events, morbidity data, and mortality data. The secondary outcome measures will include: minimization in prescribing errors (errors rates), overcoming medication omissions, reduction in adverse events, patient's preferences/satisfaction using a validated instrument, and patient's quality of life measured using standard validated tools (e.g., SF-36), [Figure 2a, 2b].

Methods for quality assessment of studies

Assessment of risk of bias (quality) The quality of the trials

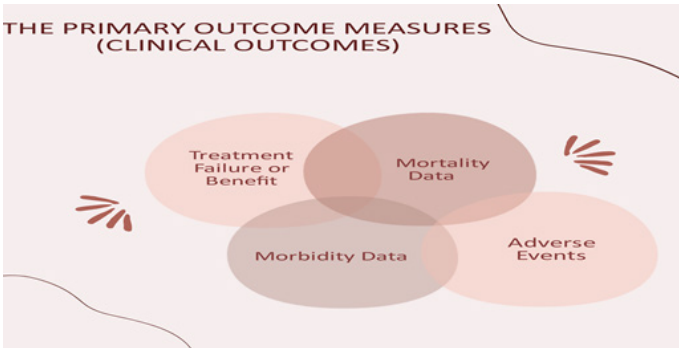

Figure 2a. The primary outcome measures (clinical outcomes)

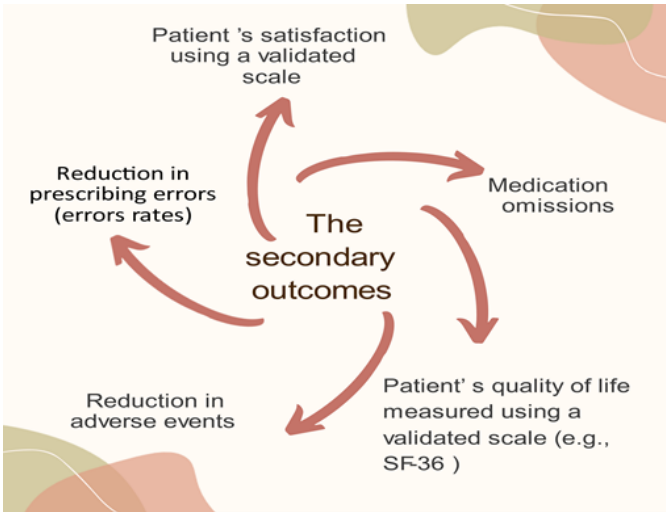

Figure 2b. The secondary outcome measures

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(both at study level and outcome) will be assessed with a five-point scale to minimize and avoid bias in the inclusion of relevant trials. The method that will be followed for risk of bias assessment will be as per the risk of bias tool (Cochrane version).

For evaluation for all outcomes measured (whether statistically significant or not) we will use Hedges' g (Cohen's d bias corrected) together with confidence intervals for the effect sizes. We will standardize the effect size calculations across our study to allow for optimum comparability. Hedges' g is the effect size used in United States, Department of Education's, What Works Clearinghouse (WWC) and Campbell Collaboration, and therefore, provides the greatest external credibility.[12-14]

The methodological quality of the evidence from all the included trials will be assessed by two investigators. The risk of bias will be assessed using the Cochrane Collaboration's tool. We will assess each criterion as low risk of bias, high risk of bias, or unclear risk of bias based on the recommendations of Higgins and Green.[15] We will be covering the following criteria: 1. random sequence generation; 2. allocation concealment; 3. blinding of participants and personnel; 4. Blinding of outcome assessment; 5. incomplete outcome data; and 6. selective reporting and other bias (e.g., baseline differences between control and active arms, use of invalid questionnaires).

Data analysis and strategy for data synthesis

The data synthesis (quantitative, qualitative, descriptive, inferential statistics and meta-analysis) will be performed. The qualitative synthesis will be based on essential characteristics of study quality (risk of bias, consistency, precision, directness, and reporting bias. The quantitative synthesis for the variation in effects (clinical heterogeneity) in the trials included in the current systematic review and meta-analysis will be at all levels of trials (relevant population level, the intervention level, outcomes level [intention to treat ITT: clinical success, superiority/inferiority and statistical magnitude of difference]) and planned summary measure.

Analysis of subgroups or subsets

The pharmacist's prescribing is supported by versatile intervention strategies and models. We will apply inferential statistics for each collated type of intervention such as dependent prescribing, independent prescribing, emergency prescribing, collaborative prescribing, ambulatory/community pharmacist's prescribing, supplementary prescribing and other types of prescribing patterns. We will perform measures of statistical uncertainty, sensitivity analysis, changes in the protocol, assumptions, and subgroup analysis based on the prescribing model. Meta-regression as an extension to subgroup analyses may be used to allow the effect of continuous, as well as categorical, characteristics to be investigated, and allows the effects of multiple factors to be investigated simultaneously (conditional to the sufficient number of trials). Analyzing the meta-analytic databases, we will calculate the effect sizes based on the conservative Hedges and Olkin (1985) approach to meta-analysis[16] via the Review Manager (RevMan) or comprehensive meta-analysis.

Bias corrected standard difference (G)

Data from the randomized controlled trials meeting the inclusion criteria will be considered for meta-analysis. Pooling of data will be performed depending on clinical homogeneity in terms of the population, intervention, outcome measures and timing of outcome measures. Clinical heterogeneity will be determined by discussion among the review investigators and clinically heterogeneous trials will not be combined statistically. Statistical heterogeneity will be determined by using the chi-square (x2) and I2 statistic. Statistical heterogeneity will determine the choice of using the random-effects model for meta-analysis. Ax2 p-values of greater than 0.1 and an I2 value of less than 50% will be used to indicate statistical homogeneity.[16]

The random-effects model will be used to combine clinically homogeneous but statistically heterogeneous clinical trials, whereas clinical and statistically homogeneous trials will be combined using the fixed-effects model. We will interpret and present meta-analytic results either as a benefit or lack of benefit of the pharmacist's prescribing (interventions) as indicated by the effect size. Indicating the gain (or loss) in outcomes seen in the intervention group relative to the control group.

RESULTS

Pharmacist prescribing has grown largely in the last 25 years, with more developed countries joining the race for more privileges for their pharmacists in taking a more proactive role in prescribing. Recently, developing countries have taken more steps towards implementing pharmacist prescribing and have established policies and prepared relevant skills and competencies to embrace these milestone changes in the role of pharmacists in prescribing.

The Gulf countries have initiated further steps towards pharmacist prescribing. Recently, in Qatar, a sequential explanatory mixed-methods design study was conducted in Hamad Medical Corporation [HMC], has explored the pharmacists' aspirations, readiness, facilitators, and barriers to implement pharmacist prescribing (pharmacists, n = 554) with response rate 62.8% (n = 348). The pharmacists have expressed that they were largely aspired to, and ready to be prescribers.[17]

In 2020, a cross-sectional survey study was conducted on hospital pharmacists in Saudi Arabia about views, prescribing legislation and barriers to implementing pharmacist prescribing. The survey responses lend great support to confidence in prescribing by pharmacists. The surveyed pharmacists have expressed that the lack of prescribing training, limitations in resources, health providers practice culture, and pharmacist's competency were key barriers to pharmacist prescribing.[18]

When prescribing by protocol, pharmacists adhere to dose standards better and make much fewer prescription mistakes than when recording patients' normal drugs on arrival to the hospital.[19]

If pharmacist prescribing is going to be implemented in health care facilities, effort must be paid to overcoming recognized challenges to implementation, such as building a favorable socio-political environment and prescriber competency. As a result, a concerted effort is needed to develop clear policy pathways, including targeted training courses, raising stakeholder awareness of pharmacists prescribing, and identifying specific funding, infrastructure, and resourcing requirements to ensure the smooth integration of pharmacist prescribers into inter-professional clinical teams.[4]

In 2016, researchers at Alberta, Canada conducted a large RCT of CVD risk reduction by community pharmacists in 56 community pharmacies, which enrolled 723 adults with uncontrolled dyslipidemia, followed for 3 months. The pharmacist-directed interventions included Medication Therapy Management (MTM) review from their pharmacist and CVD risk assessment and education. Pharmacists prescribe medications and order laboratory tests as per their scope of practice to achieve treatment targets. The primary outcome was difference in change in estimated CVD risk between groups at 3 months (estimated using the Framingham, International, or United Kingdom Prospective Diabetes Study-UKPDS risk scores). The trial reported a 21% difference in change in risk for CVD events ($p < 0.001$) between the intervention and control groups. The intervention group had greater improvements in low-density lipoprotein cholesterol (-0.2 mmol/l; $p < 0.001$), systolic blood pressure (-9.37 mm Hg; $p < 0.001$), glycosylated hemoglobin (-0.92%; $p < 0.001$), and smoking cessation (20.2%; $p = 0.002$). The RxEACH study provided significant reductions in risk for CVD events in the intervention group.[20]

In 2016, researchers at Alberta, Canada conducted an RCT in 14 community pharmacies, which enrolled 99 adults with uncontrolled dyslipidemia. The pharmacist-directed interventions included dyslipidemia care, including assessment of cardiovascular risk, review of low density lipoprotein cholesterol (LDL-c), prescribing of medications, health behavior interventions and follow-up every 6 weeks for 6 months. The primary outcome was the proportion of participants achieving their target LDL-c (<2 mmol/L or ≥50% reduction) at 6 months between groups. 43% of the intervention group have had achieved the LDL-c target versus 18% of the control group ($p = 0.007$) which was 3.3 times higher for the intervention group ($p = 0.031$), who also achieved greater reduction in LDL-c (1.12 mmol/L, SE = 0.112) versus control (0.42 mmol/L, SE = 0.109), for an adjusted mean difference of 0.546 mmol/L (SE = 0.157), $p < 0.001$.[21]

Pharmacists in Idaho can prescribe drug preparations of ephedrine, diphenhydramine and short-acting beta-agonists in emergency situations.[6] In the United Kingdom hospital emergency departments, pharmacists practice prescribing medications like paracetamol, salbutamol, and sodium chloride; among the least prescribed include etanercept and digoxin.[7] Patients with a history of asthma who visit a remote area and require albuterol can be attended to by a pharmacist.[22]

Pharmacists have shown they can enhance care by lowering morbidity and mortality rates, minimizing adverse medication events, and lowering health-care expenditures.[23,24] However, the barriers were the lack of time and compensation (wages/remuneration/reimbursement), and even the requirement to interact directly with numerous pharmacists/physicians, were important obstacles. Clinicians expressed a desire for further coordination in the areas of insurance approvals and patient counsel, whereas pharmacists expressed some interest in assisting with the diagnosis and assessment of patients' drug-related complications. Both parties really like to work together more to increase patient compliance.[25]

There is substantial need for research to evaluate the benefits of pharmacist prescribing models and assess its value with respect to drug budgets (pharmacoeconomic aspects), quality of care, and clinical, humanistic and economic outcomes. More reliable research is needed targeting specific patient groups, chronic diseases (diabetes, hypertension, asthma, cardiovascular diseases, rheumatoid arthritis, gastrointestinal diseases, respiratory diseases etc…) and most commonly rational and safely prescribed medications. RCT-s are of paramount importance to reveal the real benefits of pharmacist' prescribing versus physicians' prescribing.[5,19,22,26] [Table 1]

The pharmacist's prescribing (falling under nonmedical prescribing) models have been well implemented in Canada, New Zealand, the UK, and the United States of America.[27-29] This has been preceded by education, skills development, training programs, and competencies for pharmacists. Many chronic conditions or acute episodes of infections and minor ailments have been covered by pharmacists' prescribers. The main goals of pharmacist prescribing are to improve patient care; provide more opportunities for patients (select from alternative options); and maximize the skills and competences of pharmacists [Figure 3]

CONCLUSION

There is a lack of research in developing and under developing countries concerning the prescribing by pharmacists. Enhancing the engagement of community pharmacists with an extended scope of practice such as pharmacist prescribing could have significant population health implications. This protocol is expected to report the evidence and explore the magnitude of impact of pharmacist prescribing, if any, on clinical, humanistic, and economic outcomes. We need to support the pharmacist's prescribing experience by compelling evidence and set guidelines and policies to govern this new trend. The academia, pharmacist's associations, accreditation bodies, insurance schemes, and health authorities should lead in enforcing education, curricula, bylaws and training to support pharmacist prescribing.

The impact on practice

The clinical implication of the research findings on current clinical practice are:

Table 1. Pharmacist prescribing models

Pharmacist prescribing model	Examples of medication	Type of disease	Comments
Independent[5]	All statins (e.g. atorvastatin, rosuvastatin)	Liver disease	Patients feel satisfied and comfortable with regards to their pharmacist's prescribing their medication (humanistic outcome)
Emergency[19]	ACE inhibitors, Diuretics, Nitrates, CCBs, Antianginal, Lipid level regulating, Pain medications, Anxiolytics, hypnotics, bronchodilators, corticosteroids	Cardiovascular, Nervous system therapy, respiratory conditions, endocrine disorders, Gastrointestinal disease	Emergency pharmacists' prescribers have a unique ability to prescribe medications in situations where patients cannot access their healthcare services, (economic outcome).[4]
Collaborative practice[22]	Blood pressure medication, blood sugar control medications and medications for cholesterol management	Cardiovascular disease, diabetes	Pharmacists were as effective as doctors in prescribing these medications (clinical outcome).
Dependent[26]	Warfarin	Anticoagulant; admission to hospital or preoperative	Pharmacists achieve better adhering to dosing than doctors (clinical outcome). They also have less prescribing errors and omissions than doctors (clinical outcome).

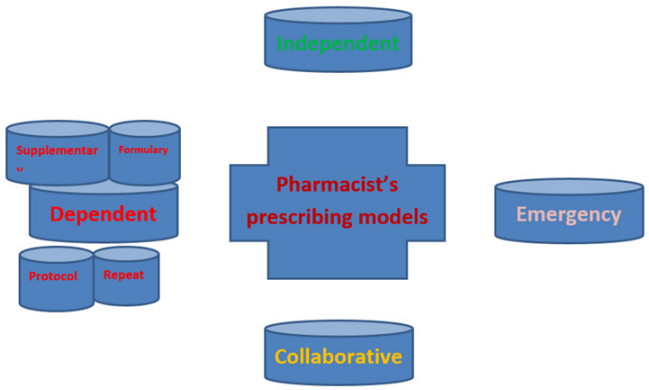

Figure 3. Pharmacist's prescribing models

Highlight the current evidence-based clinical pharmacy services in supporting pharmacist's prescribing models.

Increase the awareness about the benefits of pharmacist's prescribing to international audiences.

Contribute to the implementation of pharmacist's prescribing at the international level.

Identify the facilitators and barriers to the implementation of pharmacist's prescribing.

KEY MESSAGES

What is already known?

It is well known that pharmacist prescribing improves clinical, humanistic and economic outcomes. However, the exact pharmacist prescribing models of dependent, independent and collaborative, and emergency prescribing have not been well differentiated based on the level and grade of evidence.

What this study adds?

The current protocol is intended to identify facilitators and barriers to the implementation of pharmacist prescribing.

The systematic review will contribute to the implementation of pharmacist prescribing at the international level.

How might this study affect research, practice or policy?

Our study will highlight the current evidence-based clinical pharmacy services in supporting pharmacist prescribing models.

The current protocol increases awareness about the benefits of pharmacist prescribing to international audiences.

ABBREVIATIONS

CRD Centre for Reviews and Dissemination

CI confidence interval

HMC Hamad Medical Corporation

ITT intention to treat

LDL-c low density lipoprotein cholesterol

PROSPERO International database of prospectively registered systematic reviews in health and social care

MH Mantel-Haenszel

MeSH medical subheadings

OR odds ratio

PICO population/intervention/comparator/outcomes

RCT-s randomized controlled trials

RR relative risk

SD standard deviation

SMD standardized mean difference

PRISMA-P The Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol

WWC What Works Clearinghouse

AUTHOR'S CONTRIBUTIONS

All authors have contributed equally to the protocol of systematic review and meta-analysis of randomized controlled trials on pharmacist's prescribing: The evidence and the magnitude of impact on clinical, humanistic, and economic outcomes.

DECLARATIONS

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

The research does not need ethics approval.

Consent to participate

Not applicable.

Consent for publication

We declare our consent for the publication of our article.

Availability of data and material (data transparency)

There was no any associated data.

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