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Mechanisms of Pharmacists Interventions on Medication Management and Adherence in Patients with Type 2 Diabetes

by

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Dedication

I would like to dedicate this work to my dear parents *MHD Said Omran* (R.I.P) and *Afaf Barhoum*, to whom I owe all my successes and achievements. This thesis is also dedicated to my beloved husband *MHD Kamal Al Hallak* and my little angel *Nizar*, without whose limitless love and engorgement this work would not have made possible.

Abstract

Optimal management of type 2 diabetes requires a collaborative, team-based approach; however, the role of pharmacists on these teams has not been well-defined. In the first study of this thesis, a systematic review examined components of pharmacist interventions to improve adherence to oral antidiabetic medications. The second study was a retrospective cohort analysis to determine how the pharmacist intervention in a randomized controlled trial achieved a significant improvement in blood pressure control.

The systematic review identified that pharmacist interventions to improve adherence include educational strategies combined with behavioural, affective, or provider-targeted strategies. In the cohort study, the observed improvement in blood pressure was likely due to pharmacist interventions to optimize antihypertensive medication management rather than improve medication adherence.

Pharmacists can be effective additions to collaborative care teams by providing education-based interventions to improve adherence and helping to optimize medication regimens to achieve treatment targets in patients with type 2 diabetes.

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Chapter 1

INTRODUCTION

1.1 Introduction:

Diabetes mellitus is a metabolic disorder that is characterized by markedly elevated blood glucose levels that result from either insufficiency in insulin secretion, the body's resistance to insulin action, or both.[1] This disease is classified into 3 main categories (type 1, type 2, and gestational diabetes) which differ mainly by patient characteristics, age at diagnosis, and management strategies. [1] Diabetes can affect people from all ages and ethnic groups. In 2012, 1.9 million Canadians (or about 6.5% of the population) were reported to have diabetes,[2] with 195 thousand of these individuals living in Alberta.[3] Globally, there are 285 million people living with diabetes, and this number is projected to reach 438 million by 2030.[4] The dramatic increase in diabetes prevalence worldwide is thought to be due to the substantial influence of sedentary life style, obesity, and population aging.[4]

Diabetes represents a global burden for healthcare systems due to its high prevalence, chronic nature, and long term complications.[5] In fact, the management of diabetes accounts for approximately 15% of national healthcare budgets, possibly because people with diabetes consume 2-3 times more health care resources compared to the general population.[6] The Canadian Diabetes Association reported that the estimated cost of diabetes was $12.2 billion in 2010 and this figure is projected to increase by $4.7 billion by 2020.[7] In Canada, diabetes was placed as the sixth leading cause of mortality,[8] and in 2030 it is projected to be the seventh leading cause of death worldwide.[5] Living with diabetes can negatively affect patients' quality

of life, shorten life expectancy, and increase the risk of hospitalization due to other diabetes-related health problems.[9]

Patients with type 2 diabetes, who account for almost 90% of the diabetes cases, are at increased risk of diabetes-related complications, including microvascular complications like retinopathy, nephropathy and neuropathy, and macrovascular complications such as coronary artery diseases compared to the general population.[10] If they persist, these complications may lead to end organ damage and life threating diseases such as kidney failure and myocardial infarction.[11,12]. Type 2 diabetes represents a major risk factor for cardiovascular diseases that accounts for over 50% of death in these patients.[12] Certain characteristics such as age and weight, and the presence of cardiovascular risk factors such as hypertension and dyslipidemia are considered to cluster in patients with type 2 diabetes and contribute to the elevated risk of cardiovascular diseases.[10,13,14] Hypertension is a common comorbidity that has been reported in 63% of patients living with type 2 diabetes.[15] When blood pressure is not controlled adequately, it is associated with a 4-fold increase in the risk of diabetes-related death.[16,17]

Management of type 2 diabetes requires multifaceted and long-term programs that aim at treating not only hyperglycemia, but other cardiovascular risk factors such as hypertension and dyslipidemia.[18] These programs should promote a healthy lifestyle through weight management plans and exercise counseling, along with educational strategies that encourage self-management and feedback. Pharmacological management aiming for tight control of blood glucose, blood pressure, and lipid levels should also be a major component of these programs because these will significantly reduce the risk of diabetes-related complications and death. In the Steno-2 study, for example, patients who received intensive pharmacologic management to lower blood glucose, blood pressure, and lipid levels, had a significantly lower risk of developing

cardiovascular disease end points (hazard ratio, 0.47; 95% CI, 0.24 to 0.73), nephropathy (hazard ratio, 0.39; 95% CI, 0.17 to 0.87), retinopathy (hazard ratio, 0.42; 95% CI, 0.21 to 0.86). [18] Interestingly, these benefits were retained when a long-term follow-up study compared patients in the intensive group to controls and found the reduction in adverse events remained and risk of mortality was also significantly lower.[19] In the United Kingdom Prospective Diabetes Study, patients who were randomly allocated to the tight blood pressure control arm had a 37% (95% CI, 11% to 56%; P=0.0092) lower risk of macrovascular diseases and a 32% (95% CI, 6% to 51%; P=0.019) lower risk of diabetes-related death compared to patients randomly allocated to conventional therapy.[20] In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial, patients who received a fixed combination antihypertensive therapy in addition to current therapy had 9% reduction (Hazard ratio 0.91, 95% CI 0.83-1.00, p = 0.04) in the risk of macrovascular or microvascular events, and 18% reduction (Hazard ratio 0·82, 95% CI 0·68–0·98, p=0·03) in cardiovascular related death when compared to patients who received matched placebo. [21]

Although it is encouraging to note that the 2011 Survey on Living with Chronic Diseases in Canada reported that 87% of Canadians with diabetes take antihyperglycemic medications, and 86% of those with co-existing hypertension take antihypertensive medications,[22] optimal control of blood glucose and other cardiovascular risk factors remains elusive.[15] For example the Diabetes In Canada Evaluation study (DICE) reported that one in every two Canadians living with diabetes had a blood glucose level above the recommended target (A1c <7%), and that glycemic control was worse in patients with longer diabetes duration.[15] Adequate blood pressure control is also very difficult to achieve in people with diabetes. According to the Canadian Diabetes Association 2013 Clinical Practice Guidelines, the target blood pressure in patients with

diabetes is <130/80 mm Hg; [23] although the proportion of patients with both diabetes and hypertension who have a blood pressure below the recommended target have improved from 12% to 36%, however these proportions are still beyond optimal.[24,25]

One common suggestion for the prevalence of uncontrolled blood pressure in patients with diabetes is the complexity of pharmacologic management required.[26] Indeed the proportion of patients with diabetes who take their medication as prescribed is still far from ideal. [27] Adherence to prescribed medication is defined as the extent to which the patient's behaviour matches agreed recommendations from the prescriber.[28] Poor medication adherence has been associated with a significantly higher risk of diabetes-related complications, hospitalization and mortality.[27,29] Although there is no definitive threshold to dichotomize between good and poor adherence, a rate of 80% or more has been considered an acceptable level of adherence in chronic diseases such as hypertension and diabetes.[30]

Many factors contribute to the patient's medication-taking behaviour, with these factors generally categorized into three levels: patient, health care provider, and health care system.[31] Patient-level factors include their perceptions and beliefs regarding adapting to new regimen, complexity of treatment regimens (making it more difficult to follow all recommendations, especially in chronic diseases such as diabetes), knowledge about the disease and the treatment regimen, and the intolerance of drug side effects.[32] Limited accessibility and capacity of health care facilities, extended waiting times, and medication costs, especially in the absence of a full or partial drug coverage, are considered health care system-level barriers to adherence. At the health care provider level, reluctance to initiate or intensify treatment to the maximal recommended doses is a common factor preventing optimal medication use.[33] This reluctance, often referred to as clinical inertia, is characterized by the lack of treatment changes despite

indications and robust evidence to support the decision.[34] In blood pressure management, for example, clinical inertia may explain the lack of dosage increases or initiation of additional antihypertensive medications when blood pressure levels remain elevated.[35] Many factors can contribute to clinical inertia, including the lack of physician awareness of options to optimize treatment and concern regarding possible adverse outcomes (e.g., adverse effects or drug interactions) of higher doses or more complex drug regimens.[34]

A collaborative, team-based approach is essential to attaining optimal management of type 2 diabetes.[36] Pharmacists are one member of this team who are well positioned to help optimize pharmacologic management.[37] Pharmacists can work with patients to recognize and manage patient-level barriers to medication adherence, while communication between health care professionals can help recognize possible areas of clinical inertia at the health care provider level.[37,38] They can improve the patients' knowledge by providing information about diabetes, the pros and cons of different treatment options, and the importance of adherence to medication and other life style modifications.[39] Through patient counselling, pharmacists can synchronize medication administration times within the patient's daily routine, and provide techniques and treatment options that simplify complex regimens.[40] In addition to these patient-level activities, pharmacists can also perform medication assessments and discuss with physicians appropriate changes to optimize treatment.[41]

Several studies evaluated the impact of pharmacist intervention in improving glucose, blood pressure, and lipid levels in patients with diabetes. [42-44] Although these studies have demonstrated that pharmacists have a positive impact in diabetes management and can achieve significant reductions in blood glucose, blood pressure, and lipid levels; the nature of these interventions remains unclear. In a randomized trial conducted by Rothman *et. al.* [43] for

instance, patients who received pharmacists interventions had a significant reduction in systolic blood pressure (difference 9 mm Hg; 95% CI -16 to -3 mm Hg) and in diastolic blood pressure (difference 5 mm Hg; 95% CI: 1 to 9 mm Hg) compared to patient in remained under usual care; however the mechanism of these reductions, and the association between pharmacist role in improving medication use and the positive change in health outcome remains unclear. In order for others to use evidence from these studies to advocate for inclusion of pharmacists in the diabetes management team, it is important to understand how these beneficial effects were achieved.

1.2 Objectives:

The purpose of this thesis is to examine elements of pharmacist interventions on medication management and adherence in patients with type 2 diabetes. Two projects were conducted to address the question: "How does a pharmacist intervention lead to improvements in medication management and outcomes in patients with diabetes?" The first project was a systematic review to identify components of pharmacist-led interventions aimed at improving adherence to oral antidiabetic medications. We used a classification scheme developed by Roter and colleagues to determine how educational, behavioural, affective, and provider-targeted strategies were used in the pharmacist interventions.[45] The second project was a retrospective cohort study to determine if the beneficial effect of pharmacist intervention on blood pressure control was due to optimization of medication therapy or to improvements in patient medication adherence. Data from a randomized controlled study, supplemented with pharmacy refill data were used for this second project.

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Chapter 2

Systematic Review of Pharmacist Interventions to Improve Adherence to Oral Antidiabetic Medications in People with Type 2 Diabetes[1]

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Abstract

Objective: Poor adherence is an important challenge to healthcare professionals because it jeopardizes treatment success and increases the risk of serious complications, especially in patients with chronic diseases like diabetes. The purpose of this study was to summarize the effects of pharmacist interventions aimed at enhancing adherence to oral antidiabetic medications in patients with type 2 diabetes.

Methods: Five electronic databases were searched through to March 12, 2011 to identify controlled trials reporting the effects of pharmacist interventions to improve medication adherence rates in adults with type 2 diabetes. Components of the intervention were categorized as educational, behavioural, affective, or provider-targeted strategies. In addition to the impact on medication adherence rates, we recorded any reported effects on health outcomes.

Results: Eight studies were included in this review. Education-related strategies were the most frequent (seven of eight studies), and six of eight studies used a combination of two or more strategies for the adherence intervention. Change in adherence rate was assessed using a variety of measurement methods, and six studies reported the effect of pharmacist intervention on clinical, economic, or humanistic outcomes. Compared to a control group, five studies reported significant improvements in adherence rate with pharmacist intervention; however, glycemic control improved significantly in only 2 studies.

Conclusions: Pharmacist interventions to improve medication adherence in diabetes generally use an educational component combined with behavioural, affective, or provider-targeted strategies. Although these interventions appear to improve adherence, the effect on health outcomes has not been established.

Key Words: Medication Adherence, Pharmacist Intervention, Systematic Review, Diabetes

2.1 Introduction

Diabetes is a serious, complicated, and overwhelming disease affecting people of all ages and ethnic groups. Currently, approximately 346 million people worldwide have diabetes[1], with the prevalence expected to increase dramatically over the next 20 years due to population aging, sedentary lifestyle, and the dominance of obesity worldwide.[2,3] Diabetes complications present a considerable burden of morbidity and mortality, with the risk of both microvascular and macrovascular complications significantly increased when diabetes management is less than optimal.[4] Indeed, tight control of blood glucose, blood pressure, and cholesterol are essential to reduce risk of diabetes complications.[5] Thus, a comprehensive management program that compromises healthy life-style and optimal pharmacologic treatment is vital to control diabetes and minimize its complications.[6]

Despite well-recognized therapies to help manage diabetes and lower the risk of complications, many patients have difficulties taking their medications as prescribed.[7] Adherence to prescribed medication is defined as the extent to which the patient's behaviour matches agreed recommendations from the prescriber.[8] Although good adherence is considered essential to achieve desired treatment outcomes, a review of 21 studies in diabetes reported that the adherence rate to oral antidiabetic medications ranged from 36% to 93% (median 81%).[7] Poor adherence will significantly increase the burden on our healthcare system by increasing the likelihood of treatment failure, onset of diabetes-related complications, hospitalization, and mortality.[9-11] Numerous factors can affect adherence to oral antidiabetic medications, including complexity of the treatment regimen, the chronic nature of diabetes, poor communication with healthcare providers, and lack of knowledge.[12,13]

With these issues in mind, pharmacists can play an important role to help improve adherence to antidiabetic medications. Indeed, several strategies have been introduced to help patients achieve optimal adherence and manage barriers to adherence.[14] Pharmacists can help educate patients about diabetes and discuss the advantages and disadvantages of different treatment options.[15] As one of the most accessible health care professionals in the community, pharmacists can also contribute to diabetes management by providing regular medication reviews, organizing complex treatment regimens, and helping patients recognize and manage barriers to optimal adherence.[16,17]

A systematic review of studies published until 2006 concluded that pharmacist involvement may be beneficial by increasing adherence rates and improving glycemic control.[18] However, of the five studies in this review, only two reported the effect of pharmacist intervention on medication adherence and found conflicting results.[19,20] The remaining three studies examined the effect of pharmacist intervention on blood glucose control and although there were significant reductions in all three studies, it was unclear if these changes were due to improvements in medication adherence.[21-23] Although the previous systematic review focused on outcomes – adherence rate and blood glucose changes – the nature of pharmacist interventions to help improve adherence to antidiabetic medications has not been well described to date. The goals of this systematic review were to update the previous review and describe pharmacist interventions to improve adherence to oral antidiabetic medications in patients with type 2 diabetes. We were specifically interested in identifying if a health behaviour theory was used to develop the intervention; characteristics of the intervention, including its delivery method and components; methods used to measure adherence; and impact of the intervention on adherence rate and health outcomes.[24]

2.2 Methods

2.2.1 Literature search

Controlled clinical trials published in any language were eligible for inclusion if they examined the effect of pharmacist intervention on adherence to oral antidiabetic medications in adults with type 2 diabetes. Medline, Embase, International Pharmaceutical Abstracts (IPA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Library were searched through to March 12, 2011. Each database was searched using database-appropriate terms for pharmacist, type 2 diabetes, and medication adherence. The Embase search strategy is provided in Table 2.1. The electronic database search was supplemented by hand-searching reference lists of potentially relevant studies and review articles describing pharmacist intervention on adherence to antidiabetic medications.

2.2.2 Study Selection

Two authors independently screened the English title and abstract of all citations to identify potentially relevant studies. The full published article of each potentially relevant study was obtained and reviewed to determine if it met pre-specified inclusion criteria: study patients were community dwelling adults with type 2 diabetes using oral antidiabetic medications; the intervention was delivered primarily by a pharmacist and targeted adherence to oral antidiabetic medications; medication adherence was reported as a pre-specified outcome; and a control group was included. Studies including patients with various chronic diseases were excluded as the impact of pharmacist intervention on diabetic patients could not be specifically evaluated. Any discrepancies regarding study inclusion were resolved by discussion.

2.2.3 Assessment of Methodological Quality

The assessment tool developed by Downs and Black was selected because we anticipated including randomized controlled studies as well as cohort studies.[25] This 27-item checklist evaluates reporting quality, external validity, internal validity, and power.

2.2.4 Data Extraction and Synthesis

One author used a standardized form to extract data from each included study and a second author verified accuracy and completeness. The following study characteristics were recorded: lead author, year of publication, study design, duration of observation, study setting, country, and study group sizes. We searched for the use of a theoretical framework, such as the health belief model[26] or theory of reasoned action[27], to develop the intervention; and training programs to help pharmacists prepare to provide the study intervention. The pharmacist intervention was characterized by recording the delivery method (in-person, by telephone, or indirectly) and components according to the classification scheme developed by Roter and colleagues (described below).[28] The methods used to measure medication adherence were categorized according to direct methods, such as measuring drug levels in blood, or indirect methods, such as a medication possession ratio, patient self-report, pill counts, or medication event monitoring system (MEMS).[29-32] Last, we recorded the change in adherence rate and any health outcomes (categorized as clinical, economic, or humanistic[24]) that were used to measure impact of the pharmacist intervention.

Components of the pharmacist intervention were categorized into one of four strategies as described by Roter and colleagues.[28] The aim of an education-based strategy is to improve a patient's knowledge and awareness of their disease, medication administration techniques, and drug side effects. This strategy also includes interventions addressing a patient's beliefs concerning the advantages and disadvantages of therapy.[15] Behavioural-based strategies use

reminder systems, memory aids, and drug packaging to help organize medication taking. This strategy also includes the provision of advice to synchronize therapeutic activities with usual daily activities, set goals, and monitor blood glucose to determine drug effectiveness.[15] Affective-based strategies provide the patient with emotional support and encouragement. These types of interventions could include enhancement of patient-provider communication through frequent telephone contact, home visits, or in-person counselling with a pharmacist.[33] Provider-targeted strategies mainly involve educational programs aimed at healthcare professionals to help raise their awareness of treatment options and clinical guideline recommendations, and enhance communication amongst different health care disciplines.[32]

2.3 Results

The literature search identified 802 unique citations (Figure 2.1). After screening the titles and abstracts, 39 were considered potentially relevant. Three of these citations were subsequently excluded because we were unable to obtain a copy of the article through our library system or contact the corresponding author.[34-36] Of the remaining 36 potentially relevant articles, authors disagreed on allocation of 2 (6%) and after discussion, determined that 8 (22%) met all inclusion criteria.[20,37-43]

Characteristics of the 6 randomized controlled trials[20,37,39,40,42,43] and 2 controlled trials[38,41] are summarized in Table 2.2. Five studies were conducted in community pharmacies, and 3 were conducted in academic or hospital-based clinics. The total number of patients enrolled ranged from 77 to 2,696 (median 210) and the observation periods ranged from 3 to 12 months. The median methodological quality score was 17 (range 15 to 19) out of a possible 27.[25] All 8 studies scored high (median 8 out of 10) in reporting quality section, but lower (median 7 out of 12) in the internal validity section, which can be expected, since it is difficult to use blinding in health service intervention studies.

Seven of the 8 studies examined the effect of implementing a new pharmacist-based intervention program.[20,37-40,42,43] However, none of these studies used concepts from a health behaviour model to develop the pharmacist intervention. Only 1 study conducted a 2-day training program for pharmacists prior to implementation.[38] The training program helped pharmacists learn to follow a clinical protocol, conduct a medication review, and design a comprehensive diabetes management program.

An educational-based strategy was used in 7 studies and delivered through a combination of 2 or more methods, including in-person sessions, by telephone, or indirectly through leaflets (Table 2.2).[37-43] The educational component was designed to improve patient knowledge of drug

therapy, explain drug side effects and methods to help minimize them, describe the risk of diabetes complications, or discuss the advantages and disadvantages of adapting healthy lifestyle choices. Only the educational intervention developed by Krass and colleagues addressed the patient's beliefs about medications.[38] Behavioural interventions, such as the use of reminder systems and adherence aids, were used in 4 studies.[20,38,41,43] Affective interventions, primarily focused on improving communication and follow-up between the pharmacist and patient, were used in four studies.[37-40] Two studies incorporated provider-targeted interventions by attempting to improve communication between pharmacists and physicians.[38;42] Two studies used only one type of intervention strategy[20,42], while the remaining 6 studies used a combination of 2[37,40,41] or 3[38,39,43] strategies.

Table 2.3 summarizes the methods used to measure adherence and observed changes to adherence rates. Adherence to medication was measured using patient self-report,[37-40,43] pharmacy refill records,[20,38,41] or pill counts.[42] Only 1 study used multiple methods (patient self-report and pharmacy refill records) to measure adherence.[38] Since different methods were used to measure adherence rates, it was impractical to pool data into a summary statistic.

A variety of questions were used to measure self-reported adherence. Three studies used previously-validated questionnaires to measure adherence[38-40] while 2 used investigator-generated questions.[37,43] Andres Rodriguez and colleagues used the Morisky-Green questionnaire to identify patients who were unable to adhere to their medications.[40,44] Krass and colleagues used the regimen screening component of the brief medication questionnaire to determine if patients were adherent to their medications.[38,45] Odegard and colleagues used a 2-question recall technique to identify if patients had difficulties remembering to take their medications and the number of missed doses in the past 2 weeks.[39,46] Al Mazroui and colleagues

asked patients if they had any problems taking their medications and classified those reporting missing doses or taking extra doses, either intentionally or unintentionally, as non-adherent.[43] Grant and colleagues asked patients how many doses were missed in the past 7 days.[37]

All 3 studies using pharmacy refill data to measure adherence rates employed a similar formula to calculate a medication possession ratio (total days supplied divided by the duration of observation).[29] The main difference amongst studies was duration of the observation period, with 2 studies using the entire follow up period of either 6 months[38] or 12 months[20] and the third study using the interval between first and last refill for each patient within the follow-up period.[41] Krass and colleagues[38] used a medication possession ratio between 80% and 115% to identify adherent patients, while the other 2 studies reported the rates only.[20,41]

Medication adherence was reported to be significantly higher in the intervention group compared to the control group by the end of follow-up in 5 studies (Table 2.3). [20,38,40-42] In addition, Skaer and colleagues reported that patients who received both interventions (unit-of-use packaging and refill reminder) achieved a significantly higher adherence rate compared to patients who received only one intervention.[20] Kalsekar and colleagues found that adherence rates were higher in patients filling their prescriptions at an independent pharmacy compared to those filling prescriptions at a chain pharmacy.[41]

The apparent benefit of pharmacist intervention on medication adherence was not, however, consistent within studies or across all 8 studies. As noted previously, Krass and colleagues used 2 different methods to measure adherence rates and observed a significant difference in adherence rates using the self-reported method, but no difference when adherence was measured using pharmacy refill data.[38] Grant and colleagues[37] and Al Mazroui and colleagues[43] did not observe any significant difference in adherence rate changes between groups. In contrast to the

other studies, Odegard and colleagues observed higher adherence rates in the control group throughout the study compared to the intervention group (data were not provided, but authors reported p=0.003).[39]

Clinical, economic, and humanistic outcomes reported in the studies are summarized in Table 2.4. Changes in A_{1C} were measured for both groups in 4 studies.[39,40,42,43] The between group differences in these studies favoured the intervention group, with 2 studies reporting statistically significant differences.[40,43] Two studies also reported changes in other clinical outcomes, including fasting blood glucose, blood pressure, cholesterol, body mass index, and predicted 10-year risk of cardiovascular events.[42,43]

Economic outcomes were estimated by assessing health care expenditure in 1 study. Skaer and colleagues reported a significant decrease in health care expenditure for each of the 3 interventions relative to the control group; however, there were no significant cost differences amongst the three interventions.[20]

Humanistic outcomes were evaluated in only one study. Using the Short Form 36 questionnaire, Al Mazroui and colleagues found a significant improvement in patient-perceived health-related quality of life that favoured the intervention relative to controls.[43]

2.4 Discussion

This systematic review evaluated the characteristics and effects of pharmacist interventions on adherence to oral antidiabetic medications in adults with type 2 diabetes. Summarizing data from 8 studies, the most common intervention was to use an educational strategy combined with either a behavioural, affective, or provider-targeted strategy to help patients optimize the use of their medications. In 5 studies, these interventions resulted in a significant improvement in adherence rate compared to controls. However, the impact on health outcomes, especially blood glucose, was not consistent.

Patient education was the most common strategy, used in 7 of the 8 studies included in this review.[37-43] The educational component of these interventions generally focussed on 2 main themes. The first theme involved improving the patient's knowledge of their medications by discussing the expected benefits and possible side effects. The second theme focused on the disease to improve knowledge and awareness of diabetes, risk of complications, and the importance of lifestyle changes. Almost all studies provided the educational component through in-person meetings between the pharmacist and patient, with some studies supplementing this information with printed information.[39,42,43]

The pharmacist intervention resulted in a significantly greater improvement in adherence rate, compared to controls, in 5 studies.[20,38,40-42] Two studies reported no significant difference in adherence rate changes between groups. [37,43] However, the study by Grant and colleagues[37] may have been influenced by a ceiling effect, with the baseline adherence rate already quite high, and the study by Al Mazroui and colleagues[43] may have been under powered to detect differences between groups. Odegard and colleagues observed a consistently higher adherence rate in the control group, which they felt could have been influenced by co-intervention, since controls visited their physicians more frequently than intervention patients, and a Hawthorne effect, since

the time spent with pharmacists at baseline to identify barriers to adherence may have motivated control patients to improve adherence.[39] Although the methods used to measure adherence rates varied across studies, these observations would support conclusions from the previous systematic review that pharmacist intervention improves medication adherence.[18]

Four studies reported the effect of a pharmacist intervention on blood glucose control, with 2 of these studies observing a significant improvement in the intervention group compared to controls.[39,40,42,43] With these limited data, it was not possible to examine any possible links between changes in adherence rate and blood glucose control. Other clinical outcomes, such as changes in blood pressure, cholesterol, and body mass index, as well as economic outcomes and humanistic outcomes favoured pharmacist intervention, but were reported in very few studies.

Interestingly, despite our initial intent to update the previous systematic review by Lindenmeyer and colleagues,[18] we included a different set of studies. Between the 5 studies in the previous systematic review and 8 in ours, only the study by Skaer and colleagues was included in both reviews.[20] We believe that the differences in included studies may have been due to the inclusion criteria employed. Both reviews sought to include controlled studies examining the effect of pharmacist-led interventions to improve medication adherence in patients with type 2 diabetes. However, we also required that studies had to measure adherence rate changes as a pre-specified outcome. We felt that exclusion of studies reporting adherence rate changes as an incidental finding would eliminate selective reporting of positive observations and therefore decrease the risk of bias in our review.[47] This decision led to exclusion of the studies by Matsuyama and colleagues,[19] Jaber and colleagues,[21] Coast-Senior and colleagues,[22] and Davidson and colleagues[23] that had been included in the review by Lindenmeyer and colleagues.[18]

Behaviour models, such as the health belief model[26] and the theory of reasoned action,[27] were developed to help understand patient views on medications and health recommendations. These models provide a theoretical framework that could help clinicians create interventions aimed at changing a patient's behaviour and enhancing medication adherence. Although none of the included studies used a health behavioural model to guide development of the pharmacist intervention, this is something to consider when developing future intervention programs.

A major limitation of this systematic review is that very few studies have examined the effect of pharmacist intervention on adherence to oral antidiabetic medications. However, we were able to identify and include more studies published after the initial systematic review on this topic by Lindenmeyer and colleagues.[18] Second, there was a wide variety of methods used to measure adherence. In the absence of a standard, well-validated method, we were unable to directly compare the effect of different intervention strategies across studies. Last, there is very little information on the effect of pharmacist intervention on health outcomes. Although all studies examined the effect of the pharmacist intervention on adherence rate, there is insufficient information from available studies to determine if these improvements lead to reductions in physiological parameters, such as blood glucose and blood pressure. Indeed, there is no evidence linking these interventions to changes in the risk of organ damage or hospitalization from diabetes.

In conclusion, observations from this systematic review support the hypothesis that pharmacists can help patients with type 2 diabetes improve adherence to antidiabetic medications. Interventions to help improve medication adherence generally included an educational strategy combined with one or more other strategies to address behavioural, affective, and provider-related issues of adherence. Consideration of a theoretical model, such as the health belief

model, may facilitate the creation of future interventions to improve adherence. Although preliminary evidence suggests pharmacist-led interventions improve medication adherence rates, the impact on health outcomes, such as blood glucose control and risk of developing diabetes-related complications needs to be evaluated.

Table 2.1: Embase Search Strategy

1. exp Patient compliance/

Medication adherence

and

2. Patient education/
3. exp Patient counselling/
4. Drug packaging/
5. Drug monitoring/
6. Patient care/
7. Medication therapy management/
8. Intervention.mp.
9. Pharmacist/
10. Pharmaceutical care/
11. Pharmacy/
    Or /2-11

Pharmacist intervention

and

12. Diabetes mellitus/
13. Non-insulin dependent diabetes mellitus/
    12 or 13

Type 2 diabetes

and

14. Controlled clinical trial
15. Randomized controlled trial
    14 or 15

Study design

Table 2.2: Characteristics of Included Studies and Pharmacist Interventions

Lead Author (Year)	Observation Period	Study Design	Setting (Country)	Group Size		Study Quality	Intervention Strategy			
				Control		Intervention				
Skaer (1993)	12 months	RCT	Ambulatory Care Centre (United States)	78	Packaging (53) Refill Reminder (79) Combination (48)	19	**Educational**	**Behavioural**	**Affective**	**Provider-targeted**
Grant (2003)	3 months	RCT	Academic Affiliated Community Health Centre (United States)	114	118	16		Unit-of-Use Packaging Refill Reminder System Combination of Both		
Krass (2005)	9 months	Parallel groups, multisite, repeated measures	Community Pharmacies (Australia)	82	106	17	Individual patient education (by telephone)		Improve physician-patient communic-ation	
Odegard (2005)	12 months	RCT	University Medical Clinics (United States)	34	43	17	Individual patient education Discussion of patient's health beliefs	Reminders Adherence Aids Blood Glucose Monitoring	Feedback on blood glucose measures Regular follow-up	

Andrés Rodríguez (2007)	12 months	RCT	Community Pharmacies (Spain)	56	56	16	Individual patient education Disease management		Improve pharmacist-patient communic-ation	Improve pharmacist-physician communic-ation
Kalsekar (2007)	12 months	Retrospecti-ve cohort study	Community Pharmacies (United States)	Chain 1709	Independent 987	15	Individual patient education		Regular follow-up	
Phumipamorn (2008)	6 months	RCT	Community Hospital (Thailand)	67	63	18	Individual patient education	Adherence Aids		
Al Mazroui (2009)	12 months	RCT	General Medical Wards (United Arab Emirates)	120	120	18	Individual patient education Diabetes pamphlets			

RCT=Randomized Controlled Trial

Table 2.3: Medication Adherence Rates

Lead Author (Year)	Measurement Method	Control Group			Intervention Group			Between Groups Difference Measured at the End of Study
		Baseline	End of study	*P* value	Baseline	End of study	*P* value	P value
Skaer (1993)	MPR	NR	0.58±0.07	NR	NR	Packaging=0.71±0.09 Reminder=0.73±0.09 Both=0.87±0.08	NR	Packaging vs Control ≤0.05 Reminder vs Control ≤0.05 Both vs Control ≤0.05
Grant (2003)*	Self Report	6.9±0.4	0.1±0.4†	NR	6.7±0.9	0.1±1†	NR	0.8
Krass (2005)‡	Self Report MPR	50% 77%	48% 77%	0.70 NS	59% 70%	48% 67%	0.15 NS	0.008 NR
Odegard (2005)§	Self Report	35%	NR	NR	56%	NR	NR	0.003
Andrés Rodríguez (2007)‖	Self Report	0.8±1	0.9±1	0.195	0.6±0.9	0.2±0.5	<0.001	<0.001
Kalsekar (2007)¶	MPR	NR	0.88±0.13	NR	NR	0.90±0.13	NR	0.009
Phumipamorn (2008)**	Pill Count	87.2%±14.2	84.4%±13.7	0.29	81.8%±17.0	88.6%±11.9	0.005	0.004
Al Mazroui (2009)††	Self Report	49.1%	32.5%	<0.05	48.3%	21.4%	<0.05	0.06

MPR = Medication Possession Ratio (calculated from pharmacy refill information); NR = Not Reported; NS = Not Significant

*Number of days in the past week with no missed doses

†Reported as change from baseline to 3 months (number of days in the past week with no missed doses)

‡Proportion of patients with poor adherence

§Proportion of patients having difficulty remembering to take medications as prescribed

‖Mean number of failures in medication adherence

¶Control Group=Chain Pharmacies; Intervention Group=Independent Pharmacies

**Average number of doses taken

††Proportion of non-adherent patients

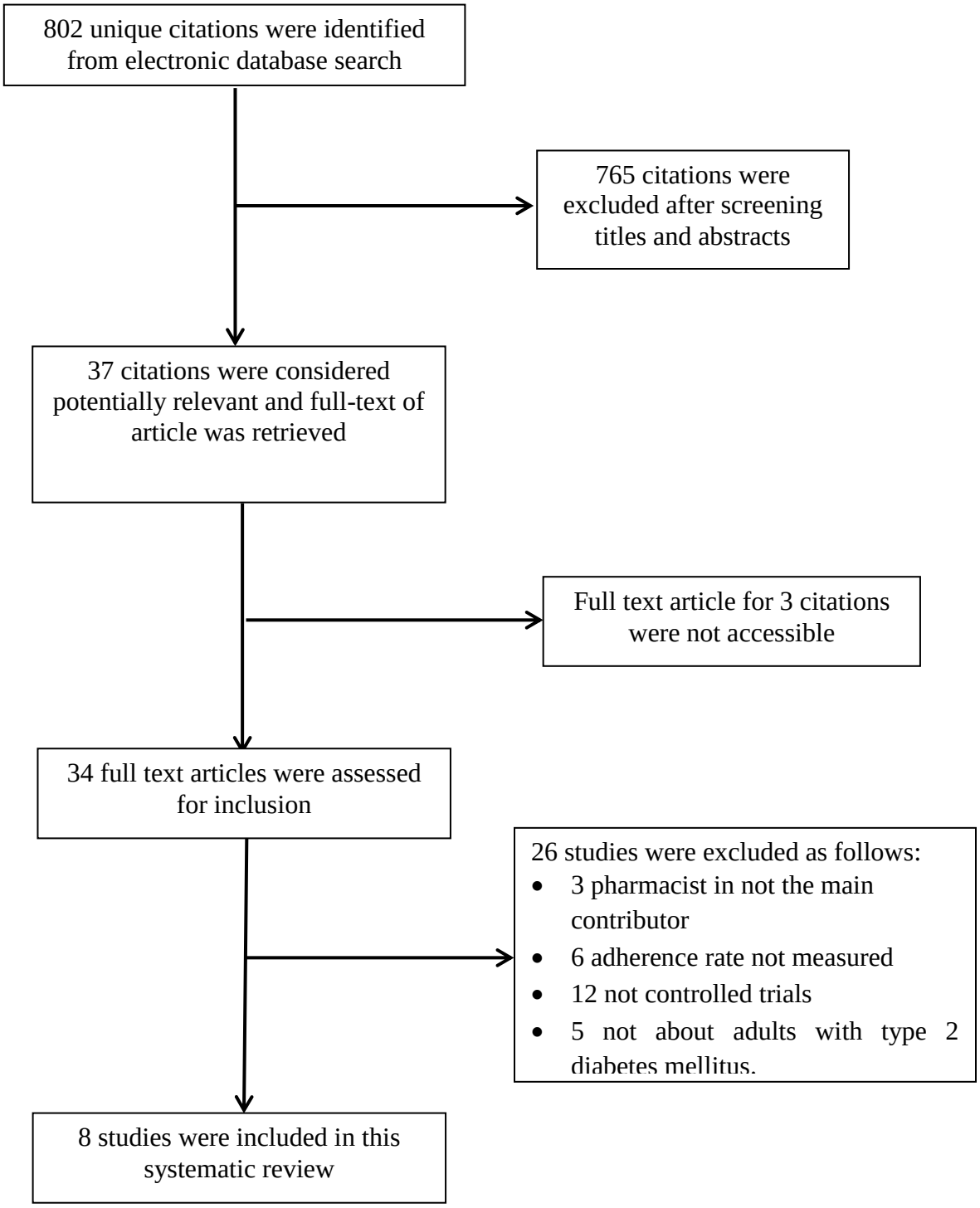
Table 2.4: Changes in Clinical Economic and Humanistic Outcomes

Lead Author (Year)	Clinical Outcomes				Economic Outcomes	Humanistic Outcomes
	Within-Group Change in A1c (p value)	Between-Groups Difference in A1c Change (p value)	Within-Group Change in Other Clinical Outcomes (p value)	Between-Groups Difference in Other Clinical Outcome Changes (p value)		
Skaer (1993)*	NR	NR	NR	NR	packaging group: 22.94 (NS) reminder group: 23.51 (NS) combination group: -67.67 (≤0.05)	NR
Grant (2003)	NR	NR	NR	NR	NR	NR
Krass (2005)	NR	NR	NR	NR	NR	NR
Odegard (2005)	C: NR (0.001) Int: -2.0% (0.001)	NR (0.61)	NR	NR	NR	NR
Andrés Rodríguez (2007)	C: 0.7% Int: -0.5%	NR (<0.001)	NR	NR	NR	NR
Kalsekar (2007)	NR	NR	NR	NR	NR	NR
Phumipamorn (2008)	C: -0.6% (0.006) Int: -0.8% (0.001)	NR (0.56)	Control / Intervention TC: -0.03 (0.86) / -0.82 (<0.001) LDL-C: 0.39 (0.14) / -0.24 (0.003) HDL-C: -018 (<0.001) / -0.25 (<0.001) TG: -0.8 (0.37) / -2.5 (0.016)	TC (<0.001) LDL-C (0.002) HDL-C (0.06) TG (0.23)	NR	NR

Al Mazroui (2009)†	C: -0.01% Int: -1.06%	NR (0.003)		Control	Intervention	NR	Bodily Pain (<0.001) General Health (<0.001) Mental Health (<0.001) Physical Functioning (<0.001) Role-Emotional (<0.001) Role-Physical (<0.001) Social Functioning (<0.001) Vitality (<0.001)
			FBG	-0.78	-3.05	FBG (<0.001)	
			SBP	-0.5	-4.2	SBP (<0.001)	
			DBP	0.2	-8.9	DBP (<0.001)	
			TC	0.05	-0.79	TC (<0.001)	
			LDL-C	0.13	-0.55	LDL-C (<0.001)	
			HDL-C	0.01	0.12	HDL-C (<0.01)	
			TG	0.19	-0.35	TG (<0.001)	

NR=Not Reported; NS=Not Significantly Different (as reported in original study); C=Control Group; Int=Intervention Group; BMI=Body Mass Index; LDL-C=Low Density Lipoprotein Cholesterol; HDL-C=High Density Lipoprotein Cholesterol; TG=Triglycerides
*Difference in total per capital expenditures relative to control group
†Short Form 36 used to collect patient self-reported quality of life (Humanistic Outcome)

Figure 2.1: PRISMA Citation Flow Diagram



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Chapter 3

Effect of Adding Pharmacists to Primary Care Teams on Medication Management and Adherence to Achieve Blood Pressure Control in Patients with Type 2 Diabetes[2]

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Running head: Pharmacist intervention improves medication management in hypertension

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Tables: 2
Figures: 2
References: 40

Trial Registry: ISRCTN97121854

Abstract

Aims: In a randomized trial, we previously demonstrated that addition of pharmacists to primary care teams significantly improved blood pressure control in 260 patients with type 2 diabetes; however, the mechanism for this improvement was unknown.

Methods: Secondary analysis of medication management data collected during a randomized controlled trial. The primary outcome was "treatment optimization", defined as the addition, dosage increase, or switching of an antihypertensive medication during the 1-year study period. A secondary outcome was change in adherence to antihypertensive medications using the medication possession ratio (MPR).

Results: The 200 evaluable trial patients had a mean age of 59 (SD 11) years, 44% were men and mean blood pressures were 130 (SD 16)/74 (SD 10) mm Hg at baseline. Treatment optimization occurred in 45 (42%) of 107 intervention group patients and 25 (27%) of 93 controls (RR=1.56 95% CI: 1.05-2.34). Addition of a new medication was the most common type of optimization, occurring in 35 (33%) intervention patients and 17 (18%) controls, p=0.020. Adherence to antihypertensive medications was high at baseline (MPR=93%). Although there was a small improvement in the intervention group (97%) and small decline in controls (92%), the difference between groups was not significant (p=0.24).

Conclusions: When pharmacists were added to primary care teams, improvement in blood pressure control is more likely achievable through optimization of antihypertensive medication management (largely through addition of new medications) rather than improvements in adherence.

3.1 Introduction

Over 9.5% of the global population has diabetes, with the majority (over 90%) having type 2 diabetes.[1] This chronic disease can significantly impact on the patient's quality of life because it can produce a wide range of complications affecting the eyes, kidneys, nerves, and heart. Indeed, adults with diabetes are seven times more likely to be hospitalized for heart failure or stroke compared to the general population,[2] and diabetes has recently become the sixth leading cause of mortality in Canada.[3]

Hypertension is one of the most common comorbidities in patients with type 2 diabetes,[4,5] and when it is left uncontrolled, will significantly increase the risk of cardiovascular disease and diabetes-related death.[6-8] Adequate management of type 2 diabetes requires a long term, comprehensive program that comprises a healthy diet, exercise, and optimal pharmacologic management to achieve good control of blood pressure as well as blood glucose and lipid levels.[9,10] These goals can be achieved with collaboration among health care professionals, including pharmacists.[11,12]

Despite well recognized pharmacological options, the proportion of diabetic patients achieving blood pressure targets has been as low as 12%,[13] and although recent data suggests some improvement, it is still less than ideal at 36%.[5] There are numerous barriers to optimal blood pressure control, which many have classified at the patient and provider levels.[14-16] For example, clinicians may be concerned about the risk of adverse effects or drug interactions, which may influence their willingness to intensify therapy despite uncontrolled blood pressure and awareness of clinical practice guideline recommendations.[17-19] At the patient level, poor adherence to prescribed medications could be a factor because of patient beliefs, worries about medication side effects, medication costs, and limited access to health services.[20,21]

With these issues in mind, pharmacists can play an important role in management of type 2 diabetes, especially when multiple risk factors are present. Pharmacists can communicate with health care professionals to help recognize possible areas of clinical inertia at the health care provider level and work with patients to recognize and manage patient-level barriers to medication adherence.[11,22-24] We previously reported that addition of pharmacists to primary care teams resulted in a significant and clinically important reduction in blood pressure in patients with type 2 diabetes.[25] Although several other studies have also demonstrated that pharmacists can improve blood pressure control in diabetes, the mechanisms for the benefit of these interventions remains unclear.[22,26] The purpose of this secondary analysis of our trial data was, therefore, to determine if the improvement in blood pressure was due to the pharmacists' recommendations to optimize antihypertensive medication management or to changes in patient medication adherence.

3.2 Methods

The trial proper [25] and longer-term results [27] have been previously reported in detail. In summary, the trial was conducted in five primary care clinics affiliated with the Edmonton Southside Primary Care Network in Edmonton, Canada. A total of 260 patients with type 2 diabetes were enrolled and randomly assigned to either control or intervention groups; with both groups followed for one year. Patients in the control group received usual care from primary care providers without any contribution from pharmacists. Licensed pharmacists, who were also Certified Diabetes Educators, were added to the primary care team and followed intervention group patients. Prior to study implementation, the pharmacists completed online courses that covered the current guideline recommendations for hypertension and diabetes management.[28,29] This training ensured consistency in the assessment and recommendations generated by study pharmacists.

The primary outcome in the main study was a 10% or greater reduction in systolic blood pressure after one year, which was considered a clinically important improvement in blood pressure control.[30] A total of 48 (37%) intervention group patients and 30 (23%) controls achieved the primary outcome (relative risk [RR] = 1.58, 95% confidence interval [CI] 1.07 to 2.32, p=0.019).[25]

3.2.1 Main Study Intervention

Patients randomly allocated to the intervention group met with a study pharmacist who measured their blood pressure, heart rate, height, and weight. The study pharmacists measured blood pressure by following the Canadian Hypertension Education Program recommendations [28] and using a BPTru® BPM-100 (VSM Med Tech, Coquitlam, BC) automated machine that recorded the average of five measurements with 1-minute intervals. After recording these measurements, the pharmacist conducted a complete medication review by asking patients to

identify all prescription, non-prescription, supplementary, and herbal medications they were currently taking. After evaluating the patient's current medications and blood pressure, pharmacists made recommendations that were consistent with the current clinical practice guidelines for blood pressure management [28,31,32]. Study pharmacists were not authorized to initiate or change ongoing therapy; therefore all recommendations were discussed with the patient's family physician, who made the final decision in medication changes. The pharmacist also worked with intervention patients to manage any barriers to optimal medication adherence, such as the use of reminders or a medication organizer. During the follow-up period, intervention patients were contacted in-person or by telephone to address any issues with medication management or adherence. The nature and frequency of these interim visits were at the discretion of the pharmacist, the patient, or the physician.[25]

3.2.2 Inclusion criteria for sub-study

Patients with type 2 diabetes who were regularly followed in the participating family medicine clinics were eligible to participate in the main study. All 260 patients enrolled in the main study eligible for this sub-study.[25] Evaluation of the medication optimization outcome required information from the patient's pharmacy dispensation records; therefore, we excluded patients if these records were not available. To evaluate medication adherence using a medication possession ratio (MPR), we required a minimum of two dispensation records for the same antihypertensive medication.[33] Therefore, we included patients in this assessment if they had ≥2 dispensation records for an antihypertensive medication and at least one of these dispensations fell within six months prior to enrolment in the main study or within the last six months of the study follow-up period (**Figure 3.1**).

3.2.3 Data collection

During recruitment into the main study, pharmacists identified all community pharmacies the patient used to fill prescriptions and obtained the patient's consent to contact these pharmacies. At the end of the one-year follow-up period, study pharmacists contacted these pharmacies to request dispensation records within the past 2 years for each patient. The date of dispensation, active ingredient, daily dose, and number of days supplied for each dispensation record of all antihypertensive medications were documented.

3.2.4 Optimization of antihypertensive medications

The first objective of this study was to examine the effect of pharmacist intervention on optimization of antihypertensive medications during the main study. The patient's dispensation records during the six-month period prior to study enrolment were reviewed to establish a baseline antihypertensive medication regimen. Any changes to the baseline regimen during the main study follow-up period were identified and categorized as an addition of a new antihypertensive medication, dosage increase to an existing antihypertensive medication, or switch between antihypertensive medications. The primary outcome for medication optimization was a composite binary outcome of any of these changes to the antihypertensive medication regimen. Individuals with more than one change to their antihypertensive medication (e.g., increase in dose and addition of a new antihypertensive medication) were only counted once for the primary outcome analysis. We also evaluated each component of the primary composite outcome separately.

3.2.5 Medication adherence

The second objective was to evaluate the effect of pharmacist intervention on adherence to antihypertensive medications. Medication adherence was measured using the MPR, which was calculated for each antihypertensive medication using the following formula: MPR = (total

number of days supplied/interval between first and last fill) × 100%.[33] The average MPR for all antihypertensive medications was then calculated for the six-month period prior to study enrolment and for the final six months of the main study follow-up period.

3.2.6 Statistical analysis

The unit of analysis for both objectives was the individual patient. To examine the first objective, we compared the proportions of patients in each group with at least one change to their antihypertensive medications. The χ^2 statistic was used to test for between-group differences and we calculated an unadjusted RR and 95% CI to measure the association between medication optimization and treatment group and to measure the association between medication optimization and achievement of the main study outcome (≥10% reduction in systolic blood pressure after 1 year). We only adjusted for patient-level characteristics that were significantly different between groups in this sub-study because these data were drawn from a randomized trial that achieved adequate balance in known (and presumably unknown) confounders.[25] The adjusted associates were similar in magnitude, direction, and statistical significance to the main observations; therefore, we will only report the latter associations. Similar analyses were conducted for each component of the primary outcome. In addition, we conducted a subgroup analysis of the primary outcome by restricting to patients with elevated blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg) at baseline because these patients were more likely to have changes to their antihypertensive medications. To examine the second objective, we used a paired t-test to examine the change in MPR from baseline to follow-up for intervention and control groups. A Student's t-test was used to test between-group differences in MPR. A p-value of <0.05 was considered statistically significant for all tests and all analyses were conducted with STATA 11.

3.3 Results

From 260 patients included in the main study, 60 patients were excluded because we were not able to retrieve their pharmacy dispensation records (Figure 3.2). A similar proportion of patients were excluded from both treatment groups and there were no significant differences in age, sex, or baseline blood pressure, between the 60 excluded patients and the 200 patients included in the sub-study ($p>0.05$ for all comparisons). We therefore assumed the unavailable data were missing completely at random and not related to any values in the dataset. Of the 200 patients with pharmacy dispensation records, 43 patients were never dispensed an antihypertensive medication and 6 patients had less than 2 dispensations for the same antihypertensive medication. All remaining 151 patients had at least one dispensation record during the baseline or follow-up periods and had sufficient information to calculate an MPR in the baseline or follow-up period (Figure 3.1).

3.3.1 Study Patient Characteristics

Baseline patient characteristics were similar between the 107 intervention patients and 93 controls included in this analysis with the exception of diabetes duration (Table 3.1). There were 87 (44%) men, mean (± SD) age 59.4 (11.2) years, mean diabetes duration 5.5 (6.5) years, mean blood pressure 129.5 ± 15.7/73.6 ± 10.4 mm Hg, and the average number of antihypertensive medications was 1.4 (±1.3). At baseline, 70 (65%) in the intervention group and 49 (53%) in the control group had an elevated blood pressure ($p=0.067$).

3.3.2 Optimization of antihypertensive medications

During the study period, 45 (42%) patients in the intervention group and 25 (27%) controls had at least one change to their antihypertensive medications (RR = 1.56, 95% CI: 1.05, 2.34, $p=0.025$) (Table 3.2). Addition of a new antihypertensive medication was the most common component of medication optimization. There were 35 (33%) patients in the intervention group

and 17 (18%) controls who had an addition to their antihypertensive medication regimen (RR = 1.79, 95% CI 1.08 to 2.98, p=0.020). Of the 60 patients with no antihypertensive medications at baseline, 11 of 29 intervention and 5 of 31 controls started new antihypertensive therapy (p=0.056). A total of 28 patients had a dosage increase and 10 patients had a switch in antihypertensive medications; however, there were no differences in the proportion of patients with these changes between groups (p>0.05 for both comparisons). Sixteen (15%) patients in the intervention group had a combination of two or more changes to their medication regimen compared to 8 (9%) controls (p=0.17). After restricting the analysis to the 119 patients who had elevated blood pressure at baseline, 34 (49%) of 70 intervention patients and 20 (41%) of 49 controls had one or more changes to their antihypertensive medications (p=0.40).

Patients who received changes to their antihypertensive regimen were more likely to achieve the main study outcome of a 10% or greater reduction in systolic blood pressure (RR = 1.65, 95% CI 1.13 to 2.41, p=0.010). The association between treatment optimization and reduction in blood pressure was only observed in the intervention group patients (RR = 2.07, 95% CI 1.25 to 3.42, p=0.0036) and not in the control group (RR = 1.09, 95% CI 0.55 to 2.15, p=0.81).

3.3.3 Medication adherence

All baseline characteristics were similar with the exception of diabetes duration between the 87 intervention patients and 64 controls who met the inclusion criteria for the medication adherence assessment. There were 63 (42%) men, mean age 61.1 (± 10.7) years, and mean blood pressure 130.6 ± 16.2/74.0 ± 10.7 mm Hg. The mean duration of diabetes was 4.8 (± 3.9) years for intervention patients and 7.5 (± 9.0) for controls (p=0.015). The mean number of refill intervals used to calculate an MPR for each antihypertensive medication was 2.4 (±1.6). Adherence to antihypertensive medications was high (93% ± 29%) and similar between groups at baseline (p=0.70). The mean MPR change was a 4% absolute increase in the intervention

group and 3% absolute decrease in controls; however, the difference between groups was not significant ($p=0.24$).

3.4 Discussion

We evaluated the effects of pharmacist intervention on medication optimization and adherence in 200 patients with type 2 diabetes enrolled in a randomized controlled trial, and found that adding pharmacists resulted in a significantly higher proportion of patients receiving one or more changes to their antihypertensive medication regimen. These changes were associated with a clinically important reduction in blood pressure. In contrast, adding pharmacists to a primary care team had very little impact on adherence to antihypertensive medications. These findings have important implications for pharmacy practice in primary care settings, particularly given expanding practice roles and the potential for prescriptive authority for pharmacists.

Observations from this sub-study are consistent with those reported by Heisler and colleagues who examined the effect of a clinical pharmacist outreach program for patients with type 2 diabetes and hypertension.[34] Although both studies observed a significantly higher proportion of intervention patients with antihypertensive medication changes compared to controls, Heisler and colleagues reported a much higher proportion of their patients having medication changes (70%) compared to our study (42%). There are two possible explanations for this higher proportion. First, Heisler and colleagues included patients with persistently poor blood pressure control and poor adherence. Second, pharmacists in the study by Heisler and colleagues were authorized to make changes to the blood pressure medications, while pharmacists in our study made recommendations to the prescribing physician. Collectively, these observations would suggest that pharmacists working within a primary care team can have a significant impact to optimize medication management of hypertension.

In contrast, the pharmacist intervention in our study did not seem to have a significant effect on adherence to antihypertensive medications. The high baseline adherence rate and small

changes in the intervention and control groups differed from prior studies that have examined the effect of pharmacist intervention on adherence rates in patients with diabetes.[23,35-37] Indeed, the systematic review by Cramer reported that only 64% of patients with diabetes achieved an MPR > 80% during a 12-month period.[38] There are three possible explanations for these differences. First, previous studies of pharmacist intervention on adherence rates in patients with diabetes have focused on adherence to oral antidiabetic medications rather than antihypertensive medications. There may be differences in the patient's ability to adhere to these different medication regimens.[38,39] Second, the high baseline adherence rate may have been due to volunteer bias, whereby motivated patients with good adherence to medications and other healthy lifestyle choices were more likely to participate in the study. This could have created a ceiling effect and limited our ability to detect differences between groups. Third, we assessed MPR over a six-month period, which reduced our ability to detect variations.

Previous reviews of antihypertensive management in patients with type 2 diabetes have suggested that 2-3 medications are often required to achieve adequate blood pressure control.[40] Although guidelines incorporated these observations into recommendations to consider combination therapy with at least 2 antihypertensive medications,[32] 64 (54%) of 119 patients with blood pressure levels above target were taking one or no antihypertensive medications at baseline. This highlights the need for ongoing evaluation of treatment regimens to achieve and maintain blood pressure targets. Indeed, intervention patients were more likely to have more than one change to their antihypertensive medication regimen compared to controls.

There are several limitations to our study that should be considered when interpreting the results. First, the number of patients with very high adherence rates included in this sub-study made it difficult to determine if addition of pharmacists to the primary care teams could impact

medication adherence. Based on the observed differences in adherence rates at the end of the follow-up period, we estimate that a future study would require 400 patients in each group to have sufficient power to detect a significant difference. Second, we measured changes in medication optimization based on dispensation records alone, which could underestimate the true impact of the intervention. Information in the medical chart could have provided more accurate information regarding medication changes if, for example, the patient was instructed to adjust the dose of an existing supply of medications (take two 5 mg tablets to achieve a 10 mg dose) before obtaining a supply at the new, higher dose. Third, communication between study pharmacists and the patients' family physicians was not recorded. Therefore, we can only infer that the observed medication changes for the intervention patients were influenced by pharmacist recommendations. Last, this sub-study shares the same limitations of the main study, the most important being the potential for contamination because intervention and control patients were recruited from the same primary care teams. As this last limitation would bias to the null, it suggests again we may have underestimated the benefit of the pharmacists.

3.5 Conclusion

We showed that the significant and clinically important reduction in blood pressure observed in a randomized controlled trial was likely due to pharmacist interventions to optimize antihypertensive medication management rather than interventions to improve adherence. These findings support the hypothesis that pharmacists can play an important role in improving antihypertensive medication management in patients with type 2 diabetes.

Table 3.1: Baseline Characteristics

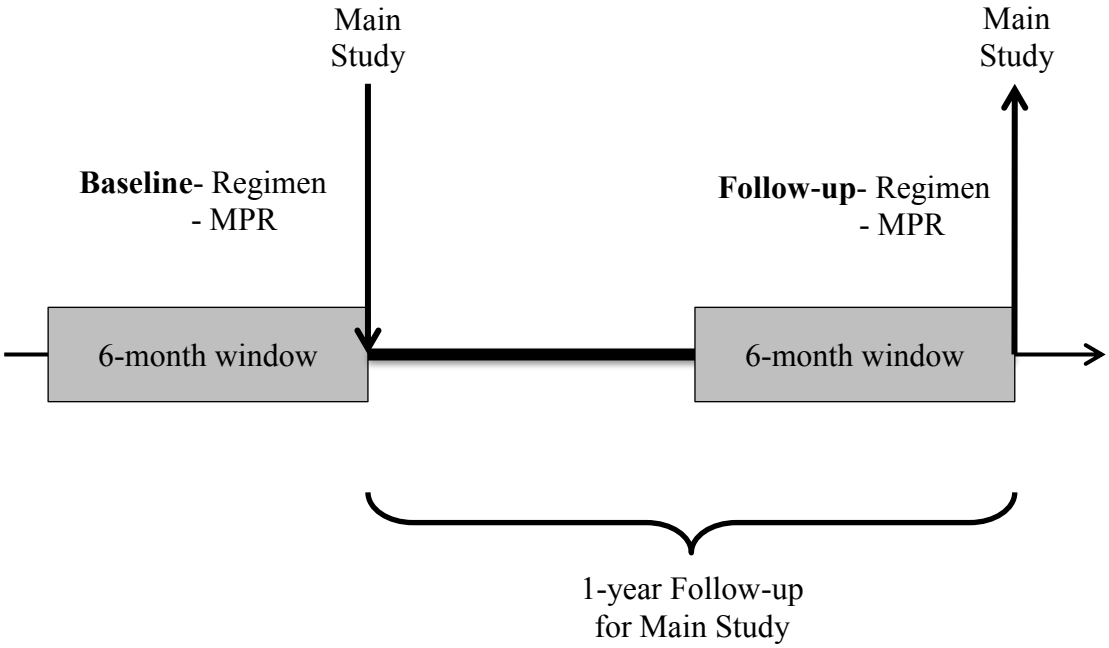
	Intervention	Control	p-value
Number of patients	107	93	
Men, n (%)	46 (43)	41 (44)	0.88
Age, years (SD)	59 (11)	60 (12)	0.40
Diabetes duration, years (SD)	5 (4)	7 (8)	0.029
Systolic blood pressure, mm Hg (SD)	131 (15)	128 (16)	0.20
Diastolic blood pressure, mm Hg (SD)	75 (10)	72 (11)	0.16
Blood Pressure ≥130/80 mm Hg, n (%)	70 (65)	49 (53%)	0.067
Current smokers, n (%)	7 (7)	9 (10)	0.41
Vascular disease, n (%)	23 (22)	20 (22)	0.99
Blood pressure medications, n (%):			0.46
None	29(27)	31 (33)	
1	34(32)	24 (26)	
2	18(17)	21 (23)	
3	21(20)	11 (12)	
≥4	5(5)	6 (6)	

Table 3.2: Antihypertensive Medication Changes

	Intervention*	Control*	RR (95% CI)
Any antihypertensive treatment optimization	45 (73)	25 (37)	1.56 (1.05-2.34)
Addition of a new antihypertensive medication	35 (43)	17 (25)	1.79 (1.08-2.98)
Antihypertensive medication dose increase	18 (23)	10 (10)	1.56 (0.76-3.22)
Switch antihypertensive medications	6 (7)	4 (4)	1.30 (0.38-4.48)

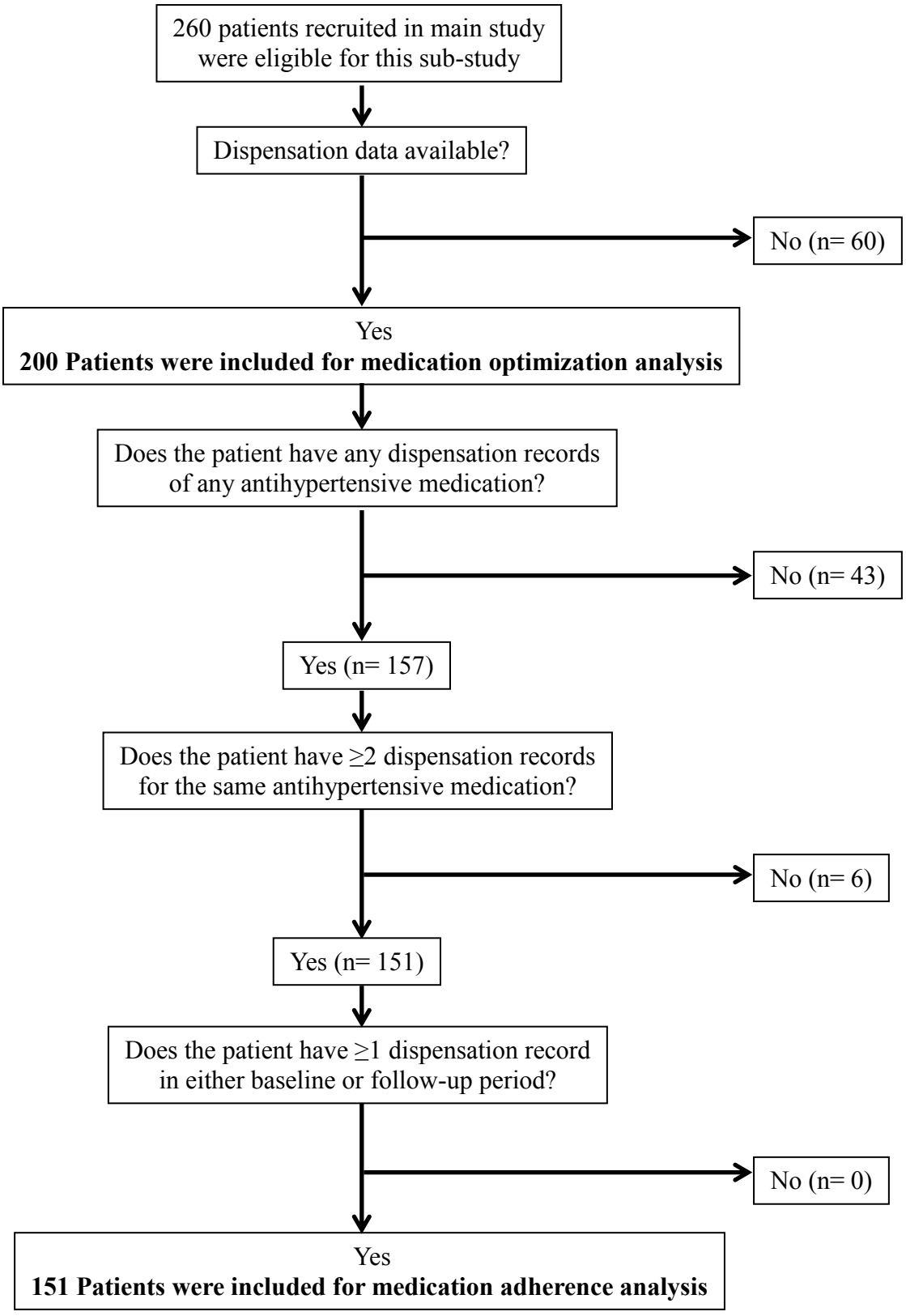
*Data are reported as number of patients (number of events)

Figure 3.1: Main Study Timeline and Observation Windows for Sub-study



Regimen: Antihypertensive medication regimen
MPR: Medication possession ratio

Figure 3.2: Patient Flowchart



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Chapter 4

General Discussion and Conclusions

4.1 General discussion

Optimal management of type 2 diabetes requires a collaborative, team-based approach.[1] Although pharmacists are well-trained to help optimize medication management, their role on these collaborative care teams has not been well-defined. It is therefore important to determine not only the effect of adding pharmacists to these teams, but also identify the mechanisms that helped create the observed benefits. In this thesis, two specific questions were addressed using different methodologies (a systematic review of the literature and a cohort study using trial data) to better understand how pharmacists can successfully help manage patients with diabetes. Observations from both of these studies will help define the role of pharmacists in collaborative teams and help shape the interventions of future pharmacist-based intervention programs.

4.1.1 Systematic Review of Pharmacist Intervention in Oral Antidiabetic Medication Adherence

The first study was a systematic review that evaluated pharmacist interventions to improve adherence to oral antidiabetic medications in patients with type 2 diabetes. We summarized the results of six randomized controlled trials and two controlled trials that measured improvement in medication adherence in patients with type 2 diabetes. We used a classification system developed by Roter and colleagues [2] to identify strategies within the pharmacist's intervention (educational, behavioural, affective, or provider-targeted) as well as the delivery method. We found that education-related strategies, such as improving the patient's knowledge of their medications and improving awareness of diabetes and the risk of complications, was the most frequently used strategy. In addition, most interventions used a combination of 2 or more

strategies to help improve adherence to oral antidiabetic medications. Although 5 of the 8 included studies reported significant improvements in adherence rates, there was insufficient information to examine the effect of pharmacist intervention on other outcomes, such as blood glucose levels. Based on these observations, we concluded that pharmacist interventions can improve adherence to antidiabetic medications and that these interventions should be a combination of educational strategies and other strategies.

Our observations from the systematic review are consistent with observations by Morgado and colleagues,[3] who assessed the effect of pharmacist interventions on medication adherence and blood pressure control in patients with hypertension. Morgado and colleagues also identified that pharmacist interventions were often multifactorial, with patient education being the most common strategy included in 14 (88%) of the 16 interventions. In addition 9 (56%) of 16 interventions included educational strategies aimed at the health care providers.[3] Similar to our systematic review, Morgado and colleagues observed a positive impact of pharmacist intervention on medication adherence. In addition, Morgado and colleagues were also able to determine that these interventions led to significant improvements in blood pressure control.

Collectively, observations from our systematic review as well as the systematic review by Morgado and colleagues[3] provide information on how pharmacists can improve medication adherence. We believe pharmacists can have a significant impact on medication adherence and that these improvements can come mainly through educational-based interventions that are combined with other strategies.

4.1.2 Cohort Study of Factors Influencing an Observed Improvement in Blood Pressure

The second study was a retrospective cohort analysis that used clinical trial data to determine how an observed improvement in blood pressure occurred. Data for this study were collected during a randomized controlled trial that showed addition of pharmacists to a primary

care team resulted in a significant and clinically important reduction in blood pressure in patients with type 2 diabetes.[4] The aim of this sub-study was to determine if the improvement in blood pressure was due to the pharmacists' recommendations to optimize antihypertensive medication management, to help improve patient medication adherence, or both interventions. We defined optimization of antihypertensive medication management as an addition, increase in dose, or switching of antihypertensive medications to the patient's baseline regimen. Significantly more patients in the pharmacist intervention group had one or more of these events compared to controls. In contrast, medication adherence, measured as the medication possession ratio (MPR), was already high at baseline in both groups (mean 93%) and we were unable to detect any significant differences in MPR changes. Based on these observations, we concluded that the improvement in blood pressure observed in the main trial is likely due to pharmacist interventions to optimize antihypertensive medication management rather than improvement in medication adherence.

Our findings are consistent with those of Heisler and colleagues[5] who conducted a cluster randomized trial to evaluate the effect of a clinical pharmacist outreach program on type 2 diabetic patients with poorly controlled blood pressure. In this study, patients who received the pharmacist-led intervention program had more changes in their antihypertensive medications compared to patients in the control group. Interestingly, the proportion of intervention patients with a change to their antihypertensive medications was much higher (70%) than what we observed in our study (42%). We believe there are two possible explanations for this difference. First, Heisler and colleagues included patients with persistently poor blood pressure control and poor adherence, whereas our study did not restrict enrolment based on blood pressure or adherence rate. Second, pharmacists in the study by Heisler and colleagues were authorized to

make changes to blood pressure medications, while pharmacists in our study made recommendations to the prescribing physician. It is therefore possible that pharmacists with additional prescribing authorization could have a larger impact on blood pressure reduction, as Wubben and Vivan observed with pharmacist interventions to improve blood glucose control.[6]

With regards to pharmacist intervention to improve adherence to antihypertensive medications, Heisler and colleagues [5] did not report the changes in medication adherence. However, the systematic review by Morgado and colleagues [3] reported that 7 (44%) of 16 interventions significantly improved adherence rates in the intervention group compared to controls. More importantly, all studies reporting improvements in adherence rate also reported significant reductions in blood pressure for intervention group patients compared to controls.

Collectively, these observations suggest that improvements in both medication adherence and medication optimization are important to achieve optimal control of blood pressure.[7,8] We believe this information provides additional insight into the role pharmacists can play on a collaborative care team.

4.2 Implications and Future Directions

4.2.1 for clinical practice:

A core element of the pharmacist's expertise is knowing how to optimize medication management. Pharmacists are trained to conduct medication reviews, identify potential drug-drug interactions, and recognize possible opportunities to optimize therapy in order to achieve desired health outcomes. Observations from these two studies suggest that pharmacists, working in collaboration with other health care professionals, can optimize medication management and improve medication adherence. In addition, interventions aimed at improving medication adherence should incorporate a combination of educational strategies and other strategies, such as behavioural changes (e.g., using medication organizers), affective strategies (e.g., provide

ongoing, proactive contact with the patient), and provider-targeted strategies (e.g., improved communication between pharmacists and physicians). Diabetes and coexisting hypertension are very prevalent, chronic conditions in Canada and worldwide.[9,10] Current management patterns suggest there is substantial opportunities to improve management of these conditions.[10] Therefore, we believe our findings can have important contributions to help engage pharmacists in collaborative care teams, which in turn will achieve better management for patients with type 2 diabetes.

4.2.2 for research:

Our studies have identified important gaps in understanding the effect pharmacists can have in patient management. First, our systematic review revealed a substantial deficiency in evidence to support the hypothesis that pharmacist interventions to improve medication adherence in patients with type 2 diabetes will have a positive effect on clinical outcomes (e.g., blood glucose control) or other health outcomes (e.g., risk of hospitalization or onset of diabetes-related complications like neuropathy or nephropathy). Second, although we identified that almost all interventions incorporated a combination of educational strategies and other strategies, is still not clear what combination of strategies would be most effective in improving medication adherence in patients with type 2 diabetes. Third, the question of economic impact, such as the cost-effectiveness of adding pharmacists to primary care teams – compared to other interventional strategies – remains uncertain. We believe, therefore, more trials are needed to elaborate on the role of pharmacists in optimizing medication adherence and medication management in patients with diabetes. More importantly, these studies should have a broader perspective of assessing the effects of these interventions on long term blood glucose control and risk of diabetes-related complications, such as nephropathy and diabetes-related hospitalizations.

4.3 Conclusion

This thesis examined the elements of pharmacist interventions on medication management and adherence in patients with type 2 diabetes. Our findings from two different methodologies, a systematic review and a cohort study, suggest that pharmacists can be effective additions to a collaborative care team by providing education-based interventions to improve adherence and helping optimize medication management of patients with type 2 diabetes.

4.4 References

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