THE EFFECT OF EARLY PHARMACIST-LED MEDICATION REVIEW IN ACUTE CARE ON HEALTH OUTCOMES: A SYSTEMATIC REVIEW

Introduction:
Prescription and over-the-counter medications are the second largest category of healthcare spending in Canada, and totaled over $31 billion in 2010.\(^1\) The cost of medications will likely continue to rise due to an aging population, broader treatment indications for older pharmacotherapies, and licensing of new medications that are generally more expensive.\(^2\) Therefore, the direct costs of medications will continue to consume a large proportion of healthcare budgets for years to come. In Canada, a large proportion of this cost is borne by publicly funded drug insurance programs, and therefore, the provinces have prioritized the identification of effective drug use interventions to optimize health value for expenditure.\(^3\)

As medication use has increased, patients, clinicians, health researchers and decision-makers have become increasingly aware of the indirect costs of medications, brought on unintended effects of medications, or their inappropriate use. Adverse drugs events, unintended and harmful effects associated with medication use,\(^4\) have been recognized as a leading cause of ambulatory care and emergency department (ED) visits, and of unplanned hospital admissions.\(^5\)\(^-\)\(^10\) These events rank between the 4\(^{th}\) and 6\(^{th}\) leading cause of mortality in the United States, and may cause more deaths than all other injuries combined.\(^8,9,11\)

Medication review interventions, including medication reconciliation, have been developed in attempts to optimize medication use, and reduce the burden of adverse drug events on the healthcare system.\(^12,13\) Medication review is a structured review of a patient’s medications which includes: (i) Documentation of a best-possible medication history (BPMH); and (ii) Optimizing the use of medications by identifying and addressing inappropriate medications, and potential and real adverse drug events. It often includes communication with other healthcare providers involved in the patient’s care, and may include a discussion with the patient to promote his or her understanding of their medications and achieve concordance about a treatment plan.\(^13,14\)

Institutions such as Accreditation Canada, the Institute for Healthcare Improvement and the Joint Commission are encouraging healthcare institutions to implement medication review interventions at various stages during the delivery of care in order to reduce adverse drug events.\(^12\) Their recommendations have been largely based on favorable process outcome measures, such as reduced errors and reduced potential adverse drug events.\(^15\) The available evidence suggests, that medication review interventions may only be effective if provided by pharmacists and focused on high-risk patient groups.\(^15,16\) This makes their implementation labor-intensive and costly, possibly diverting valuable resources from other important patient care areas. Therefore, synthesizing the evidence about the comparative effectiveness of medication review interventions on patient-oriented outcomes, such as health services use, cost and mortality is important in order to justify continued investment in this process.\(^15,17,18\)
EDs act as a central hubs within our healthcare system where patients with acute and unexpected medical conditions are evaluated and either discharged home, redirected to more appropriate care facilities, or admitted to hospital. Because EDs are areas in which patients transition from one care environment to another (e.g., from the outpatient to inpatient setting), EDs have been targeted as areas in which medication review should be implemented. Therefore, reviewing the evidence for this intervention in this setting, or shortly after hospital admission is important.

**Objective:** To synthesize the evidence on the effectiveness of pharmacist-led medication review in adults presenting to in the ED, or admission to hospital.

**Research Question:**
What is the effect of pharmacist-led medication review on adult patients in the ED, or on admission to hospital on health outcomes?

**Methods:**

**Search Strategy**
We will develop a search strategy in collaboration with a professional librarian. We will seek to develop relevant search terms allowing us to identify studies that report on interventions delivered by pharmacists. We will then seek to identify studies that report on medication review interventions. This search will include all forms of medication review from those targeting patient knowledge to more broad-based medication review and medication reconciliation interventions. We will focus on developing our search for the Medline database first by mapping keywords to MeSH terms and reviewing the scope notes of each term to find alternative indexing terms. After developing our Medline search, we will adapt our search to each electronic reference database by finding the specific indexing terms for each electronic reference database.

We will not use filters to exclude pediatric patients, as those will be identified and excluded at the abstract review stage. We will not apply language filters, as many foreign language journals publish some articles in English.

After completing our initial search we will use the MeSH headings “randomized controlled trials” and “multi-centre studies” and subsequently use filters for randomized controlled trial filters to identify all randomized controlled trials in the body of literature. We will however retain our original search in order to identify non-randomized comparator studies at a later stage.

We will exclude abstracts and letters unless we are able to contact the authors and obtain access to the trial protocol and data for inclusion into our review. The purpose of including abstracts for which we can get detailed information about the study protocol and data is to minimize publication bias in case there are negative studies that were only published in abstract format, and to include studies nearing completion but not yet published in manuscript format.
Medication review is a relatively new intervention that has developed with a recent change in pharmacists’ scope of practice. Therefore we will limit the start year of all searches to 1990.

**Electronic Reference Databases:**
We will search the following general medical electronic reference databases: Medline, Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), International Pharmaceutical Abstracts (IPA), and Web of Science (WOS). We will review the systematic review databases Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE). We will search the trial databases Cochrane Central Register of Controlled Trials (CENTRAL), Biomed (US Trials Registry), metaRegister of Current Controlled Trials, the NHA National Research Register, Clinical Practice Research Datalink, and ClinicalTrials.gov.

**Conference Proceedings:**
We will search conference proceedings from 2008 onwards for the following conferences: British Pharmaceutical Conference (BPC), the UK Clinical Pharmacy Association Conference, Health Services Research and Pharmacy Practice Conference, Pharmacy Care Network Europe Conference, the Canadian Association of Health Services and Policy Research Conference, the Agency for Healthcare Research and Quality Meeting, the International Forum on Safety and Quality in Healthcare, Canadian Society of Hospital Pharmacists Conference, American Society of Health-System Pharmacists Conference and the International Society for Pharmacoepidemiology Conference. We will exclude any abstracts that have subsequently been published as papers, and will review the papers instead.

**Other Search Mechanisms:**
We will use the search engine Google to search the electronic grey literature for other relevant studies or abstracts using search terms identified through our electronic references database search. In addition, we will contact content experts in the field for any ongoing studies they may be aware of. We will also hand search the reference lists of all included studies for any unidentified manuscripts or papers.

**Types of Studies to be Included**
Our initial focus will be randomized controlled trials that report at least one outcome of interest. Randomized controlled trials will be defined as prospective comparator studies with random allocation of subjects to the intervention and comparison groups. We will stipulate a follow-up period of a minimum of one month.

In a second step, we will focus on quasi-experimental studies including quasi-randomized trials, interrupted time series, stepped wedge designs, and controlled before-after designs.

We will exclude medication review interventions that are not primarily led by clinical pharmacists, those conducted only over the phone, interventions focusing primarily on
information technology, and interventions that do not meet the criteria outlined below (See Section “Intervention”).

**Population**

Studies should include adult patients (≥ 18 years of age) who have predominantly been on at least one regular daily medication for two weeks before the intervention, and present to an acute care hospital for an unexpected illness. The intervention needs to be a broad-based medication review intervention, as opposed to focused in one specific disease area (i.e., such as heart failure, or asthma etc.) Presenting to an acute care hospital for unexpected illness will be defined as presenting to the ED, or having an unplanned hospital admission to an acute care facility. We will exclude patients who are being admitted to hospital electively (e.g., for elective surgical procedures). If studies include patient populations presenting for both unplanned and elective admissions, we will contact the study authors and attempt to obtain and include data on patients with unplanned admissions, otherwise these study will be excluded.

Studies will be categorized according to the population in which the intervention was delivered, as follows:

1. **According to the patient population in which the:**
   
i. Intervention was applied to all patients (no risk stratification)
   
ii. Intervention was applied to high-risk subgroups only, identified by
      
   i. Age,
   
   ii. Number of medications, and/or
   
   iii. Number of co-morbidity,
   
   iv. Other.
   
   iii. Intervention was applied to patients who were grouped by subspecialty area a (i.e., geriatric ward) without confining the patient population to one disease category.

**Intervention**

The intervention of interest is medication review. Medication review will be defined as an intervention that include at a minimum:

i. Obtaining a BPMH including prescription and non-prescription medications and natural health products; and

ii. Optimizing the use of medications by screening for, identifying and addressing medication-related problems, including adverse drug events.

An intervention targeted at reviewing a patient’s medical chart and making therapeutic recommendations is an acceptable form of medication review as long as both of the components listed have been completed. Interventions such as medication reconciliation that may extend beyond the components of medication review outlined above (i.e., to the prescribing stage) will be included as long as components (i) and (ii) are performed. It is expected, but not mandatory, for pharmacists completing medication review to
communicate with prescribing physicians, the primary care physicians and/or the most-responsible physician in the clinical care environment the patient is in at the time of the intervention. Other co-interventions such as discussing the medication regimen with the patient to promote his or her understanding of their medications may be included.

Medication review delivered by pharmacists in combination with other health care professionals such as physicians or nurses will be considered and included, if at least component (ii) is delivered by a pharmacist. Other healthcare providers may obtain the BPMH (i.e., pharmacy technicians, nurses or physicians). The intervention of interest must be targeted at patients and not health professionals (i.e., not academic detailing or educational interventions to ED staff).

Studies will be categorized according to the intervention delivered, as follows:

2. According to the components of the medication review intervention:
   i. Medication review with completion of a BPMH (i) and optimizing the use of medications by screening for, identifying and addressing any existing medication-related problems (ii).
   ii. Interventions that extend beyond the two components of medication review listed above, by their category of components which may include:
       a. Patient education;
       b. Communication with the prescriber or general practitioner;
       c. Other.

3. According to the setting of the medication review intervention:
   i. Medication review in the ED;
   ii. Medication review on a hospital ward;
   iii. Medication review in an intensive care unit.

4. According to the timing of the medication review intervention:
   i. Within 24 of presentation to the emergency department or hospital;
   ii. Between 24 and 72h of arrival.

5. Ability of medication reviewer to independently enact recommendations:
   i. Fully able to enact drug and monitoring recommendations themselves (i.e., by ordering laboratory tests or monitoring, and/or altering prescriptions).
   ii. Partly able to enact drug and monitoring recommendations themselves (i.e., recommendations require counter-signing by physicians).
   iii. Unable to enact any recommendations themselves.

6. According to the integration of the medication reviewer into the treating team:
   i. Medication reviewer fully integrated as part of healthcare team with close contact with treating physician in the ED or on the ward (i.e., face-to-face);
   ii. Contact via telephone or electronically with treating physician(s).

7. According to types of pharmacists performing the review:
i. Pharmacists with post-graduate training, defined as either residency-training in a clinical area or trained as PharmD’s;
ii. Pharmacists without post-graduate training;
iii. Research pharmacists;
iv. Pharmacy technicians;
v. Mixture.

8. According to the number of pharmacists performing the medication review.

Comparison:
The comparison group will consist of adult patients managed without pharmacist-led medication review in the ED or on hospital admission.

Studies will be categorized according to the comparator group, as follows:

1. According to any co-interventions delivered in the comparison group:
   i. Standard care without any routine contact with a pharmacist during the ED or hospital length of stay.
   ii. Standard care with some contact with an ED or inpatient pharmacist without medication review.
   iii. Standard care with delayed (>72h after admission) pharmacist-led medication review.
   iv. Standard care with medication review explicitly delivered by another healthcare provider other than a pharmacist.

Outcomes:
The primary outcome of interest for this review is length of hospital admission for admitted patients. Secondary outcomes include 30-day mortality, the proportion of patients admitted (for ED patients), the proportion of ED bounce back visits within 72 hours of discharge (for patients discharged from the ED), the proportion re-admitted patients (for patients admitted from the ED), cost, quality of life measures, and recurrent adverse drug events. We will attempt to ascertain whether patients re-admitted to hospital or bouncing back to the ED return for a related or unrelated problem. If possible, will exclude readmissions and ED bounce back visits for unrelated problems.

The definition of adverse drug events applied in the literature varies widely, and data on adverse drug events and other measures of prescribing have been collected using a wide variety of measures and scales. Therefore, in order to facilitate the synthesis of the effect of the intervention on the occurrence of adverse drug events, we will summarize the effect of the intervention on adverse drug events for each study as follows:

+ Between-group comparison significantly favors intervention group.
(+) Between-group comparison favors intervention but not significantly.
0 No between-group difference was found.
(-) Between-group comparison favors control group but not significantly.
- Between group comparison significantly favors control group.
**Review Procedures and Data Extraction**

In a first step, we will focus on reviewing and synthesizing data from randomized controlled trials. We will proceed to reviewing and synthesizing data from non-randomized studies in a second step.

Two reviewers will independently review the titles resulting from our searches. We will put forward any studies that may be potentially relevant by either author. The reviewers will not be blinded to title or authors.

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Two reviewers will proceed to abstract review using a piloted abstract review form. All abstracts that are identified by either or both reviewers as potentially requiring full-text will proceed to full-text review.

Abstract reviewer 1  
Abstract reviewer 2

Two reviewers will proceed to full-text review using a piloted full-text review form. We will measure the inter-rater agreement between the two reviewers on the inclusion or exclusion of papers into the systematic review using $\kappa$ statistics.

Full text reviewer 1  
Full text reviewer 2

After all included full-text papers have been identified, one author will hand-search all bibliographies to identify any additional unidentified studies.

Hand Reviewer

We will exclude titles without accompanying abstracts, abstracts without full-text English manuscripts.

Pairs of reviewers will independently extract data from all included studies, classify studies according to the criteria listed above (See Section “Intervention” and “Comparison”), and assess the quality of studies using standardized data extraction forms. Pairs of reviewers will review the data extraction forms together and resolve any disagreements by achieving consensus through discussion.
We will contact study authors to clarify any questions on study methodology, and for additional unpublished data on included studies when required. We will record and report the total numbers of papers identified in each database, and the total number of titles requiring abstract review, the total number of abstracts requiring full-text review, and the inclusion/exclusion criteria of all papers going through full-text review.

**Quality Assessment**
We will assess the quality of included studies using the Risk of Bias (RoB) quality assessment tool recommended by the Cochrane collaboration. Accordingly, we will rate the quality of studies in the domains of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases focusing on how bias may have affected the primary outcome of the systematic review (length of hospital admission). If the trial does not report this outcome measure, we will focus our quality assessment on primary outcome measure of the study. Two reviewers will rate the quality of all included studies. Any disagreements will be resolved by a third reviewer.

Quality Rater 1
Quality Rater 2
Quality Rater 3

Our systematic review will comply with the PRISMA statement on the reporting of systematic reviews.

**Data Analysis**
After data extraction is complete, we will assess studies qualitatively for clinical heterogeneity. We will use RevMan to analyze both continuous and dichotomous outcomes. For continuous data reporting the same outcome measures, mean differences (MD) and 95% confidence intervals (CI) will be reported for individual trials and pooled results. Individual and pooled continuous data will be reported as standardized mean differences (SMD) and 95% CI for continuous outcomes when the studies report different measures of a similar outcome (e.g., quality of life). Dichotomous outcomes will be reported as relative risks (RR) with 95% CIs for both individual studies and any pooled results. Data will be reported using a random effects model to account for random variation among studies. Forrest plots will be used to display the results of individual studies, and visually assess heterogeneity. I-squared ($I^2$) statistics will be used to assess statistical heterogeneity. A funnel plot will be used to assess publication bias, when more than 10 trials contribute to the primary outcome.

We will explore the reasons for any statistical heterogeneity using subgroup analysis by sequentially excluding the results of studies that differ in quality (See Section “Quality Assessment”), as well as those that differ by the type of intervention and comparison studied (See Sections “Intervention” and “Comparison”).
References


