IMPACT OF COMMUNITY PHARMACIST INTERVENTIONS TO MANAGE MEDICATION ADHERENCE

THESIS

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CERTIFICATE OF ORIGINAL AUTHORSHIP

I, Andrea Johanna Torres Robles declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Discipline of Pharmacy, in the Graduate School of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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Abstract

Background: As medication non-adherence continues to be a global public health problem, the development, evaluation and implementation of interventions to address this prevalent problem represent a key priority. Community pharmacists' role is evolving from the dispensing of medications to the provision of professional services aiming at improving patient outcomes. Pharmacists have, therefore, the potential to deliver interventions to manage medication adherence. Nonetheless, there is still a lack of evidence on the effect of community pharmacist-led interventions on medication adherence and clinical outcomes.

Objectives: To explore and evaluate the impact of medication adherence interventions undertaken by community pharmacists across different chronic diseases. This research aims to provide evidence on the efficacy and effectiveness of community pharmacist-led interventions in Australia and Spain on medication adherence to interventions and disease-specific outcomes.

Methods: Multiple methods were applied in this research. Chapter 2 presents a systematic review and network meta-analysis, following the PRISMA guidelines, comparing long term interventions on the impact on medication adherence across different chronic diseases. Chapter 3 describes a retrospective observational study evaluating the impact of a real-life practice intervention in Australia provided by community pharmacist to patients with chronic medications (rosuvastatin, desvenlafaxine, irbesartan). Chapter 4 present a cRCT to evaluate the impact of a medication adherence management service in a community pharmacy setting in Spain. Chapter 5 describes a sub-analysis of the cRCT including patients with asthma and COPD being prescribed inhaled medications. A multilevel regression model was used to measure the impact of the medication adherence management service on medication adherence and disease-specific clinical outcomes (Chapter 4) and inhaler technique (Chapter 5). Chapter 6 presents an effectiveness-implementation hybrid design evaluating the clinical impact of the medication adherence management service when translated to routine practice during an implementation study. For this

analysis, patients were classified in three groups: A) those allocated to the intervention group during the cRCT and continue during implementation, B) those allocated to the control group during the CRCT and continue during implementation, and C) new patients in the implementation study.

Results: Chapter 3 presents the impact of a real-life community pharmacist-led intervention in Australia. De-identified data of 2,530,562 patients and 3,328 Australian community pharmacies from 2014 to 2017 were contained in the database. A total of 1,805 pharmacies and 20,335 patients who met the inclusion criteria were included in the analysis, with an average age of 67 (SD: 11.76). Three months after the intervention was provided, there was an increase from 50.2% (SD: 30.1) to 66.9% (SD: 29.9) for rosuvastatin, from 50.8% (SD: 30.3) to 68% (SD: 29.3) for irbesartan and from 47.3% (SD: 28.4) to 66.3% (SD: 27.3) for desvenlafaxine, in adherence rates. Rates decreased over 12 months to 62.1% (SD: 32.0) (rosuvastatin), 62.4% (SD: 32.5) (irbesartan) and 58.1% (SD: 31.1) (desvenlafaxine).

The results of the cRCT are highlighted in Chapter 4. Patients (n=1,186) were recruited from 98 pharmacies and 87.5% (n=1,038) completed the six-month study. Compared to control patients, patients receiving the intervention had an Odds Ratio (OR) of 5.12 of being adherent at the end of the study. ORs for hypertension control, asthma control and COPD low clinical impact were 1.22 (95% CI: 0.78-1.91), 1.88 (95% CI: 1.05-3.36) and 2.01 (95% CI: 1.07-3.75), respectively, favouring the intervention group. For patients using inhaled medications (i.e. sub-analysis of patients suffering from asthma or COPD in the cRCT), the odds of improvement of patients with correct inhaler technique were 4.57 favouring the intervention group. The impact of the medication adherence management service resulted on an improvement on clinical outcomes (e.g. medication adherence and disease-specific outcomes) for all patients during the implementation study (i.e. routine-practice), with greater improvements observed on those patients who have not been exposed to the intervention before (groups B and C).

Conclusion: Community pharmacist-led interventions lead to an improvement in medication adherence and disease-specific clinical outcomes. A real-life intervention

in Australia resulted in the improvement of adherence after providing the intervention with an eventual decline on adherence rates post-intervention, highligthling the importance of continuous follow-up. To improve the effectiveness of this intervention, factors such as follow-up, fidelity measures and addition of other components to the intervention should be considered. These factors were considered when developing a medication adherence management service in Spain. This intervention resulted in the improvement of medication adherence and disease-specific outcomes under the cRCT (controlled environment) and the implementation study (real practice). The intervention also improved inhaler technique on patients suffering from asthma and COPD and contained multiple components (e.g. educational, attitudinal, technical), which have been found effective at improving medication adherence. The essential role that community pharmacists have in the management of medication adherence should be considered in the development of future interventions.

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Dissemination of Research

Peer-reviewed Publications

1. **Torres-Robles A**, Wiecek E, Tonin FS, Benrimoj SI, Fernandez-Llimos F, Garcia-Cardenas V. 'Comparison of Interventions to Improve Long-Term Medication Adherence Across Different Clinical Conditions: A Systematic Review With Network Meta-Analysis'. *Frontiers in pharmacology*. 2018;9:1454.
2. **Torres-Robles A**, Wiecek E, Cutler R, Drake B, Benrimoj SI, Fernandez-Llimos F, et al. 'Using Dispensing Data to Evaluate Adherence Implementation Rates in Community Pharmacy'. *Frontiers in pharmacology*. 2019;10:130.
3. **Torres-Robles A**, Benrimoj SI, Gastelurrutia MA, Martinez-Martinez F, Peiro T, Varas-Doval R, Perez-Escamilla B, Rogers K, Valverde-Merino MI, Garcia-Cardenas V. 'Effectiveness of a medication adherence management service in a community pharmacy setting. A cluster randomised controlled trial'. *BMJ Quality and Safety.* 2021 **(Accepted –Sent to production)**
4. **Torres-Robles A**, Benrimoj SI, Bosnic-Anticevich S, Gastelurrutia MA, Martinez-Martinez F, Peiro T, Varas-Doval R, Perez-Escamilla B, Rogers K, Valverde-Merino MI, Garcia-Cardenas V. 'Evaluation of a community pharmacist-led medication adherence management service on inhaler technique in patients with asthma and COPD: sub-analysis of a cluster randomised controlled trial'. 2021 **(To be submitted to "Journal of asthma")**
5. **Torres-Robles A**, Benrimoj SI, Gastelurrutia MA, Martinez-Martinez F, Peiro T, Varas-Doval R, Perez-Escamilla B, Valverde-Merino MI, Zarzuelo MJ, Garcia-Cardenas V. 'Evaluation of the impact of a medication adherence management service on a community pharmacy setting during an effectiveness-implementation hybrid design'. 2021 **(To be submitted to "Journal of Health Services Research")**

Conference proceedings

1. **Torres-Robles A**, Perez-Escamilla B, Valverde Merino M, Varas R, Peiro T, Martinez Martinez F, Benrimoj SI, Garcia-Cardenas V. A brief complex intervention to improve patients' beliefs and skills on inhaler use and its impact on clinical outcomes in COPD and asthma. European Society for Patient Adherence, Compliance and Persistence Conference, Portugal, 2019. (Oral presentation).
2. **Torres-Robles A**, Wiecek E, Drake B, Benrimoj SI, Fernandez-Llimos F, Garcia-Cardenas V. Big data techniques for measuring changes on medication implementation after an intervention provided by community pharmacists. European Society for Patient Adherence, Compliance and Persistence Conference, Ireland, 2018. (Oral presentation).
3. Tonin FS, Wiecek E, **Torres-Robles A**, Benrimoj SI, Fernandez-Llimos F, Garcia-Cardenas V. Impact of single and multiple component interventions to improve medication adherence: a network meta-analysis. European Society for Patient Adherence, Compliance and Persistence Conference, Ireland, 2018. (Oral presentation - Presented as second author).
4. **Torres-Robles A**, Benrimoj SI, Fernández-Llimós F, Tonin FS, Wiecek E, García Cárdenas V. [Comparisson of adherence interventions across disease states: A network meta-analysis]. II International Simpodader, Spain, 2018. (Poster presentation).
5. **Torres-Robles A**, Drake B, Benrimoj SI, Garcia-Cardenas V. Use of de-identified medication dispensing records to measure the effect of pharmacist intervention on medication adherence in a community pharmacy setting – 3 Minute Thesis Presentation. 1st International Conference Pharmacy Practice Research FIP, Portugal, 2018.

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Preface

This thesis is presented in fulfilment of the doctoral degree (Doctor of Philosophy) requirements of the University of Technology Sydney, Australia.

The thesis is structured as a PhD by compilation. Seven chapters are presented throughout the thesis, including copies of peer-reviewed publications as chapters of the manuscript. Spelling varies between US English and British English to meet journal requirements for manuscript submission. Andrea J Torres Robles is the primary author of each publication. Co-authors contributed to the conception, design of the work, data collection, data analysis, interpretation or critical revision of the manuscripts.

Chapter 1 includes the research overview, an overall rationale and the organisation and objectives of the thesis. Chapter 2 covers the contextual background of medication adherence interventions, including a systematic review and meta-analysis, highlighting the gaps and opportunities in practice.

Chapter 3 – 6 present evidence of the impact of community pharmacist-led interventions on medication adherence, addressing the specific objectives. Chapter 3 presents a retrospective analysis of the impact of a real-life intervention provided by community pharmacists in Australia. Chapter 4 describes a cRCT to evaluate the impact of a community pharmacist-led medication adherence management service in Spain, on medication adherence and disease-specific outcomes. Chapter 5 presents the impact of the intervention described in the cRCT on inhaler technique performance for patients with asthma and COPD. Chapter 6 presents the clinical effectiveness of the medication adherence management service during its implementation in routine-practice settings. Chapter 7 discusses the overall research, reflects on the strengths and limitations of the research work and provides recommendations for future research.

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Abbreviations

ACQ	Asthma Control Questionnaire
ATC	Anatomical Therapeutical Chemical
BPL	Blood pressure Levels
CCQ	Clinical COPD Questionnaire
CFIR	Consolidate Framework for Implementation Research
CGOF	General Pharmaceutical Concil of Spain
CI	Confidence Intervals
CMG	Continuous measure of Medication Gaps
COF	Pharmacy Official Body (In Spain)
COPD	Chronic Obstructive Pulmonary Disease
cRCT	Cluster randomised controlled trial
DBP	Diastolic Blood Pressure
FISpH	Framework for the Implementation of Services in Pharmacy
MA	Medication Adherence
MPR	Medication Possession Ratio
NMA	Network Meta-Analysis
PCF	Practice Change Facilitators
PDC	Proportion of Days Covered

SBP	Systolic Blood Pressure
SD	Standard Deviation
WHO	World Health Organization

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Chapter 1

Synopsis

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Research Overview

The research outlined in this thesis was driven by the collaboration between researchers, pharmaceutical professional organisations and practitioners across national and international institutions. The thesis is organised by compilation, and there are papers describing the different pieces of research undertaken. The use of network meta-analysis techniques for the analysis of long-term medication adherence interventions across clinical conditions was the result of a collaboration with researchers from the University of Lisbon (Portugal) and the Federal University of Parana (Brazil). The work conducted in Australia in collaboration with The Pharmacy Guild of Australia resulted in a retrospective analysis of dispensing data to evaluate the effect of their real-life adherence intervention. Finally, the development, evaluation and implementation of a community pharmacist-led intervention to manage medication adherence was part of a collaboration with researchers from the University of Granada (Spain), The Spanish Council of Colleges of Pharmacy and CINFA laboratories.

This thesis presents a series of studies and research designs to address the impact of medication adherence interventions on patient's outcomes. The first chapter provides an overview of the dissertation, followed by Chapter 2 presenting the background information, including a peer-reviewed version of a systematic review and network meta-analysis of adherence interventions. Chapters 3 to 6 present the main body of the research, addressing the specific objectives of this thesis. Chapter 3 includes the peer-reviewed version of the research paper. Chapters 4 to 6 are structured as research articles.

- Chapter 3 includes a retrospective analysis of dispensing data to evaluate the effectiveness of a real-life educational-based intervention on adherence rates in community pharmacies in Australia.
- Chapter 4 describes a cluster randomised controlled trial to evaluate the effectiveness of a pharmacist-led medication adherence management service

(intervention) delivered in a community pharmacy setting in terms of medication adherence and clinical outcomes.

- Chapter 5 describes a sub-analysis of patients recruited for the cluster randomised controlled trial. Results report the impact of the pharmacist-led medication management service on inhaler technique in patients with asthma and COPD.
- Chapter 6 presents an implementation-effectiveness study to analyse the clinical effectiveness of a pharmacist-led medication adherence management service once integrated into practice.

Finally, chapter 7 addresses the implications of the research, future directions and the impact of the results for practise and research (Figure 1).

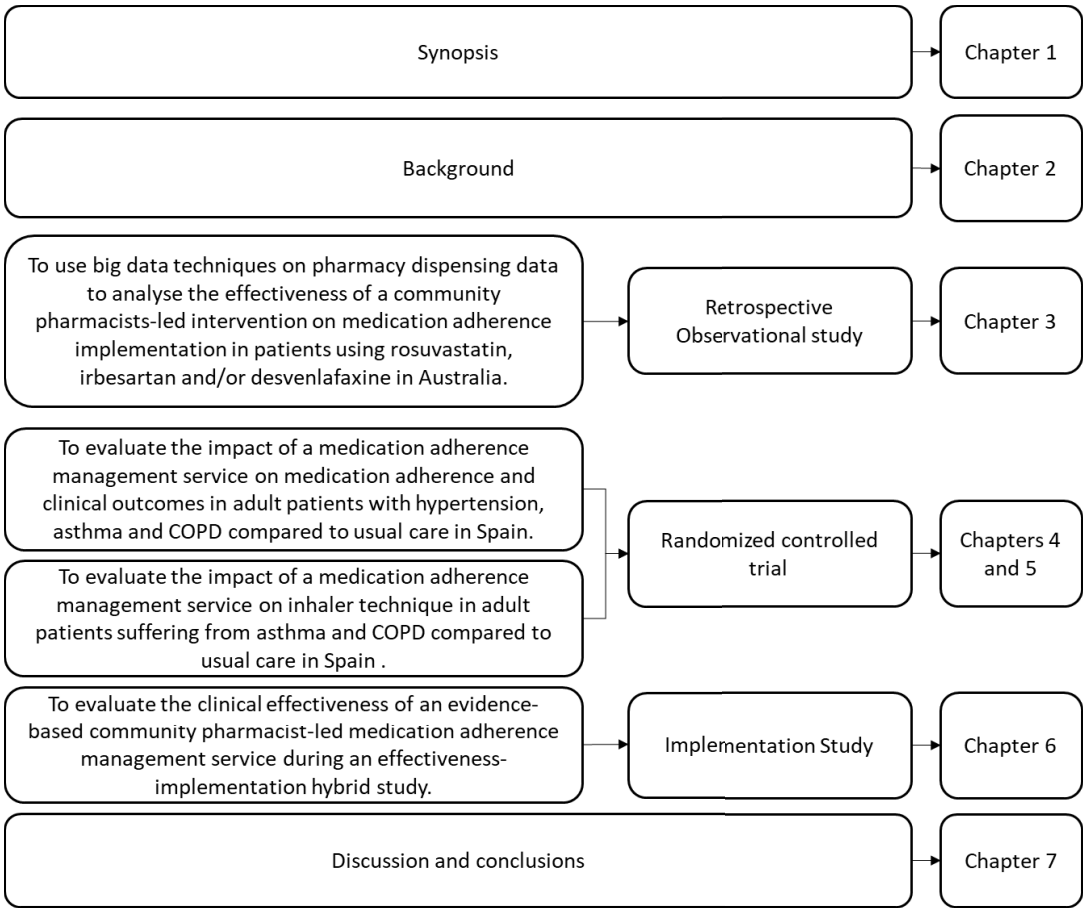

Figure 1. Thesis Structure

Rationale

Medicines are the main treatment to cure, control and/or prevent complications of chronic diseases. Nonetheless, patients fail to adhere to their medications due to multiple reasons. Determinants of non-adherence are often distributed across five dimensions (i.e. socio-economic, patient-related, healthcare system, condition-related, therapy-related) (Sabate 2003). Medication non-adherence continues to be a global burden for the healthcare system with serious and critical clinical and economic implications (Franklin, Abel & Shojania 2020).

A variety of multifaceted interventions to improve adherence has been proposed and evaluated in different settings. However, a Cochrane systematic review found inconsistency of the effect of interventions across studies (Nieuwlaat et al. 2014). One of the reasons for the dearth of evidence on the efficacy and effectiveness of medication adherence interventions is the heterogeneity of interventions. Differences in settings, patients' characteristics, adherence measures or components of the intervention are some examples of this (Nieuwlaat et al. 2014). The use of meta-analytical methods such as network meta-analysis allows making direct and indirect comparisons between drug treatments and health interventions when there is a common comparator available (Tonin et al. 2017). The application of this method for the analysis of different adherence interventions across clinical conditions may provide a broader insight of their effect size and overcome the heterogeneity barrier frequently described in the literature (Tonin et al. 2019; Wiecek et al. 2019). The results of this analysis may assist researchers in developing potential interventions that can be tested and implemented in routine practice.

Among other healthcare providers, community pharmacists have the potential to improve medication adherence management due to their expertise on the use of medications and management of chronic conditions and frequent interaction with patients. As patients regularly access a pharmacy to have their prescriptions filled, pharmacists become an important point of care, providing education and monitoring the quality use of medicines (Tsuyuki et al. 2018). However, more evidence is needed

regarding the efficacy of community pharmacists' interventions at improving medication adherence and clinical outcomes, which would support their future implementation into routine practice. In real practice, it may be difficult to evaluate the impact of interventions due to the characteristics of the settings where adherence interventions are implemented (Zullig et al. 2018); therefore, the benefits of the intervention are unknown. It is fundamental to monitor the impact of interventions when implemented in real-world settings. (Zullig et al. 2019).

In Australia, one of the leading organisations representing almost 5,000 community pharmacies is the Pharmacy Guild of Australia. Through GuildLink, they offer a range of resources and software solutions to support the provision of services in community pharmacies. An example is the MedScreen Compliance program, focused on the provision of an educational-based intervention aiming at improving medication adherence to prescribed medications in identified non-adherent patients. Although the program gathers patient and dispensing data on a regular basis, there is limited evidence on the impact of the intervention on patient's adherence rates. Retrospective analysis of the data may provide an insight into the effectiveness of a real-life intervention in Australian community pharmacies to improve medication adherence.

A Cochrane review of adherence interventions concluded that most interventions evaluated up to date are not very practical and are difficult to implement on usual practice (Nieuwlaat et al. 2014). The review also highlighted important limitations when designing or analysing the impact of adherence interventions. These limitations included the low statistical power due to small sample size, complexity and variability of interventions making them difficult to implement in routine practice, and the lack of assessment of clinical outcomes (Nieuwlaat et al. 2014). Similarly, the need for research on interventions that impact on adherence and clinical outcomes has been highlighted (Milosavljevic, Aspden & Harrison 2018). Consequently, there is a necessity to develop adherence management interventions based on previous evidence and literature recommendations. Their impact on both, medication adherence and disease-specific outcomes should be evaluated, using

research designs that provide a high level of evidence (i.e. randomised controlled trial).

As a starting point when researching on medication adherence interventions, it would be useful to include diseases such as COPD, asthma or hypertension in the design and evaluation of interventions. These diseases usually place a significant burden on the healthcare system, with a global prevalence of 1-18% for asthma (GINA 2020) and 11.7% for COPD (GOLD 2020). Similarly, hypertension is a prevalent chronic condition representing a major risk for cardiovascular and kidney diseases and accounting for 10.4 million deaths per year (Unger et al. 2020). Adherence rates reported in the literature for all the above conditions are variable, ranging from 20 to 80% (Blaschke et al. 2012; Mueller et al. 2017; Wu et al. 2015). Patients suffering from these conditions not only have multiple medications but constitute a high-risk age group that, linked to physical and cognitive limitations, would derive benefit from interventions aimed at improving the use of their medications. For respiratory conditions (e.g. Asthma and COPD), inhaled medication constitutes the main management therapy. This requires patients not only to adhere to their medicines but also to acquire the knowledge and skills to use inhalers correctly. As the inhaler technique is specific to the device, it is pivotal to consider the specific checklists when training in the use of inhalers (Bosnic-Anticevich 2018). The development of interventions to improve medication adherence in these groups of patients should include the assessment of inhaler technique as part of the adherence evaluation.

Interventions that have been proven to be effective in a controlled research environment are not always successfully translated into real practice. Previous literature has found that evidence-based interventions take a long time to reach implementation or are never implemented (Balas & Boren 2000; Kellam & Langevin 2003). One of the main reasons behind this so-called “science to practice” gap until recently has been the lack of implementation programs to guide the implementation effort (Garcia-Cardenas et al. 2017). Implementation science emerged to address this lack of translation, proposing methods to promote the uptake of research findings into routine practice so they can be utilised to improve the quality of patient care

(Eccles & Mittman 2006). To date, there is not enough evidence regarding the effectiveness of medication adherence interventions during an implementation study design, and it cannot be assumed that the benefits obtained during the clinical trial are maintained during the real-world trial (Zullig et al. 2018). Therefore, research on this field would provide insight into the further design and improvement of pharmacy services.

Adherence management is considered as one of the six professional services with national priority according to a consensus among National Spanish professional pharmacy organisations (Sexto 2016). Therefore, the development of interventions to target medication non-adherence in Spain is pivotal to target national priorities and improve patient care.

As medication non-adherence continues to have a significant negative global impact, there are still areas of research which require further investigation:

1. *What is the impact of pharmacist-led interventions to manage medication adherence on patients suffering from chronic diseases in real world and controlled settings?*
2. *How can pharmacists-led medication adherence interventions be implemented in real practice?*

These identified gaps constitute the foundation of the present thesis and will be approached with the following hypotheses:

***Hyphothesis 1**. A community pharmacist-led real-world medication adherence intervention improves medication adherence rates in patients with chronic medications in Australia.*

***Hyphothesis 2**. A community pharmacist-led medication adherence management service improves medication adherence and clinical outcomes on patients suffering from asthma, COPD and hypertension in Spain.*

***Hyphothesis 3**. A community pharmacist-led medication adherence management service improves inhaler technique on patients suffering from asthma and COPD in Spain.*

***Hyphothesis 4**. The effectiveness of a community pharmacist-led medication adherence management service is maintained during its implementation.*

Objectives

This thesis encompasses the exploration and assessment of interventions to improve medication adherence and clinical outcomes in adult patients suffering from chronic diseases.

Specific objectives

- To analyse the effectiveness of an existing community pharmacist-led intervention on medication adherence in patients using rosuvastatin, irbesartan and/or desvenlafaxine in Australia.
- To evaluate the impact of a medication adherence management service on medication adherence and clinical outcomes in adult patients with hypertension, asthma and COPD compared to usual care.
- To evaluate the impact of a medication adherence management service on inhaler technique in adult patients suffering from asthma and COPD compared to usual care.
- To evaluate the clinical effectiveness of an evidence-based community pharmacist-led medication adherence management service during an effectiveness-implementation hybrid study.

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Chapter 2

Medication Adherence Interventions

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The Concept of Medication Adherence

The use of chronic medications has increased as a result of the increasing aging population and the prevalence of chronic diseases (Liska & Beal 2017). Medicines are the core therapy for patients suffering from chronic diseases as they can reduce the progression of the disease and contribute to the improvement of patient's quality of life. They only work if patients take them as prescribed, in a process defined as medication adherence (Sabate 2003). Nonetheless, 4% of patients fail on initiating the drug therapy, and approximately 40% discontinue their medications after one year (Blaschke et al. 2012) with this representing a significant impact on patient care. Overall, the impact of medication non-adherence can be examined from clinical, humanistic and economic perspectives. As regards of the clinical impact, non-adherence has been reported to lead to disease progression, decreased functional abilities, and reduced clinical control (e.g. blood pressure, glycaemic control) (Asche, LaFleur & Conner 2011; Chowdhury et al. 2013; Ho et al. 2016) and a higher risk of mortality (Fitzgerald et al. 2011; Simpson et al. 2006; Walsh et al. 2019). Non-adherence might also be related to a decline in quality of life (Hamedi-Shahraki et al. 2019; Souza, Borges & Moreira 2016). Finally, medication non-adherence can significantly increase the use of healthcare resources, understood as a higher number of emergency department visits, increases in doctor appointments and hospitalisations. Estimated annual adjusted costs per person range from $949 to $44,190 (in 2015 US$) as reported by Cutler et al. after analysing global evidence between 1997 and 2017 (Cutler et al. 2018). Therefore, it is pivotal to implement strategies aimed at ensuring that patients take their medications as prescribed. Primary healthcare providers like community pharmacists can contribute to optimising the quality use of medicines by targeting medication adherence.

The concept of medication adherence has evolved over time. In 2003, the World Health Organization (WHO) defined it as "the extent to which a person's behaviour corresponds with agreed recommendations from a health care provider" (Sabate 2003). In 2012, Vrijens et al. proposed a new conceptual foundation involving three components: initiation (i.e. when the patient takes the first dose), implementation

(i.e. the extent to which the actual dose corresponds to the prescribed one and covers from initiation until the last dose of the medication) and discontinuation (i.e. the end of the therapy). The length of time between initiation and discontinuation has been defined as persistence (Vrijens et al. 2012). Considering these dimensions of adherence, there are many circumstances in which patients may fail to adhere to their drug regimen. Patients can be considered as non-adherent when they fail to start a new treatment, they have inappropriate dosing or they stop taking their medications without instructions from the prescriber. Driven by numerous determinants (Kardas, Lewek & Matyjaszczyk 2013), non-adherence can be classified as intentional or unintentional (Horne & Weinman 1999). Intentional non-adherence occurs when a patient makes the conscious decision to not to take their medications and may be often related to attitudes and beliefs. Unintentional non-adherence appears when the patient faces practical barriers such as lack of resources or skills that hinder an appropriate medication-taking behaviour (Horne et al. 2013).

How to measure medication adherence

Different measures of adherence and measurement methods exist, generally classified as subjective and objective methods (Sabate 2003). Subjective methods encompass those in which the healthcare provider or the patient evaluate the medication-taking process (2015, Lam), with self-report and healthcare professional assessments being the most common methods. Objective methods are independent of an observer and include pill counts, MEMS (medication event monitoring systems) and dispensing records (Lam & Fresco 2015).

An alternative classification categorises the metrics in direct or indirect methods of measuring adherence (Osterberg & Blaschke 2005) (Figure 1). Direct methods refer to the measurement of blood or urine fluids to detect the drug or directly observed therapy (DOT). Although these methods are very reliable, they are subject of bias due to variations in metabolism and “white coat adherence” (Osterberg & Blaschke 2005). Moreover, the measurement of drugs in human fluids can be expensive and may not be available for all drugs (Lam & Fresco 2015). Pill counts, self-report and

dispensing data are considered indirect methods, easier to use but also exposed to bias due to human variability (Whalley Buono et al. 2017).

Another example of the indirect methods is the analysis of pharmacy data (Osterberg & Blaschke 2005; Whalley Buono et al. 2017). With the increasing generation of real-world patient data, dispensing records have been found to be useful methods to analyse medication adherence (Raebel et al. 2013). Examples of metrics are Medication Possession Ratio (MPR), that estimates the proportion of days' supply during a time period, Medication Refill Adherence (MRA), similar to MPR, Proportion of Days Covered (PDC), which analyses days encompassed by each refill with time arrays, without double counting overlapping days, and Continuous measure of Medication Gaps (CMG), accounting the gap days in an observation period (Raebel et al. 2013). PDC and MPR are the two most common metrics validated by the Pharmacy Quality Alliance (Martin et al. 2009; Pillittere-Dugan et al. 2009). As MPR does not account for the overlapping days when there is an early supply of the medication, duplications or medication switching, it can lead to overestimation of medication adherence (Arnet et al. 2014). PDC has more advantages and is the preferred method to use when analysing dispensing data. Although they do not measure the administration of the medication, dispensing records are an objective method accessible and relatively affordable to analyse (Whalley Buono et al. 2017) that should be considered as a measure of adherence.

There is no "gold standard" to assess medication adherence. However, these measurement methods need to be considered in terms of the setting, targeted condition, type of adherence, or the expected outcome of the research (Whalley Buono et al. 2017).

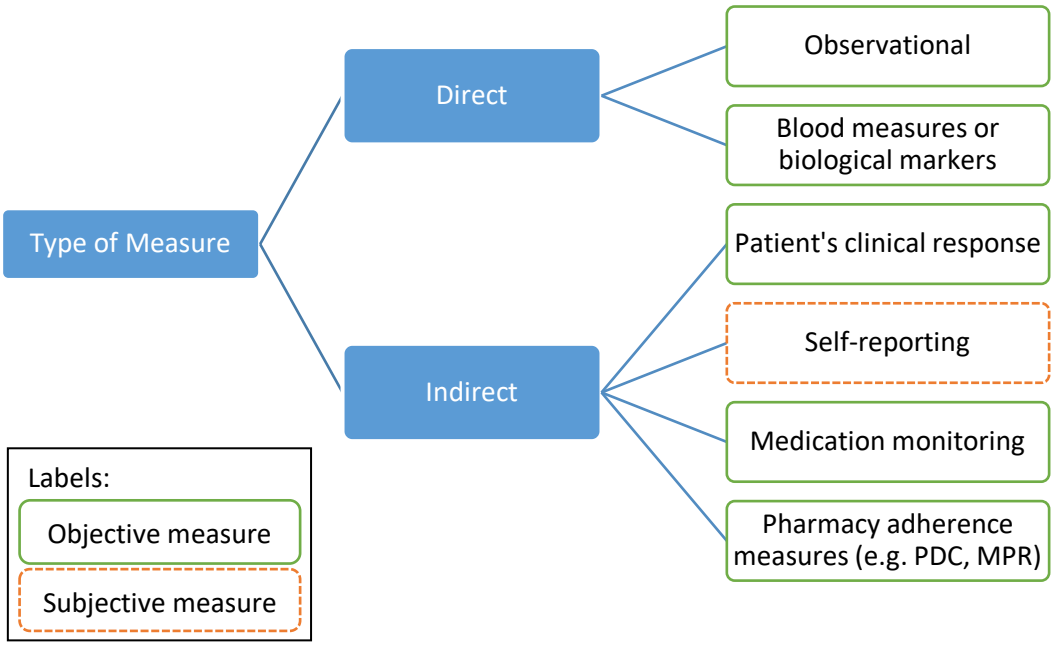

Figure 2. Medication Adherence Measures

Interventions for improving medication adherence

Despite medication non-adherence being a global problem, there is evidence of rates of non-adherence being consistent for the last decades, with almost 50% of patients failing to be adherent to their chronic medications (Brown & Bussell 2011; Fernandez-Lazaro et al. 2019; Li et al. 2016; Sabate 2003) and between 4% and 30% of patients never initiating the drug therapy (Blaschke et al. 2012; Cheen et al. 2019).

Extensive research has analysed the impact of medication adherence interventions. These interventions are variable and differ from study to study. A Cochrane systematic review analysing 182 clinical trials including interventions to improve medication adherence found a significant variability on the types of intervention, characteristics of the patients included and measurements of adherence (Nieuwlaat et al. 2014). These differences represent a significant and critical limitation when analysing the effectiveness of the interventions. There is still debate on which

interventions are the most effective or if their effectiveness depends on factors such as the clinical disease being targeted or the type of intervention. Nevertheless, interventions involving a long-term follow-up and multiple components (i.e. complex interventions) seem to be promising at addressing medication non-adherence (Wiecek et al. 2019).

Because of the multidimensional and dynamic nature of non-adherence (Franklin, Abel & Shojania 2020; Sabate 2003), it is critical to acknowledge the multiple factors affecting medication adherence when developing interventions. In 2013, Demonceau et al. proposed a new classification of medication adherence interventions (Demonceau et al. 2013). These consisted in interventions based on treatment simplification, cognitive-educational, behavioural-counselling, social-psycho-affective, based on electronically monitoring adherence feedback, based on technical reminder systems, using technical equipment to monitor the disease, and rewards (Demonceau et al. 2013). Most recently, interventions have been classified into four categories (i.e. attitudinal, economic/rewards, educational and technical) for better interpretability (Tonin et al. 2019).

Systematic Review and Network Meta-Analysis on adherence interventions

This chapter presents the review and meta-analysis of long-term interventions to improve medication adherence across diseases. Network meta-analysis is a statistical technique that allows multiple indirect and direct comparisons when a common comparator exists (Tonin et al. 2017). In the context of medication adherence interventions, this means that if two studies are comparing different interventions against *usual care*, *usual care* then becomes the common comparator that may allow a comparison between the two interventions from different studies. This statistical technique, only used in a few studies of adherence interventions in HIV (Kanters et al. 2017), can be applied to compare different interventions with multiple components across clinical conditions. Identifying the most successful combination

of components on the interventions will guide health services researchers, health care providers and policy-makers to address this problem.

This research is presented as a peer-reviewed paper in the journal *Frontiers in Pharmacology* in the speciality section *Pharmaceutical Medicine and Outcomes Research.*

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Comparison of Interventions to Improve Long-Term Medication Adherence Across Different Clinical Conditions: A Systematic Review With Network Meta-Analysis

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Background: Medication non-adherence has a dynamic, temporal and multifactorial nature with a significant impact on economic and clinical outcomes. Interventions to improve adherence are complex and require adaptation to patients' needs, which may include patient's medical conditions. The aim of this study was to assess the comparative effectiveness of medication adherence interventions per type of clinical condition on adult patients.

Methods: A systematic review with network meta-analysis was performed (PROSPERO registration number of CRD42018054598). An initial Pubmed search was conducted to select meta-analyses reporting results of interventions aiming to improve medication adherence. Primary studies were selected and those reporting results with a long-term follow up (≥10 months) on adult patients were included for data extraction. Study characteristics, description of interventions and adherence outcomes were extracted. Adherence interventions were classified in four groups: educational, attitudinal, technical, and rewards. Clinical conditions were classified in four groups: circulatory system and metabolic diseases, infectious diseases, musculoskeletal diseases, and mental, behavioral or neurodevelopmental disorders. Network meta-analyses with effect sizes expressed as odds ratio (OR) with a 95% credibility interval (CrI) were built. Ranking probabilities for each measure of adherence were calculated by using surface under the cumulative ranking analysis (SUCRA).

Results: A total of 61 meta-analysis and 149 primary studies were included in the qualitative synthesis and 80 primary studies in the quantitative analysis. The most effective interventions were: educational + technical 79.6% [OR: 0.44 (CrI: 0.26, 0.73)] and 73.3% [OR: 0.56 (0.36, 0.84)] in circulatory system and metabolic diseases and infectious diseases respectively. Attitudinal intervention had the greatest probability for musculoskeletal diseases of 92.3% in SUCRA [OR: 0.30 (0.10, 0.86)]. Finally, educational + attitudinal interventions had the greatest effect (SUCRA 73.8%) for mental, behavioral or neurodevelopmental disorders, although this was not significant according to consistency analysis.

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Conclusion: Effectiveness of interventions seems to be related to the clinical condition. Educational and technical interventions resulted in a major effect on long-term management of medication adherence in patients with infectious diseases (HIV) and circulatory system and metabolic diseases whereas attitudinal components presented a higher effect on musculoskeletal and mental, behavioral or neurodevelopmental disorders.

Keywords: medication adherence, network meta-analysis, chronic diseases, long-term, intervention, adherence implementation

INTRODUCTION

Medication non-adherence represents a continuous burden for the health-care system. Statistics remain constant since 2003, when the World Health Organization reported at least 50% of patients with chronic conditions were non-adherent to their medications (Sabate, 2003). Non-adherence can occur at different stages during the course of therapy, including initiation, implementation and persistence (Vrijens et al., 2012). A study analyzing an electronic database of nearly 17,000 patients' dosing histories across different diseases states for 1 year (including osteoporosis, diabetes, hypertension, depression and HIV), revealed 4% patients never initiated their treatment, nearly 40% discontinued, and only 55% dosed correctly (Blaschke et al., 2012).

The negative consequences of this phenomenon have been widely reported in the literature. For example, a recent systematic review found the economic impact of non-adherence, including the healthcare costs, ranged from $949 to $44,190 per patient annually across 14 disease groups (Cutler et al., 2018).

During the past 10 years there has been mounting evidence demonstrating the impact of diverse interventions on medication adherence in a range of clinical outcomes (Nieuwlaat et al., 2014). Effective adherence interventions have resulted in viral suppression in HIV patients (Mills et al., 2014), decrease of lipid levels and total cholesterol in patients taking lipid lowering medications (Deichmann et al., 2016), reduction of HbAc1, decrease hospitalizations and all-cause mortality in patients with diabetes (Ho et al., 2006), and reduction of risk of death and hospitalizations in patients with heart failure (Fitzgerald et al., 2011). Despite their proven efficacy, there is still a lack of consistent evidence on the core elements these interventions should include, limiting their implementation in routine practice. Effective interventions appear to be complex (through a combination of multiple core components) and tailored to the patient's needs (Nieuwlaat et al., 2014; Conn et al., 2016). Different intervention's success may be linked to the clinical condition being targeted. For example, there is some evidence technical interventions are effective in patients with hypertension (Conn et al., 2015), whereas interventions aiming to modify patients' beliefs and attitudes have been found to be more effective in patients with mental disorders (MacDonald et al., 2016; Readdean et al., 2018).

Heterogeneity of interventions and adherence measures is often reported to be a barrier for the quantitative analysis of interventions, hindering the comparison across different studies (Nieuwlaat et al., 2014). Some meta-analyses have overcome this limitation by directly comparing the effect of interventions on a range of adherence measures (Conn and Ruppar, 2017). However, these analyses lack indirect comparisons that could strengthen the current evidence. The use of network meta-analysis provides an advantage when compared to traditional meta-analysis methods, as it allows a comparison of multiple treatments or interventions at the same time, using both direct comparisons within randomized controlled trials and indirect comparisons across trials based on a common comparator (Tonin et al., 2017). Currently, a few network meta-analyses have been undertaken with the objective of assessing the impact of adherence interventions in HIV patients (Mills et al., 2014; Kanters et al., 2017).

Thus, the aim of this systematic review and network meta-analysis was to assess the comparative effectiveness of medication adherence interventions per type of clinical condition on adult patients being prescribed medications for the following condition groups: circulatory system and metabolic diseases, infectious diseases, musculoskeletal diseases, and mental, behavioral or neurodevelopmental disorders.

METHODS

As part of a larger project, this systematic review and network meta-analysis was performed following the Cochrane recommendations (Higgins JPT, 2011) and PRISMA statement for reporting systematic reviews incorporating network meta-analyses (Hutton et al., 2015) on health care interventions (PROSPERO registration number of CRD42018054598).

Search Strategy and Eligibility Criteria

To avoid inefficient duplication of efforts in a field like medication adherence with a vast body of primary and secondary literature, a two-steps approach was used for literature selection (Nieuwlaat et al., 2014). The first step aimed to retrieve pairwise meta-analyses assessing interventions to improve medication adherence on adult patients. In a second step, primary articles identified in the meta-analyses reporting experimental controlled trials were identified as data sources for our study.

The meta-analyses were systematically searched in PubMed, which comprises Medline and PubMed Central, in October 2017 with no restriction on publication date or language. A first screening by title and abstract of the meta-analyses was performed by two independent investigators and discrepancies were solved by a third reviewer. The search strategy can be found on the **Supplementary Material 1**.

In the second step, primary studies were selected from the identified meta-analyses and were full-text reviewed by two investigators. Primary studies with an experimental controlled design (randomized or non-randomized clinical trials) assessing the long-term effect of adherence interventions (follow-up of more than 10 months) and reporting measures of adherence (i.e., self-repot, pill count, refill data, electronic monitoring) on adult patients with prescribed medications were included for data extraction. Studies were excluded if the interventions were not patient-focused, assessed adherence to the following medications (over the counter medications, depot medications, vaccines), were not written in Roman characters, or were unpublished studies (e.g., conference posters, dissertations). From the eligible studies, those reporting adherence results as a categorical variable were included in the network meta-analysis. Studies reporting continuous data were only considered for qualitative analysis. Other studies not included in the network meta-analysis were those with the same intervention in all the study arms (same comparator) and clinical conditions without a sufficient number of studies to perform a comparative analysis. Additional information regarding inclusion or exclusion criteria can be found in **Supplementary Material 2**.

Data Extraction and Quality Assessment

Data from primary studies was extracted by two investigators and recorded on a standard data collection form. This included: authors, year of publication, country, sample size, clinical condition being targeted, sex, age, patient follow up period, study arms, interventions assessed, and measures of adherence. Targeted diseases were identified for each study and then classified in groups based on the International Classification of Diseases 11th Revision (ICD-11) (World Health Organization, 2018) into circulatory system and metabolic diseases, infectious diseases, musculoskeletal diseases, and mental, behavioral or neurodevelopmental disorders as described in **Table 1**. Circulatory system and metabolic diseases were classified as one group as they share common risk factors and patients are usually prescribed with medications from both groups (Cheung and Li, 2012).

An overall composite score was defined for each study, as the proportion of adherent patients reported by any measure. If a study had more than one method of assessment, a mean adherence rate was calculated. The validation of this score has been previously described elsewhere (Tonin et al., 2018).

For optimal comparison and interpretation of the results, adherence interventions were classified into four categories: attitudinal, rewards, educational, and technical based on previous definitions (Roter et al., 1998; Demonceau et al., 2013; Sapkota et al., 2015). Usual care was defined as standard of care (SOC) for this analysis. Included studies could have a single component or combination of multiple components comprising their intervention. The definitions for the interventions can be found in **Supplementary Material 3**.

TABLE 1 | Definition of groups for classification of clinical conditions.

Disease group	Clinical conditions included
Circulatory system and metabolic diseases	Hypertension, Coronary disease, Diabetes, Heart Failure, Stroke, Dyslipidaemia, Hyperlipidaemia, Diabetes
Infectious diseases	HIV
Musculoskeletal diseases	Osteoporosis, osteoarthritis
Mental, behavioral or neurodevelopmental disorders	Schizophrenia, bipolar disorder, psychosis, depression, tobacco dependence

Risk of bias assessment was undertaken for all the primary studies included in the analysis. It was performed by two investigators using the Cochranene collaboration risk of bias Assessment tool (RoB) (Higgins et al., 2011).

Data Analysis

A network meta-analysis using Bayesian framework was performed to compare the effectiveness of reported interventions on adherence rates of long-term interventions (with a follow-up of more than 10 months) across the condition groups previously described. This analysis was based on the Markov Chain Monte Carlo simulation. Transitivity analyses were performed by comparing population, interventions, and outcome definitions among the included studies. To analyse the multiple-arms studies a common heterogeneity parameter was considered and a conservative analysis of non-informative priors was conducted (Dias et al., 2010; Rucker et al., 2017).

Effect sizes measures were expressed as odds ratio (OR) with a 95% credibility interval (CrI). The goodness of fit of the model and consistency were assessed using the lowest residual deviance information criteria (DIC) between fixed and random-effect models tested. Convergence was attained based on visual inspection of Brooks-Gelman-Rubin plots and potential scale reduction factor-PSRF ($1 < \text{PSRF} \leq 1.05$) (Dias et al., 2010; Higgins et al., 2012).

Ranking probabilities for each measure of adherence were calculated by using surface under the cumulative ranking analysis (SUCRA) to increase the estimate precision of the relative effect sizes of comparisons and to properly account for correlations between multi-arm trials (Mbuagbaw et al., 2017). SUCRA values can range from 0% (i.e., the intervention always ranks last) to 100% (it always ranks first).

Robustness of the network when having close-loops, was assessed via node-splitting analysis ($p < 0.05$ reveal significant inconsistencies in the network) (van Valkenhoef et al., 2016). Sensitivity analyses with the hypothetical removal or inclusion of the studies were conducted when discrepancies were identified in the network. All analyses were performed using software Addis version 1.17.6 (van Valkenhoef et al., 2013).

RESULTS

A total of 920 records were identified and 61 meta-analyses, which included a median of 17.0 studies each [IQR 10.5–28.5; range 2–101], were finally selected for extraction of primary studies. From the selected meta-analyses, 1,119 primary studies were identified and 689 were assessed full-text for eligibility with 150 being included in the qualitative analysis and 80 in the network meta-analysis (**Figure 1**; and **Supplementary Material 4**). For those studies included in the qualitative synthesis, the publication years ranged between 1979 and 2016, with a median of 2007 (IQR 2006–2012). The number of studies per disease group was: 38 focused on infectious diseases (25.5%), 62 on circulatory system and metabolic diseases (41.6%), 13 on mental, behavioral or neurodevelopmental disorders (8.7%) and 14 on musculoskeletal diseases (9.4%). Five studies (3.4%) reported results in two groups of diseases and the remaining 16 studies (10.7%) corresponded to respiratory,

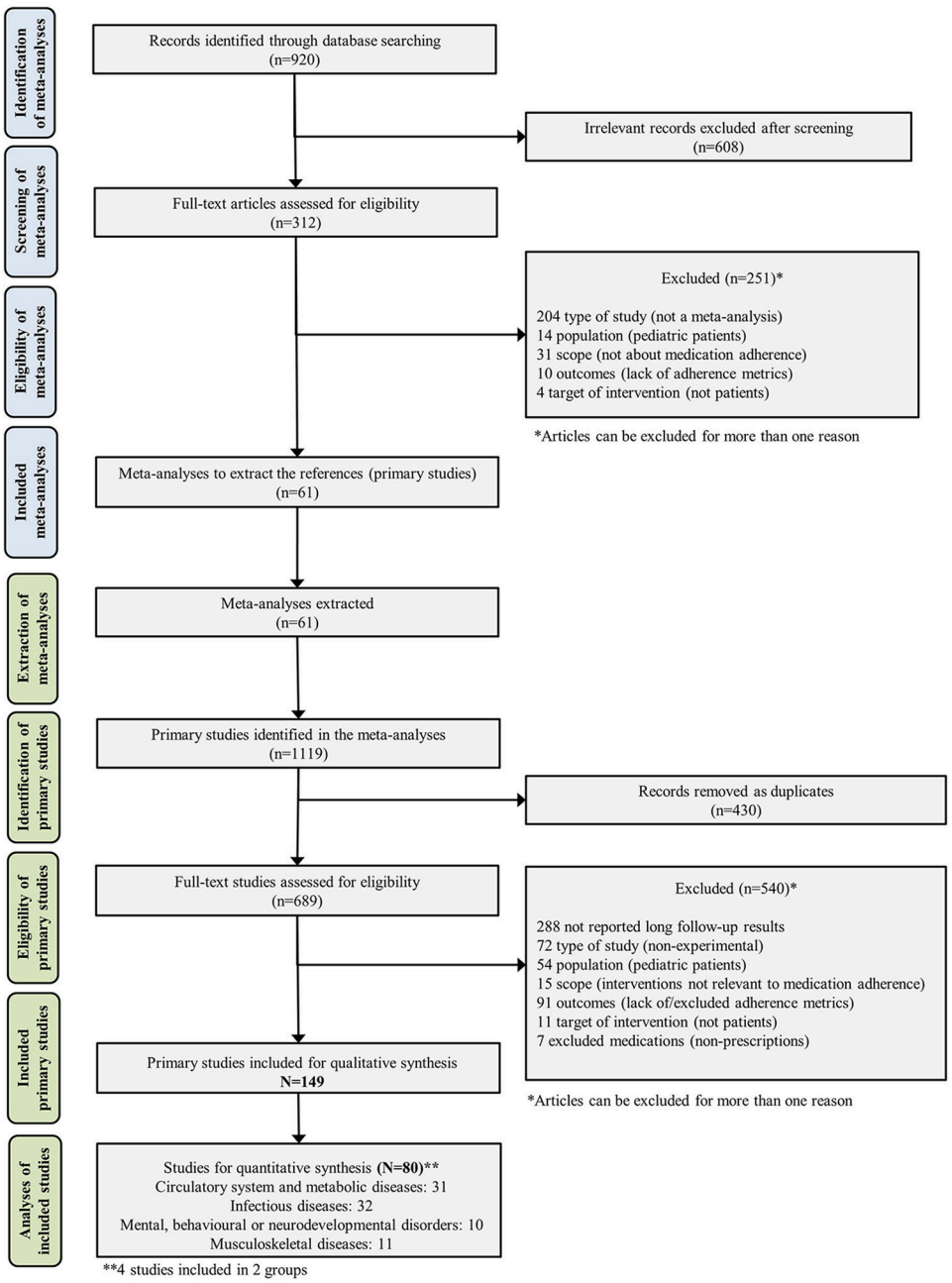

FIGURE 1 | Flowchart of systematic review and network meta-analysis process.

digestive, transplant and undefined conditions. The only available articles classified into infectious diseases were focused on HIV (Human Immunodeficiency Virus).

Overall, 178,229 patients were included in the analyses, with the following distribution across disease groups: circulatory system and metabolic diseases ($n = 59{,}959$), infectious diseases (HIV) ($n = 18{,}737$), musculoskeletal diseases ($n = 72{,}595$) and mental, behavioral or neurodevelopmental disorders ($n = 2{,}632$). The average follow-up time was 14 months with the majority reporting a follow-up of 12 months ($n = 115$ studies). The most common interventions were educational ($n = 49$ studies, 28%), followed by educational + technical ($n = 41$, 23%), technical ($n = 36$, 20%), educational + attitudinal ($n = 20$, 11%), attitudinal ($n = 21$, 12%), educational + attitudinal + technical ($n = 5$, 3%) and only 3 studies (1.7%) containing the rewards component (rewards, rewards + technical, educational + attitudinal + rewards). In 134 studies (89.3%), standard care was used as a common comparator.

The risk of bias analysis resulted in a low risk on selective reporting ($n = 146$ studies, 98%) as all the papers reported the expected adherence outcomes. Around 20% of studies presented a high risk of bias for incomplete outcome data domain ($n = 34$) due to the lack of intention-to-treat analysis or missing data. Allocation concealment was classified as unclear risk of bias in most of the studies ($n = 121$, 81.2%). Additional information can be found in the **Supplementary Material 5**.

In the quantitative analysis, 80 studies were included, with 69 excluded due to the following reasons: (1) categorical medication adherence data not reported ($n = 57$), (2) same intervention category in all study arms ($n = 3$); and (3) not enough studies to be categorized and analyzed by disease group ($n = 9$).

Network meta-analyses were conducted per disease group (**Figure 2**), as described below. The list of included studies for each network meta-analysis can be found in **Supplementary Material 6**. Networks were found to be robust, with no significant inconsistency (Table 2 consistency analysis and **Supplementary Material 7**).

Circulatory System and Metabolic Diseases

Thirty-one studies were included in this network, with seven different interventions being compared. Three studies assessed a combination of multiple intervention types, with a majority comparing educational + technical interventions (n=12 studies) and educational interventions ($n = 11$) vs. SOC.

Educational + technical interventions were more effective in improving adherence when compared to SOC [OR: 0.44 (CrI: 0.26, 0.73)] (**Table 2**). In terms of ranking probabilities (SUCRA analysis), educational + technical interventions had the

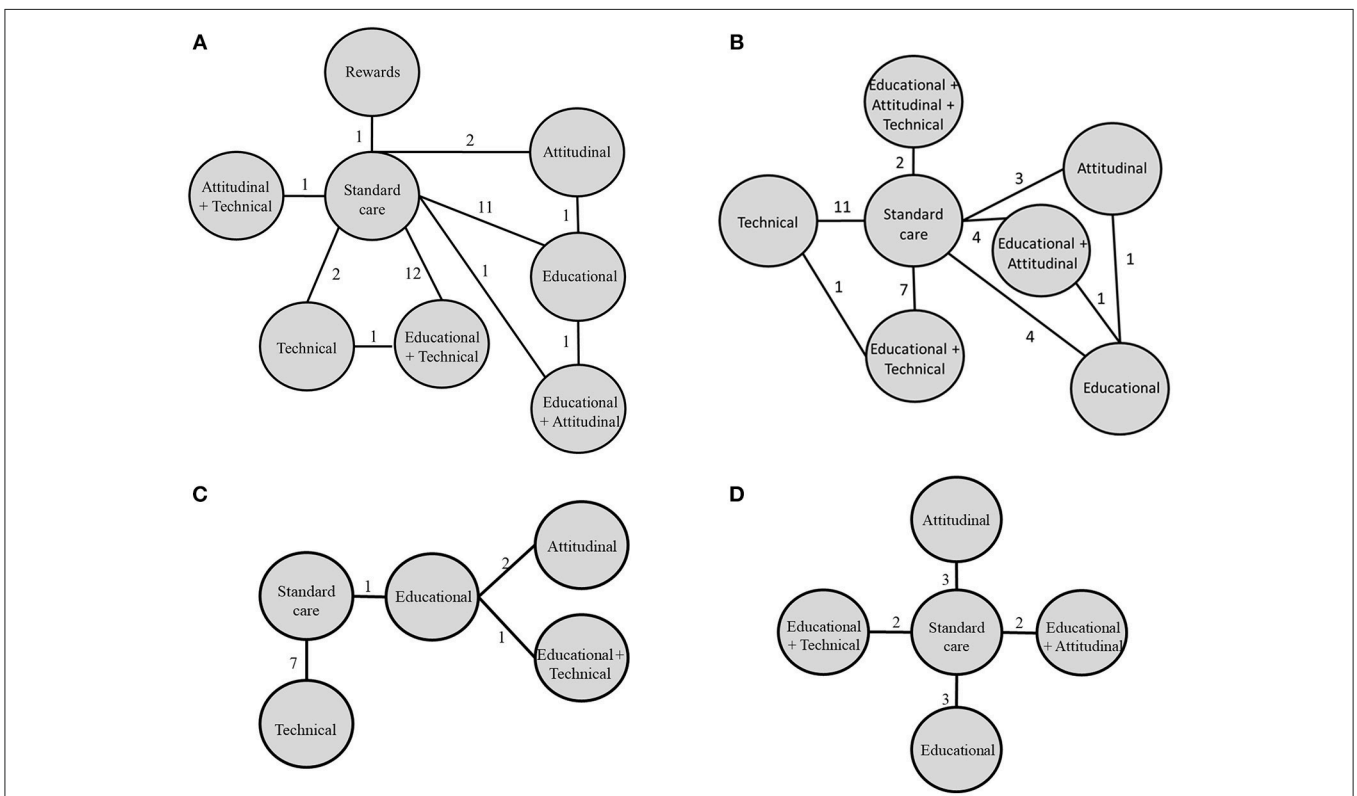

FIGURE 2 | Networks diagrams of interventions on adherence across disease groups. Each line represents a direct comparison of interventions and the number of studies reporting that comparison is written on each line. From left to right: **(A)** Circulatory system and metabolic diseases, **(B)** Infectious diseases (HIV), **(C)** Musculoskeletal diseases, **(D)** Mental, behavioral or neurodevelopmental disorders.

TABLE 2 | Consistency analyses of comparisons on different group diseases based on composite score (A) Circulatory system and metabolic diseases; (B)Infectious diseases (HIV); (C) Mental, behavioral or neurodevelopmental disorders; (D) Musculoskeletal diseases.

(A)							
Attitudinal + Technical	0.84 (0.13, 4.88)	0.98 (0.11, 8.37)	0.96 (0.14, 6.67)	1.63 (0.34, 7.71)	1.13 (0.23, 5.34)	0.71 (0.15, 3.05)	1.47 (0.32, 6.52)
	Attitudinal	1.17 (0.18, 7.63)	1.15 (0.24, 5.35)	1.95 (0.65, 5.89)	1.35 (0.49, 3.81)	0.85 (0.32, 2.21)	1.76 (0.48, 6.53)
		Rewards	0.98 (0.13, 7.46)	1.65 (0.32, 9.14)	1.16 (0.22, 6.05)	0.72 (0.15, 3.52)	1.52 (0.24, 9.67)
			Educational + Attitudinal	1.69 (0.47, 6.61)	1.18 (0.35, 3.93)	0.74 (0.22, 2.46)	1.54 (0.35, 6.92)
				Educational + Technical	0.70 (0.33, 1.42)	**0.44 (0.26, 0.73)**	0.92 (0.34, 2.32)
					Educational	0.63 (0.38, 1.03)	1.31 (0.48, 3.60)
Circulatory system and Metabolic diseases						Standard Care	2.09 (0.86, 5.09)
							Technical
(B)							
Attitudinal	0.95 (0.33, 2.73)	1.08 (0.47, 2.60)	1.20 (0.58, 2.62)	0.91 (0.43, 1.82)	0.67 (0.37, 1.25)	1.09 (0.55, 2.25)	
	Educational + Attitudinal + Technical	1.14 (0.40, 3.40)	1.26 (0.48, 3.48)	0.96 (0.34, 2.69)	0.70 (0.30, 1.74)	1.15 (0.46, 3.09)	
		Educational + Attitudinal	1.12 (0.53, 2.28)	0.84 (0.37, 1.76)	0.62 (0.33, 1.12)	1.01 (0.51, 2.03)	
			Educational + Technical	0.76 (0.35, 1.48)	**0.56 (0.36, 0.84)**	0.91 (0.53, 1.57)	
				Educational	0.74 (0.43, 1.32)	1.20 (0.65, 2.49)	
Infectious diseases (HIV)					Standard Care	**1.63 (1.16, 2.38)**	
						Technical	
(C)							
Attitudinal	1.20 (0.21, 6.45)	0.45 (0.09, 2.33)	1.13 (0.25, 4.83)	0.45 (0.15, 1.29)			
	Educational + Attitudinal	0.38 (0.06, 2.21)	0.96 (0.18, 4.52)	0.37 (0.10, 1.37)			
		Educational + Technical	2.49 (0.50, 11.55)	0.98 (0.29, 3.50)			
Mental, behavioral or neurodevelopmental disorders			Educational	0.39 (0.15, 1.11)			
				Standard Care			
(D)							
Attitudinal	0.26 (0.05, 1.13)	0.80 (0.53, 1.36)	**0.30 (0.10, 0.86)**	0.47 (0.16, 1.41)			
	Educational + Technical	3.08 (0.77, 14.25)	1.14 (0.20, 6.59)	1.81 (0.32, 10.87)			
		Educational	**0.37 (0.14, 0.91)**	0.59 (0.21, 1.52)			
			Standard Care	**1.60 (1.26, 1.98)**			
Musculoskeletal diseases				Technical			

Comparisons should be read left to right. The common cell between the intervention on the row and the one on the column represents the size effect, reported as OR (95% CrI). When comparing, values <1 indicate the intervention in the row is more effective. Values >1 indicate the intervention in the column is more effective (e.g., for HIV, comparing Edu+Tec and SOC results on OR:0.56, lower than 1, indicating Edu+Tec is more effective than SOC). Statistically significant results are in bold.

highest probability of being the best intervention at improving adherence in this disease group (79.6%). Technical interventions were ranked second (71.6%) and educational interventions third (55.9%). SOC ranked last (19.4%).

Infectious Diseases: HIV

A total of 32 studies were included in this network with 6 different interventions. Three of these interventions were multicomponent. The majority of studies compared technical ($n = 11$) or educational + technical ($n = 7$) against SOC.

There were significant differences favoring educational + technical interventions [OR: 0.56 (0.36, 0.84)] and technical interventions [OR: 1.63 (1.16, 2.38)] compared to SOC (**Table 2**). SUCRA analysis showed educational + technical as the most probable to enhance adherence with a likelihood of 73.7%, followed by technical (63.2%) and educational + attitudinal (61.0%). Again, SOC ranked last (8.5%).

Musculoskeletal Diseases

A total of 11 studies with 4 intervention combinations were analyzed in this network. The educational + technical interventions were used in 7 studies and were compared to SOC. Consistency analysis revealed statistical differences between attitudinal [OR: 0.30 (0.10, 0.86)], educational [OR: 0.37 (0.14, 0.91)] and technical [OR: 1.60 (1.26, 1.98)] interventions compared to SOC (**Table 2**).

Attitudinal interventions had the greatest probability of being the best option (92.3%) when compared to the other interventions. Educational (74.0%) and technical (48.3%) interventions ranked second and third, respectively. The lowest effect was for SOC (14.8%).

Mental, Behavioral, or Neurodevelopmental Disorders Diseases

This network was comprised of 10 studies and compared 2 single component interventions, 2 combination interventions and standard care. Three studies assessed attitudinal interventions and three evaluated educational interventions. Two included educational + technical interventions and another two studies assessed educational + attitudinal interventions. All interventions were compared to SOC. No significant differences were found between types of interventions for this disease group (**Table 2**).

According to the SUCRA analysis, educational + attitudinal interventions ranked first (73.8%). Second and third rankings consisted of educational (72.5%) and attitudinal (65.3%) interventions respectively (See SUCRAS in **Supplementary Material 8**).

DISCUSSION

To the best of our knowledge, this is the first network meta-analysis assessing the comparative effectiveness of interventions aimed at improving medication adherence to chronic medications across different disease groups, with long-term follow-up periods. Differences in the effects of the interventions were found by disease groups, suggesting that adherence interventions should be adapted to the condition being targeted. There are numerous condition-related determinants affecting medication adherence (e.g., presence of symptoms, disease severity, clinical improvement, duration of the disease, psychiatric conditions) that require tailored and multifaceted approaches (Kardas et al., 2013).

Adherence interventions in circulatory system and metabolic diseases and infectious diseases (HIV) were significantly more effective when combining educational + technical components (with SUCRA values between 70 and 80%). Interventions involving educational components only (i.e., interventions providing information regarding the medication, disease state or importance of adherence with the aim of increasing a patient's knowledge or skills that facilitate adherence) are one of the most frequent strategies used in health care to change patient behavior (Sapkota et al., 2015). As hypothesized by the Information-Motivation-Strategy model (IMS) (DiMatteo et al., 2012), "patients are only capable of doing what they clearly understand," emphasizing the importance of adequate patient information and knowledge to follow a treatment regimen (DiMatteo et al., 2012). However, the effectiveness of information provision and its effect on medication adherence can be affected by a range of healthcare team and system-related factors, such as poor patient-physician communication, patient's lack of trust, lack of shared decision making or poor follow-up amongst others (Kardas et al., 2013). Moreover, there is evidence a high proportion of patients are unable to remember the information provided during a medical consultation, highlighting that although essential, the provision of information as an isolated strategy can be insufficient to ensure medication adherence (Kravitz et al., 1993). Also suggested by the IMS model, patients can be non-adherent if they lack a strategy that allows them to follow their health care provider's recommendations (DiMatteo et al., 2012), as found especially evident in unintentional non-adherence (Horne et al., 2005). Patients must have the strategies and resources to be able to overcome practical barriers faced when attempting to follow their health care provider's recommendations (DiMatteo et al., 2012). Therefore, adding the use of technical components, that is interventions providing any gadget, instrument, or system that facilitate medication intake or increase convenience of the medication taking process, may increase medication adherence. These interventions often help patients adopt routines of medication taking when they have memory problems or have busy social lives that limit their ability to be adherent (Vervloet et al., 2012).

The results obtained for circulatory system and metabolic diseases and infectious diseases (HIV) are in agreement with previous literature reporting an increased effect when combining different interventions components (Kanters et al., 2017). A more specific analysis conducted in Africa revealed that adding educational and technical components to standard care could improve medication adherence (Mills et al., 2014). Other technical components such as regimen simplification, available for some of the medications used for HIV treatment, resulted in an increase on adherence as it reduces pill burden (Parienti et al., 2009; Nachega et al., 2014). There is also a reduction in treatment complexity and polypharmacy, important barriers preventing patients to adhere to their medications (Marcum and Gellad, 2012). Additionally, patients have to integrate doses into

daily life, a process that may sometime represent shame or fear associated with the condition stigma. Minimizing this process may also reduce burden (Katz et al., 2013).

Attitudinal interventions were found to have the best effect to increase medication adherence in patients suffering from musculoskeletal diseases, with a SUCRA of 99.25% and were found to be significantly different to standard care. These findings indicate there is a strong effect from the use of behavior change theories on the improvement of medication adherence on these diseases. This might be due to a higher prevalence of intentional non-adherence (Horne and Weinman, 1999) in patients with these conditions. The Health Belief Model suggests that a health behavior can be influenced by perceived susceptibility, severity, benefits and barriers regarding a disease or condition (Glanz et al., 2015) and it has been suggested that effective relationships between physician and patients are necessary in order to help them to cope with medication non-adherence problems (DiMatteo et al., 2007). Therefore, behavior based theories that can be provided by physicians, such as motivational interviewing, can be used to improve adherence (Easthall et al., 2013). These often consist of focused skills to help the patient solve ambivalence and find solutions (Miller and Rollnick, 2012).

Consistency analysis did not show significant differences between the effectiveness of different interventions for patients with mental, behavioral or neurodevelopmental disorders. A reason for these results may be because adherence is complex and dynamic and requires accurate assessment of practical and motivational barriers due to external factors associated to the condition itself (Chapman and Horne, 2013). However, the combination of educational + attitudinal components presented higher SUCRA values (around 75%). These results are congruent with previous research that showed that incorporating attitudinal interventions, such as psychoeducation, are an effective strategy to increase on medication adherence in patients with mental disorders (Bond and Anderson, 2015; Hartung et al., 2017). Attitudes and beliefs about the need to take medications can be moderated by the condition itself, such as dependence, the feeling of medications controlling their attitudes, or impact of medicines on daily routines (Chakrabarti, 2016).

Rewards type interventions, interventions that provide incentives, awards or penalties to facilitate medication adherence, were evaluated only for one study and for one disease group (circulatory system and metabolic diseases) with no significant long-term effect compared to other interventions or SOC. The intervention was focused on full payment coverage of medications (Choudhry et al., 2011). Usually, the application of this type of intervention requires modifications on health policies (e.g., coverage of medications) and involves ethical concerns of providing incentives to patients (Noordraven et al., 2017).

The limitations of this study include the categorization of the interventions into four major groups to perform the network meta-analyses. We acknowledge that a different categorization system may lead to some different results. However, this classification system, which was developed based on three previously used classifications, allowed us to have a clearer understanding of the interventions (Roter et al., 1998; Demonceau et al., 2013; Sapkota et al., 2015). The use of different classification systems for the clinical conditions may also lead to different results. We used the standard groups proposed by the International Classification of Diseases from the World Health Organization. Some other important conditions groups such as respiratory (e.g., asthma, COPD) could not be compared because of the lack of studies reporting long-term categorical outcomes on adherence. Results on adherence were focused only on implementation, one of the components of the current adherence definition proposed by ABC Project Team (Vrijens et al., 2012) as there were not enough studies reporting initiation or discontinuation adherence that could be analyzed. We used a previously validated composite measure of adherence to consider in one single model different individual measures and provide a broad evaluation of the effectiveness of complex interventions. The use of other measures can produce slightly different results.

CONCLUSION

Educational and technical interventions seem to be more effective on the long-term management of medication adherence in patients with HIV, circulatory system and metabolic diseases, compared to attitudinal interventions that presented a superior effect on mental, behavioral or neurodevelopmental disorders and musculoskeletal diseases. Multicomponent interventions are more effective at enhancing medication adherence in three of the four disease groups. Further analyses assessing the impact of these interventions on clinical outcomes are needed to support the translation of these results to daily practice. The use of network meta-analysis was valuable for comparing interventions aimed to improve medication adherence across chronic diseases in long-term follow-up periods.

AUTHOR CONTRIBUTIONS

VG-C, SB, FF-L, AT-R, EW, and FT contributed to the design of the study. EW and AT-R organized the database. FT and FF-L performed the data analysis. AT-R wrote the first draft of this manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2018.01454/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Medication adherence interventions in community pharmacies

Pharmacists are allied healthcare providers with the potential of delivering effective interventions to improve medication adherence (Nieuwlaat et al. 2014). In a systematic review analysing interventions of 739 studies, those delivered by pharmacists showed greater effectiveness than the ones delivered by other health care professionals (Conn & Ruppar 2017). Some evidence on the impact of community pharmacists-led adherence interventions on medication adherence and health outcomes in older adults has been reported in a systematic review (Milosavljevic, Aspden & Harrison 2018). Nonetheless, most of the interventions in this systematic review involved an educational component, leaving a gap in the literature to explore the inclusion of other components that can impact on adherence and clinical outcomes on patients with different diseases (Milosavljevic, Aspden & Harrison 2018). Furthermore, more conclusive evidence on the role of pharmacists at managing patient care (e.g. medication adherence, inhaler technique) in diseases such as COPD or asthma has been underlined in previous reviews (Armour et al. 2011; van der Molen et al. 2017). An umbrella review has also mentioned the need for research on the impact of community pharmacists' interventions on clinical outcomes, especially in respiratory diseases (Newman et al. 2020).

In Australia, GuildLink Ltd is a company owned by the Pharmacy Guild of Australia and one of the largest providers of software solutions to improve services in community pharmacies, with a significant presence on community pharmacies across Australia. To date, no previous analysis existed on the impact of these programs at assessing medication non-adherence. As these programs record a significant amount of data including dispensing records, the utilisation of big data analysis techniques to assess medication adherence through dispensing records can provide an insight of the effectiveness of the current intervention and will set the baseline for the design of pharmacy services.

In Spain, the national consensus of pharmaceutical organisations for community pharmacies defined medication adherence as the professional service in which

pharmacists work with patients, so they follow health providers' instructions regarding the correct use of medications. Therefore, patients' outcomes can be achieved (Sexto 2016).

Because of their access to the patients, community pharmacists have the potential to deliver interventions that improve patient's outcomes. As the management of medications continue to be a burden in chronic diseases such as hypertension, COPD and asthma, the evaluation of the effectiveness of interventions to improve medication adherence in these diseases is justified.

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Chapter 3

Using Dispensing Data to Evaluate Adherence Implementation Rates in Community Pharmacy

Chapter 3 presents the findings of a retrospective analysis to analyse the impact of a real-life intervention in community pharmacies in Australia.

This chapter is presented as a peer-reviewed paper in the journal *Frontiers in Pharmacology* in the speciality section *Pharmaceutical Medicine and Outcomes Research.*

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Using Dispensing Data to Evaluate Adherence Implementation Rates in Community Pharmacy

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Background: Medication non-adherence remains a significant problem for the health care system with clinical, humanistic and economic impact. Dispensing data is a valuable and commonly utilized measure due accessibility in electronic health data. The purpose of this study was to analyze the changes on adherence implementation rates before and after a community pharmacist intervention integrated in usual real life practice, incorporating big data analysis techniques to evaluate Proportion of Days Covered (PDC) from pharmacy dispensing data.

Methods: Retrospective observational study. A de-identified database of dispensing data from 20,335 patients (n = 11,257 on rosuvastatin, n = 6,797 on irbesartan, and n = 2,281 on desvenlafaxine) was analyzed. Included patients received a pharmacist-led medication adherence intervention and had dispensing records before and after the intervention. As a measure of adherence implementation, PDC was utilized. Analysis of the database was performed using SQL and Python.

Results: Three months after the pharmacist intervention there was an increase on average PDC from 50.2% (SD: 30.1) to 66.9% (SD: 29.9) for rosuvastatin, from 50.8% (SD: 30.3) to 68% (SD: 29.3) for irbesartan and from 47.3% (SD: 28.4) to 66.3% (SD: 27.3) for desvenlafaxine. These rates declined over 12 months to 62.1% (SD: 32.0) for rosuvastatin, to 62.4% (SD: 32.5) for irbesartan and to 58.1% (SD: 31.1) for desvenlafaxine. In terms of the proportion of adherent patients (PDC >= 80.0%) the trend was similar, increasing after the pharmacist intervention from overall 17.4 to 41.2% and decreasing after one year of analysis to 35.3%.

Conclusion: Big database analysis techniques provided results on adherence implementation over 2 years of analysis. An increase in adherence rates was observed after the pharmacist intervention, followed by a gradual decrease over time. Enhancing the current intervention using an evidence-based approach and integrating big database analysis techniques to a real-time measurement of adherence could help community pharmacies improve and sustain medication adherence.

Keywords: big database, dispensing records, medication adherence, community pharmacy, adherence implementation

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INTRODUCTION

Medication non-adherence remains a major burden on the health care system. Estimated annual costs of non-adherence range between $949 and $44,190 per patient (Cutler et al., 2018), up to $300 billion in the United States in avoidable funds (Institute, 2009) and €125 billion annually to the European Union (Pharmaceutical Group of the European Union, 2018). As a result, various interventions in diverse settings have shown marginal improvements in medication adherence (Nieuwlaat et al., 2014; Conn and Ruppar, 2017). However, in order to further progress the enhancement of non-adherence, we must fully understand and correctly utilize measures of adherence depending on the purpose or design of the study (Lehmann et al., 2014). The accurate and timely measurement of medication adherence is not only crucial to provide better evidence but creates problematic and expensive consequences if performed incorrectly (Lam and Fresco, 2015).

Multiple methods and tools are available for measuring adherence but guidance for the most suitable measure for healthcare professionals and researchers is still lacking (Whalley Buono et al., 2017). Moreover, measures of adherence must also take into consideration the different components of the medication taking process as recently defined by the ascertaining barriers to compliance (ABC) taxonomy. The medication taking process begins at initiation of treatment, continues at implementation or the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, and persistence or the time from initiation to discontinuation. These components all individually carry significant insight into patient medication-use behavior (Vrijens et al., 2012).

An increase in the accessibility of health system data and advancements in electronic information of medication use has permitted new insight into patients' medication behavior (Whalley Buono et al., 2017). The increased availability of big data in health has enabled the utilization of quality performance measurement across various aspects. Specifically in pharmacy, large data sets of prescription dispensing information, also known as pharmacy claims or prescription refill data, have become more readily available from the ease of electronic information, making it useful for analyzing medication adherence (Raebel et al., 2013) and providing a viable and economical approach for its estimation in real time (Vik et al., 2004). Even in the absence of a gold standard, the use of dispensing data has been a staple in adherence measurements due to their validity, relative accessibility and inexpensiveness (Simons et al., 2008; Martin et al., 2009; Greevy et al., 2011; Arnet et al., 2014; Holdford and Saxena, 2015), creating valuable data sets (Blaschke et al., 2012; Ma et al., 2015). Validated and endorsed by the Pharmacy Quality Alliance and having been used for over two decades, examples of dispensing data's use in the literature are abundant and increasingly frequent (Martin et al., 2009; Pillittere-Dugan et al., 2009). This allows the calculation of measures of adherence such as Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC), two validated measures of adherence based on the percentage of days the patient has medication available. While difficult to measure in previous traditional methods, dispensing data creates an easier system in which to evaluate and monitor all stages of the medication-use process (Blaschke et al., 2012). From this, long-term patterns can be identified and evaluated which before were often not feasible in randomized controlled trials investigating adherence due to short durations. This might also be essential in order to monitor the long-term effectiveness of medications during their post-authorization phase.

Frequently revealed in long-term monitoring are declining trends in adherence, indicating the issue of maintaining adherence over time as crucial as improving adherence at a cross-sectional time point (Cooper et al., 2011; Blaschke et al., 2012; Demonceau et al., 2013). Instant feedback during the dispensing process can allow the monitoring of patient adherence in real-time, especially by community pharmacists, and therefore, trigger adherence interventions when suboptimal adherence levels are identified (Sodihardjo-Yuen et al., 2017). Interventions to improve medication adherence in research projects delivered by community pharmacists have been shown to be effective (Nieuwlaat et al., 2014; Milosavljevic et al., 2018). This evidence has usually been generated through clinical trials, conducted in well-defined and controlled environments. However, whether these trials produce results that are applicable to everyday practice and whether the effects are maintained in real-life settings usually remains unknown. In real-life practice, patients are often exposed to community pharmacist interventions during the dispensing of medicines but no analysis of the impact of the intervention on improving adherence long-term is usually conducted. Retrospective observational designs and pragmatic trials can include measures of adherence from dispensing data that allow evaluation of the effectiveness of these interventions in real life environments (Whalley Buono et al., 2017). The objective of this study was to use big data techniques on pharmacy dispensing data to analyze the effectiveness of a community pharmacist-led intervention on medication adherence implementation in patients using rosuvastatin, irbesartan and/or desvenlafaxine in Australia. With this study, we were able to both evaluate an intervention's long-term effect on improving adherence in addition to evaluating a big data approach and methodology to analyzing adherence implementation rates.

MATERIALS AND METHODS

Retrospective observational study of dispensing records of patients receiving a real-life educational-based intervention to enhance medication adherence from community pharmacists across Australia.

Pharmacist Intervention

GuildLink Pty Ltd is part of a group of companies which is wholly owned by the Pharmacy Guild of Australia and provides software solutions to community pharmacies in Australia for documenting the provision of diverse pharmacy services. Their MedScreen Compliance Program targets non-adherent patients when a calculated MPR is below 70%, alerting the dispensing

pharmacist to offer an educational-based intervention aiming at improving medication adherence. A guided interaction between the pharmacist and patient is then offered which encompasses the following steps: (1) exploration and identification of real or perceived barriers to medication adherence, (2) provision of patient education on proper medication use in an oral or written (patient handouts about medicines information) manner and the importance of adherence, (3) goal-setting for their treatment targets, and (4) recording of the interaction. Patients could receive one or multiple interventions across multiple time periods depending on the calculated MPR, alerting the pharmacist to invite the patient to the intervention if they remain below the 70% threshold.

Data Source and Patients

GuildLink Pty Ltd GuildCare Software Databases were used for this study to assess dispensing data from Australian pharmacies that participate in the MedScreen Compliance programs. These databases contained de-identified primary care prescription data, dispensing data, and pharmacist intervention data from the affiliated pharmacies. Dispensing data (1 year before and after the first pharmacist's intervention) for patients taking desvenlafaxine, irbesartan and/or rosuvastatin who had received the intervention previously described, was analyzed. No process indicators to validate the fidelity of the intervention were available as it was a real-life intervention. In order to calculate adherence implementation rates from dispensing data, two main exclusion criteria applied. The database did not record days' supply for each individual dispense. Due to this, we assumed a once daily prescribed dose and therefore excluded patients with a prescribed quantity of less than 28 or more than 30 doses per dispense. In addition, more than two dispensing fills were needed to accurately calculate an adherence rate. This excluded patients with less than two dispensing dates before and after the intervention.

Outcome: Adherence Implementation

Adherence implementation rates were calculated using the PDC. This indicator accounts for overlapping days' supplied to allow a more conservative estimate of adherence and has been previously validated (Pillittere-Dugan et al., 2009). We selected it over MPR due to MPR's overestimating effects when analyzing multiple medications and overlapping days.

Data Analysis

The data was analyzed by integrating SQL (Microsoft SQL Server Management Studio Version 14.0.17213.0), Python (Version 2.7.14) and PyCharm (Version 2017.3.4, Community Edition) language programs to organize and retrieve the results.

In order to organize the final data table with the required components to be analyzed, some validations were performed. A unique Australian identifier code (PBSCode) linked to each script was used to infer missing quantity prescribed data per patient and organize the scripts corresponding to each drug. This code is always associated to a drug and a quantity to be prescribed, making it feasible to be used to infer missing quantities.

Analysis was conducted per trimesters, 1 year before and 1 year after the first pharmacist intervention, calculating the average PDC (%) and standard deviation (SD) for all the patients in each period of time using descriptive statistics. An additional sub-analysis regarding the number of adherent patients was performed. Cut-off for optimal adherence was defined as PDC equal or higher than 80% as this has been found to be reasonable for predictable hospitalizations in chronic diseases (Karve et al., 2009).

A sensitivity analysis was performed on patients who claimed the initial dispensing and their corresponding repeats (number of times an original prescription can be claimed in a pharmacy in Australia) to observe if there was a difference on the trend compared to the general analysis regardless of the repeat dispensing sequence.

Ethics Statement

University of Technology Sydney Human Research Ethics Committee (HREC) approved this study (approval number ETH18-2312). The study was classified as having Nil/Negligible Risk. No personal or confidential data was included in the database. Therefore no informed consent was required.

RESULTS

Study Sample

The database contained de-identified data of 2,530,562 patients from 3,318 community pharmacies across different states in Australia from 2014 to 2017. A total of 1,805 pharmacies across seven states in Australia and 20,335 patients (n = 11,257 using rosuvastatin, n = 6,797 on irbesartan, and n = 2,281 on desvenlafaxine) met the inclusion criteria and were included in the analysis. The average number of patients per pharmacy was 8.59 (SD: 5.14).

The distribution of patients according to gender was 56% female and 44% male of patients taking rosuvastatin, 61% female and 39% male on irbesartan and 70% female and 30% male on desvenlafaxine. Average age was 65 (SD: 11.76) in patients using rosuvastatin, 67 (SD: 12.42) in irbesartan and 50 (SD: 15.70) for desvenlafaxine.

Implementation Adherence – PDC

The average PDC of patients taking rosuvastatin 12 months previous to the pharmacist intervention was 59.4% (SD: 30.6) decreasing on 9.2% to 50.2% (SD: 30.1) in the last trimester before the intervention. An increase of 16.7% was observed in the 3 months following the pharmacist intervention, reaching a 66.9% (SD: 29.9) average PDC, dropping to 62.1% (SD: 32.0) during the 12 months after the intervention (**Figure 1**).

For patients taking irbesartan, a gradual decrease of the average PDC was depicted over a 1-year period from 59.7% (SD: 31.2) to 50.8% (SD: 30.3). 3 months after the pharmacist intervention it increased 17.2% to an average PDC of 68.0% (SD: 29.3). Finally, it decreased 4.8% 12 months after the intervention to 62.4% (SD: 32.5) (**Figure 2**).

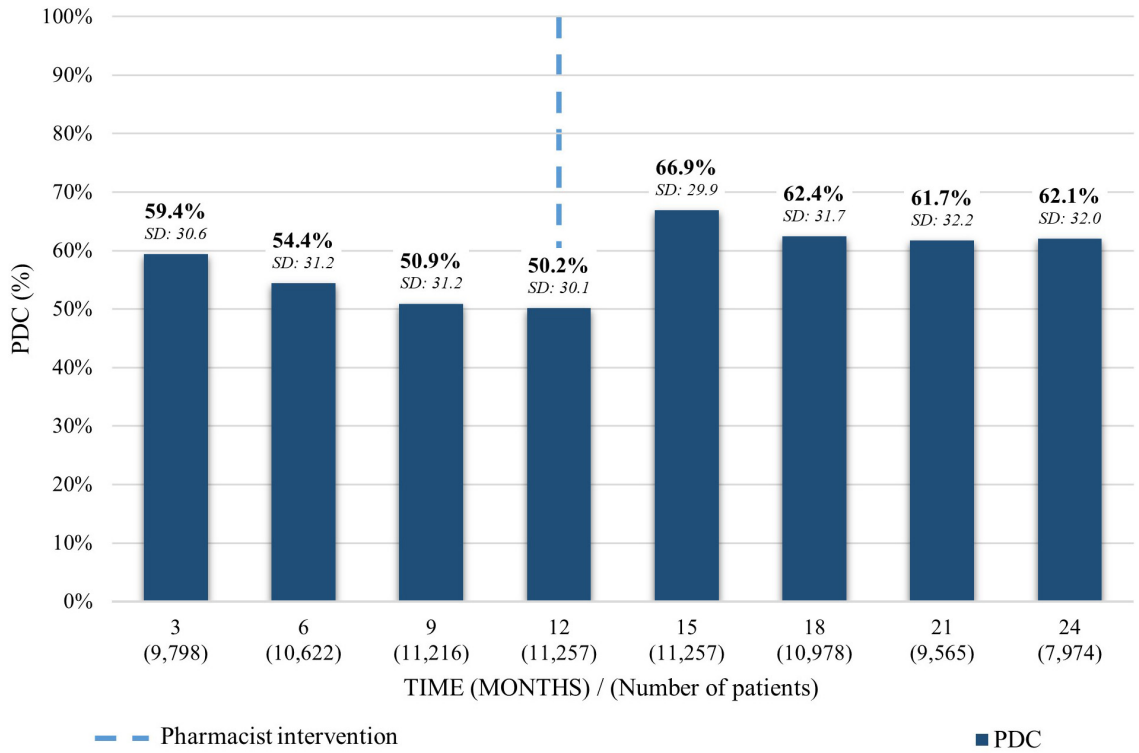

FIGURE 1 | Average PDC before and after the pharmacist intervention for patients taking rosuvastatin. Analysis performed in each trimester 12 months before and 12 months after the first intervention. Average PDC and Standard Deviation (SD) reported.

As for the average PDC on patients taking desvenlafaxine, a similar trend to the previous medications was observed. The PDC average declined on the first 12 months previous to the pharmacist intervention from 53.4% (SD: 29.9) to 47.3% (SD: 28.4). After the intervention, it increased 19% to 66.3% (SD: 27.3) and decreased 8.2% in the following 12 months to a PDC of 58.1% (SD: 31.1) (**Figure 3**).

Sensitivity analysis performed on patients claiming all dispensings in the affiliated pharmacies resulted in a similar trend with the PDC average increasing 15.7% from 59.0% (SD: 27.3) to 74.7% (SD: 27.7) after the pharmacist intervention and declining over the following 12 months on 9.6% to 65.1% (SD: 24.6).

Sub-Analysis – Proportion of Adherent Patients

The proportion of adherent patients 12 months before performing the intervention was 29.1% (n = 2,851 patients), 29.9% (n = 1,838) and 27.3% (n = 488) for rosuvastatin, irbesartan and desvenlafaxine, respectively. These percentages decreased along the first year of analysis before the intervention to 17.1% (n = 1,927), 18.0% (n = 1,223), and 17.1% (n = 391) before providing the intervention. An increase was observed 3 months after the first intervention with a proportion of 39.3% (n = 4,428), 40.2% (n = 2,734), and 44.1% (n = 1,006). Twelve months after the intervention, the proportion of adherent patients diminished to 34.5% (n = 2,750) for rosuvastatin, 35.6% (n = 1,761) for irbesartan and 35.8% (n = 522) for desvenlafaxine (**Figure 4**).

DISCUSSION

Big database analysis techniques were integrated to analyze the dispensing data of 20,335 patients across community pharmacies in Australia receiving an educational-based adherence intervention prompted by the dispensing software when an MPR below 70% was identified. Data was analyzed from 1805 different community pharmacies, which represents 31.9% of all community pharmacies across Australia (The Pharmacy Guild of Australia, 2018). Records of 12 months before and 12 months after a pharmacist intervention were included, allowing the use of "real-world" data to estimate medication implementation adherence for three drugs (rosuvastatin, irbesartan and desvenlafaxine) over time.

Trends observed before and after the intervention in each of the drugs showed: (1) a gradual decrease in average PDC rates during a 1 year pre-intervention, (2) an increase after the pharmacist's intervention was delivered, followed by (3) a subsequent decrease over time. This is consistent with previous evidence, which highlights the dynamic nature of medication adherence over time (Cooper et al., 2011; Blaschke et al., 2012; Demonceau et al., 2013). For example, a study analyzing medication adherence patterns of nearly 17,000 patients over a 1-year period revealed a gradual decrease in optimal implementation adherence by nearly 35% with approximately 40% of patients discontinuing their treatment (Blaschke et al., 2012). Another study analyzing dosing histories

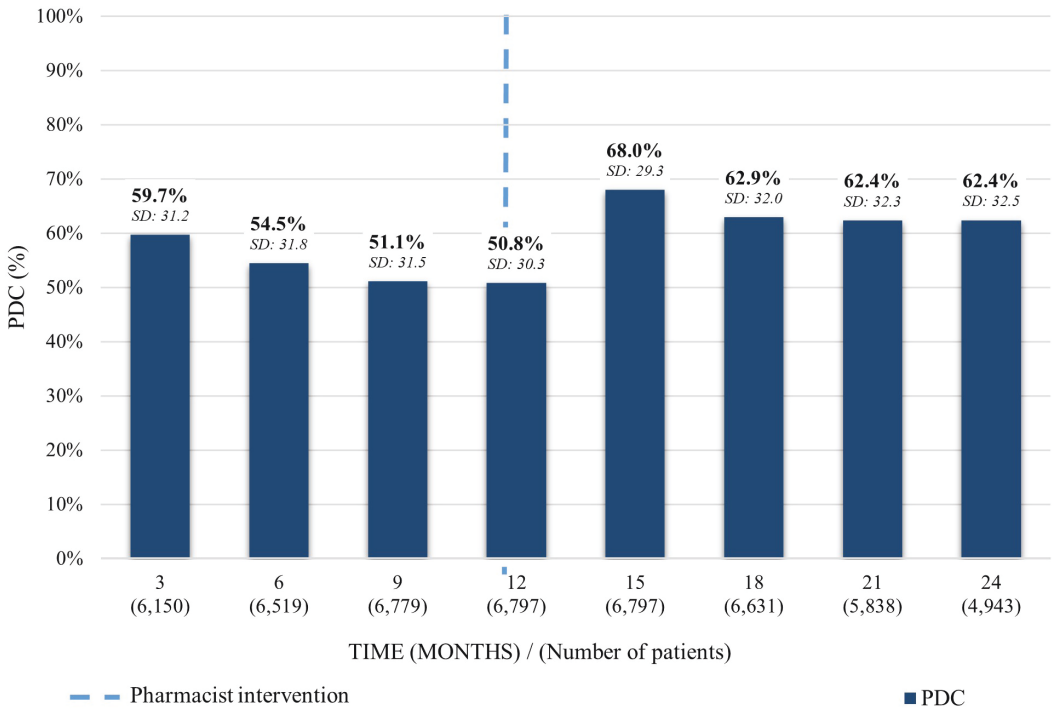

FIGURE 2 | Average PDC before and after the pharmacist intervention for patients taking irbesartan. Analysis performed in each trimester 12 months before and 12 months after the first intervention. Average PDC and Standard Deviation (SD) reported.

for hypertensive patients found that 50% of patients stopped the medications after 1 year and nearly 95% missed a dose in the year (Vrijens et al., 2008).

In terms of the effect of the pharmacist intervention, there was an increase in average PDC rates for all of the drugs after the intervention. These results align with findings from randomized controlled trials where medication adherence increases after a pharmacist intervention (Al-Jumah and Qureshi, 2012; Pousinho et al., 2016). A systematic review of interventions to improve medication adherence stated that counseling provided by health care professionals, such as pharmacists, could be not only effective but also cost-beneficial in improving medication adherence (Nieuwlaat et al., 2014). Also, face to face interventions, like the ones provided in community pharmacies, have a positive impact on enhancing medication non-adherence (Conn et al., 2016). Despite this amount of evidence, real-life effectiveness of these interventions once the evaluation phase is over remains unknown. Observational studies of implemented interventions, which usually rely on big data sources of patient registries and health records, are essential to determine whether patients in real-life practice are achieving the expected outcomes in a wider and more representative population. This implies they are crucial to assess the translatability of the results obtained in randomized controlled trials, providing key stakeholders like policy-makers evidence to support health care policies and funding allocation. Nevertheless, our study findings on real practice settings follow similar trends to those reported in randomized controlled trials.

The analysis of dispensing records after the pharmacist intervention showed an 8% decrease on average PDC 12 months after the intervention was delivered. Similar to our results, a recent meta-analysis found a 1.1% decrease in the effect of adherence interventions per month of follow-up, suggesting their impact tends to decline over time (Demonceau et al., 2013). Similarly, the number of adherent patients (PDC >= 80%) declined 1 year after the intervention. These results also align with previous evidence showing a diminution in the number of adherent patients to different chronic medications over time (Blaschke et al., 2012; Keyloun et al., 2017). This may suggest a need for continuous adherence interventions and sustained follow-up integrated into the patient's treatment plan. This would allow not only the identification of barriers in non-adherent patients, but also the monitoring of current or new risk factors in patients showing optimal adherence and the development of tailored strategies to minimize their impact. Adherence interventions and more continuous follow-ups can be implemented in standard community pharmacy dispensing practice. Community pharmacy is an ideal place to continue to evaluate and discuss adherence with a patient over time due to patients returning, often monthly, for their repeat prescriptions. In fact, pharmacists have been found to have a positive impact on medication adherence in different clinical conditions (Taitel et al., 2012; Pousinho et al., 2016).

With the majority of patients not reaching the common threshold of a PDC of 80%, there remains opportunity for improvement. Often, single component interventions only affecting one aspect of non-adherence are minimally effective

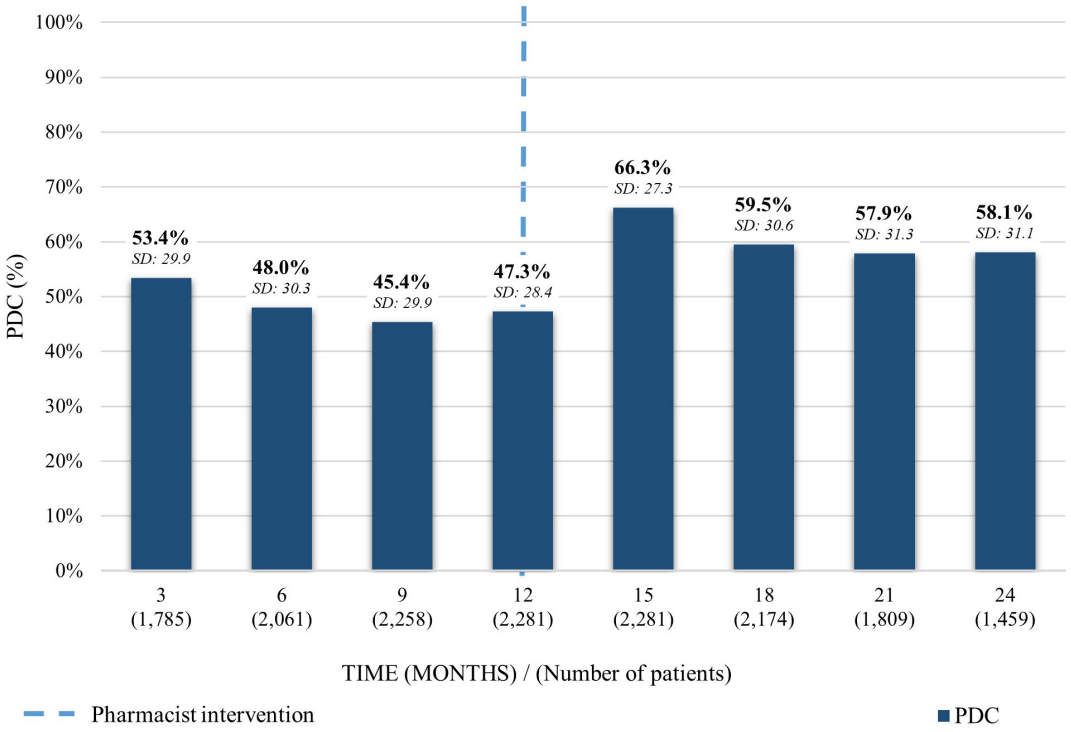

FIGURE 3 | Average PDC before and after the pharmacist intervention for patients taking desvenlafaxine. Analysis performed in each trimester 12 months before and 12 months after the first intervention. Average PDC and Standard Deviation (SD) reported.

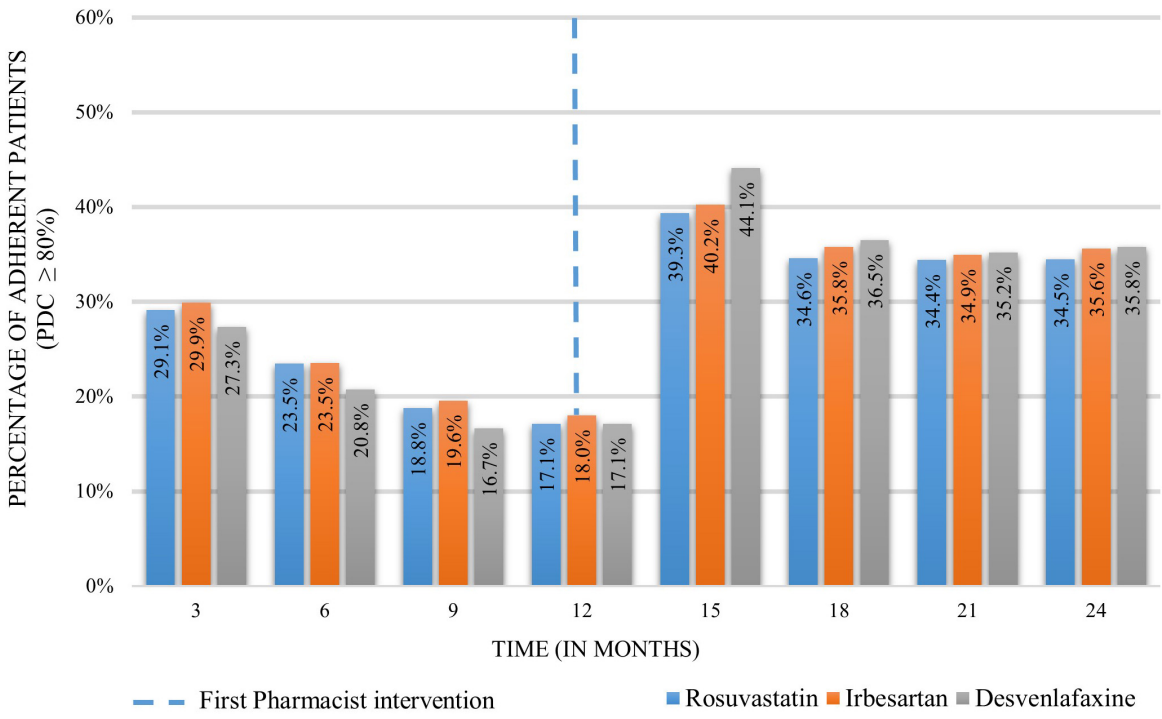

FIGURE 4 | Proportion of adherent patients 12 months before and 12 months after the pharmacist intervention.

(Choudhry et al., 2009). Medication non-adherence is a complex and multifactorial problem influenced by multiple determinants across different domains (Vrijens et al., 2012; Kardas et al., 2013). This might be the reason why complex and multicomponent interventions are often seen as the most effective strategies for improving adherence. Potential approaches to improve the current MedScreen Compliance GuildCare adherence intervention might include the use of the perceptions and practicalities approach, distinguishing between unintentional and intentional non-adherence (Horne et al., 2005). This would allow a more tailored approach to the problem, increasing the likelihood of success. Intervention for patients presenting unintentional non-adherence may target practical barriers through more technical components (i.e., interventions providing any gadget, instrument, or system that facilitate the medication intake or increase convenience of the medication taking process). Some examples include helping patients to adopt routines of medication taking trough SMS reminders or alarms (Vervloet et al., 2012; Thakkar et al., 2016). In contrast, intentional non-adherence is related to perceptual factors like lack of motivation or beliefs toward the medication therapy (Horne et al., 2005). Interventions for patients with intentional non-adherence may consider targeting behavioral intention based on modifying patient's attitudes and beliefs through the use of evidence-based frameworks such as the necessity and concerns framework (Clifford et al., 2008) or motivational interviewing (Levensky et al., 2007). A combination of both of the above mentioned scenarios might also be possible, requiring interventions with multiple components (Nieuwlaat et al., 2014). In a recent network meta-analysis, multicomponent interventions were found to have the most effective long-term improvement on adherence.

The conservative estimates of using PDC, averaging approximately 67%, produced well below considered "adherent" rates in patients, generally accepted at 80% or greater (Sodihardjo-Yuen et al., 2017). From previous research, PDC has been affirmed to be a more accurate and conservative representation of adherence compared to MPR (Martin et al., 2009). This allows the suggestion that while a MPR monitoring in real-time is helpful, a PDC calculation may be more valuable as the latter accounts for overlapping days and medication switch, two very likely conditions to happen in these community pharmacies. Therefore, measurement of medication adherence can be more consistent and accurate in this particular setting and a better intervention can be provided.

There were some limitations to this analysis. Dispense records were only associated to the pharmacy where patients were intervened. If the patient claimed a medication in a different pharmacy, this data was not recorded in this database. Because of this, it is not possible to know if patients actually discontinued their treatment. This is why only implementation adherence was reported, accounting from the first to the last available dispensing record. However a sensitivity analysis was performed on patients claiming all dispensing's in the affiliated pharmacies. Additionally, while these results showed an improvement in adherence implementation shortly after the intervention was performed, we must also crucially consider the variability of the intervention between pharmacists and pharmacies. As this was retrospective data, no fidelity measures were able to be used to understand the full extent of the execution of these adherence interventions. Conversely, this could be found as a strength of the study as this was real-life practice with no trial variables impacting the results. At the very least, these interventions cause a pharmacist to alert a patient when they are seemingly non-adherent. Feedback interventions similar to this has shown success in other studies and meta-analyses, questioning if the feedback or the actual educational approach of the intervention is the most effective (Demonceau et al., 2013). To our knowledge, this is the first study utilizing big data analysis techniques to determine the effectiveness of a community pharmacy intervention in a real-life setting in Australia. Future research in this area could further explore on the determinants of PDC decreases over time.

CONCLUSION

Integration of big database analysis techniques of dispensing records from community pharmacies across Australia provided results on implementation adherence before and after a pharmacist intervention within usual practice. Sub-optimal implementation adherence is a prevalent problem with the average PDC decreasing over time. An increase on average PDC was observed after the intervention, with a steady decline over time for each one of the drugs analyzed. Establishing follow-up mechanisms, enhancement of the intervention using an evidence based approach and incorporating a more accurate method for the real time analysis of dispensing data by using big data techniques would assist community pharmacists in improving medication adherence.

AUTHOR CONTRIBUTIONS

VG-C, SB, AT-R, EW, and RC contributed to the design of the study. BD organized the database and contributed to data analysis. AT-R performed the data analysis. AT-R, EW, and VG-C wrote the first draft of this manuscript. VG-C, SB, AT-R, EW, RC, BD, and FF-L contributed to manuscript revision, read and approved the submitted version.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Chapter 4

Effectiveness of a medication adherence management service in a community pharmacy setting. A cluster randomised controlled trial

Chapter 4 describes the results of a cluster randomised controlled trial to evaluate the impact of a medication adherence management service on medication adherence and disease-specific clinical outcomes in community pharmacies in Spain.

This chapter is presented as an accepted version for publication in the journal *BMJ Quality and Safety*. dx.doi.org/10.1136/bmjqs-2020-011671

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ABSTRACT

Background

Non-adherence to medications continues to be a burden worldwide, with significant negative consequences. Community pharmacist interventions seem to be effective at improving medication adherence. However, more evidence is needed regarding their impact on disease-specific outcomes. The aim was to evaluate the impact of a community pharmacist-led adherence management intervention, on adherence and clinical outcomes in patients with hypertension, asthma and Chronic Obstructive Pulmonary Disease (COPD).

Methods

A six-month cluster randomised controlled trial was conducted in Spanish community pharmacies. Patients suffering from hypertension, asthma and COPD were recruited. Patients in the intervention group received a medication adherence management intervention and the control group received usual care. The intervention was based on theoretical frameworks for changing patient behaviour. Medication adherence, disease-specific outcomes (Asthma Control Questionnaire (ACQ) scores, Clinical COPD Questionnaire (CCQ) scores and blood pressure levels) and disease control were evaluated. A multilevel regression model was used to analyse the data.

Results

Ninety-eight pharmacies and 1,186 patients were recruited, with 1,038 patients completing the study. Patients receiving the intervention had an Odds Ratio of 5.12 (95%CI: 3.20 to 8.20, $p<0.05$) of being adherent after the six months. At the end of the study, patients in the intervention group had lower diastolic blood pressure levels [Mean Difference (MD): -2.88 (95%CI: -5.33 to -0.43), $p=0.02$], lower CCQ scores [MD: -0.50 (95%CI: -0.82 to -0.18); $p<0.05$] and lower ACQ scores [MD: -0.28 (95%CI: -0.56 to 0.00); $p<0.05$] when compared to the control group.

Conclusions

A community pharmacist-led medication adherence intervention was effective at improving medication adherence and clinical outcomes in patients suffering from hypertension, asthma and COPD. Future research should explore the implementation of these interventions in routine practice.

Trial registration ACTRN12618000410257

Keywords: Medication adherence, chronic diseases, cluster randomised trial, clinical outcomes, COPD, asthma, hypertension, community pharmacy, pharmacy practice, adherence interventions

INTRODUCTION

Patients with chronic conditions rely on medications to treat and control their diseases.[1] However, medication adherence (i.e. the process by which patients take their medications as prescribed) is sub-optimal.[2] Medication adherence is composed of *initiation*, *implementation,* and *discontinuation*.[3,4] There is evidence that nearly 40% of patients with chronic conditions discontinue their medication after one year and 4% never initiate their treatment.[5] Similarly, implementation of the dosing regimen (i.e. the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen) has been shown to decline over time.[6] This complex phenomenon is a preventable[7] source of patient harm and poor health outcomes. It often leads to disease progression, lower quality of life, increased use of healthcare resources,[8] and increased morbitidy and mortality.[9,10] It accounts for an estimated 125,000 deaths per year in the USA,[11] with annual costs per patient ranging from $949 to $44,190 ($US2015).[12] This problem is especially relevant in chronic conditions such as hypertension, asthma and COPD, three of the most prevalent non-communicable diseases in developed countries, whose prevalence continues to increase.[13-15] Medication non-adherence rates in these conditions are high, reaching 50% for antihypertensive medications[5] and between 20-80% for inhaled medications,[16,17] with 14-20% patients failing to fill in their first prescription.[18]

Medication adherence interventions have the potential to improve clinical outcomes, patient's health-related quality of life[19,20] and the efficiency of the healthcare system.[21-23] Long-term multicomponent interventions involving behavioural change theories seem promising at improving adherence,[24-26] probably because they target multiple determinants.[27] However, previous research has reported a lack of convincing evidence regarding the efficacy of these interventions, mainly due to the wide heterogeneity in settings, participants, intervention types, or adherence measures among others. Moreover, there seems to be a paucity of randomised controlled trials reporting an improvement in both adherence and clinical outcomes,[28] despite ethical standards for adherence research dictating that attempts to improve adherence should be judged by their clinical benefits.[28] In this regard, some evidence suggests that community pharmacist-led interventions may enhance both medication adherence[29-32] and disease-specific clinical outcomes. [33,34] However, these usually involve interventions that would be difficult to implement in usual care settings. The development of effective interventions that are implementable in routine practice settings still represents a challenge for quality improvement in patient care.[35]

Quality use of medicines is often included as a key objective in many national medicines policies, through the implementation of initiatives aiming at ensuring medicines are safely and effectively used. This usually include mechanisms to monitor and manage medication adherence, which constitutes one of the overarching goals to improve healthcare quality and patient safety.[36] In Spain, adherence management is one of the six professional services with national priority following a consensus among Spanish national professional pharmacy organizations,[37] However, there is a lack of evidence on the effectiveness of a medication adherence intervention that can be further implemented into regular practice.

The objective of this study was to evaluate the effectiveness of a community pharmacist-led medication adherence management intervention for adult patients

being treated with hypertension, asthma or COPD medications on medication adherence and clinical outcomes compared to usual care.

METHODS

This study has been reported following the CONSORT guidelines for cluster randomised trials.[38]

Study design

A cluster randomised controlled trial was undertaken in community pharmacies across six Spanish provinces (A Coruña, Albacete, Ciudad Real, Guadalajara, Soria and Tenerife), representing about 12% of the provinces and 7% of community pharmacies in Spain.[39] Pharmacies were the unit of randomisation to minimize cross-contamination between study groups. A study protocol has been registered and approved by the Spanish Medication Agency (Agencia Española de Medicamentos-4DZRC79213). No incentives were provided to pharmacists or patients.

Pharmacy Recruitment

An invitation letter to enrol in the study was sent to all the pharmacies in each province by the local pharmacy professional body. The inclusion criteria for pharmacies were: availability of a counselling area; availability of at least one pharmacist to provide the intervention and; the attendance of all pharmacists to an initial training session before the beginning of the study. Inclusion criteria were verified by the local pharmacy professional bodies and by members of the research team. Due to the nature of the intervention, cluster-randomization was used to minimize cross-contamination between study groups. Eligible pharmacies were the unit of randomization. They were assigned by an independent researcher after they agreed to participate in the study to either an intervention (IG) or control group (CG), using a computer-generated list of random numbers with ratio 1:1.

Sample size calculation/Sampling

Sample size calculations were based on the difference of expected proportions between adherent patients in control and intervention groups at the end of the

study. An absolute difference of 20% in the prevalence of adherent patients between both groups was considered of clinical relevance.[40,41] A two-tailed comparison test was applied, considering an 80% power, alpha=0.05 and assuming a 50% prevalence of non-adherent patients at baseline[58].

The sample size was increased to take into account the design effect (DEFF), calculated as: DEEF= 1 + [*nc* - 1]*ICC (Intraclass Correlation Coefficient) (where *nc*=7, average size of the cluster estimated for 102 clusters; *ICC*=0.05), resulting in 1,025 patients. This number was increased to account for a potential 20% loss to follow-up. Therefore, 1,230 patients and 102 pharmacies were estimated to be required. Each pharmacy was required to recruit 12 patients: four suffering from hypertension, three from asthma and three from COPD.

Patient Recruitment

Patients were recruited consecutively in the participant community pharmacies for two months. Filling a prescription (for new or/and existing prescribed medications) was the prompt for the pharmacist to initiate a conversation about the study with potential eligible patients. Patients' inclusion criteria were: 18 years or older; signature of the informed consent; ability to complete EuroQol-5D,[42] Morisky-Green-Levine medication adherence questionnaire (MGL MAQ),[43,44] Asthma Control Questionnaire (ACQ)[45] or Clinical COPD Questionnaire (CCQ)[46] and; to have a prescribed a medication for hypertension (i.e. medications included in the Anatomical Therapeutic Chemical Classification System (ATC) groups CO2, CO3, C07, C08 or C09), asthma or COPD (ATC group R03). Medication groups were defined as per the ATC classification system developed by the World Health Organization (WHO).[47] Hypertension, asthma and COPD were the target conditions due to their high prevalence and non-adherence rates.[13-15] If patients suffered from more than one of those diseases, data was only collected for one condition. This was selected by the pharmacist on the basis of the number of patients to be recruited per disease. Patients were excluded if they: were collecting someone else's medication; were pregnant or lactating; could not attend the pharmacy on a regular basis; had previously participated in any adherence education program or study; had

communication limitations or any other impairment the recruiting pharmacist considered as precluding them from participating in the study. During recruitment, the pharmacist explained the general characteristics of the study (i.e. study involving monthly visits to the pharmacy, in which patients had to respond to pharmacist's questions about their medications and health), assessed the patient's willingness to participate and their eligibility criteria. Patients were blinded to the study design, group and hypotheses. Patients willing to participate received an information sheet and their signed informed consent was obtained. Subsequently, the pharmacist and the patient agreed on a date for the initial and subsequent visits.

Patients attended six face-to-face monthly visits, undertaken in the pharmacy's counselling area. Patients allocated to the intervention group (IG) received a protocolised medication adherence management intervention (Figure 1) whereas patients in the control group (CG) received usual care (defined as the supply of medicines and medication-taking advice). In each visit, patients' data was collected and clinical variables recorded.

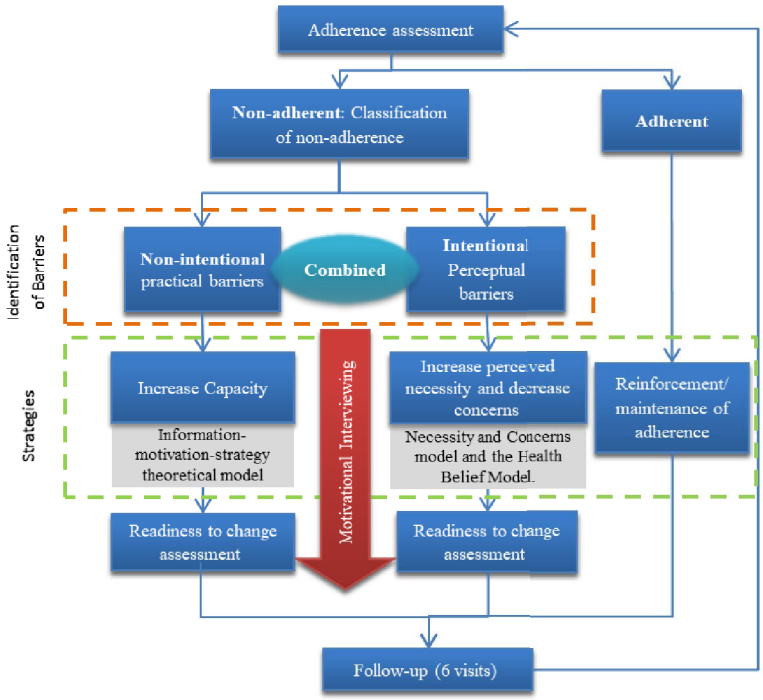

Figure 1. Adherence management service intervention Overview

Intervention group (IG)

Patients in the IG received the medication adherence management intervention. It involved the provision of a complex intervention,[48] based on behaviour change frameworks, aiming at identifying and addressing barriers for medication adherence through tailored strategies. The intervention included:

1. Pharmacist interview to assess adherence to medications for asthma, COPD or hypertension, using the MGL MAQ.[43,44]
2. Classification of patients as non-adherent (non-intentional, intentional or combined) or adherent.
3. Identification of barriers for medication adherence. Barriers could be practical, defined as gaps in knowledge or skills; or perceptual, namely those associated with patient's health beliefs and perceptions about the condition and their medications.
4. Intervention proposal, using strategies tailored to the type of non-adherence and identified barriers (Supplementary appendix 1).
5. Application of the Transtheoretical Model of behavioural change[49] by which the pharmacist elicited the patient's readiness to change whilst discussing the proposed strategies.[50]
6. Follow-up through monthly scheduled visits to review patient progress and provide feedback or new strategies to improve or maintain adherence.
7. Application of motivational interviewing principles and skills,[26,51] during the patient-pharmacist interaction.

Pharmacists training

Group and individualised training sessions were provided by the research team and by Practice Change Facilitators (PCFs, external pharmacists who solved any problems or queries during the study through monthly visits and ensured compliance with the study protocol). Pharmacists in the IG received an initial training which covered the following topics: study protocol, management of the targeted conditions, frameworks for changing patient behaviour, and educational skills to provide the

intervention, over a two-day session. Pharmacists in the CG were only trained in data collection and study procedures.

Study outcomes

Medication adherence (appropriate implementation of the dosing regimen) was the primary outcome, assessed by the MGL MAQ[43,44] and reported as the percentage of adherent patients. Secondary outcomes included asthma control, COPD clinical health status and hypertension control. Asthma control was assessed using the ACQ-5.[45] Results were reported as mean ACQ scores (scale 0-6, with lower scores indicating a better clinical control) and as the percentage of controlled patients (ACQ ≤0.75). A difference of ≥0.5 in mean scores was considered clinically significant.[52] COPD clinical health status was assessed using the CCQ.[46] Results were reported as mean CCQ scores (scale 0-6, with lower scores indicating a better clinical control) and as the percentage of patients with low clinical impact of the disease (Scores <1.0)[53]. A difference ≥0.4 between mean scores was considered clinically significant.[54] In COPD, "disease control" is not achieved, as normalisation of pulmonary function is not possible and patients may continue with exacerbations or limitations during daily life activities regardless of receiving treatment.[55] Hypertension control was assessed through systolic and diastolic blood pressure levels (SBP, DBP) using a Visomat®-Roche (2 measures, 3min interval). Proportion of controlled patients (values <140mmHg/90mmHg)[56] and mean blood pressure (BP) levels were reported. All outcomes were measured in all study visits.

EuroQol data was collected in order to assess the cost-utility of the service. Results will be reported elsewhere.

Blinding

Patients were blinded to the intervention but given the nature of the intervention pharmacists were not. Only pharmacists in the intervention group were trained in the skills and knowledge required to deliver the intervention.

Data Collection and Quality

Study data was collected in an electronic data collection form, accessible by individual pharmacists through a personal username and password. Pharmacists directly recorded patient demographic data and observer-reported outcomes not involving judgement (i.e. BP levels). Patient-reported outcomes (i.e. medication adherence, ACQ scores and CCQ scores) were directly collected from patients. They completed the questionnaires in the electronic data collection form, requesting assistance from the pharmacist if needed.

PCF monitored the quality of data entry and had their own access to the electronic data collection form to ensure data was being collected according to the protocol instructions.[57] Patient data was protected and exported as dissociated for the statistical analysis. Only de-identified data from patients, pharmacist and pharmacies was available to the study researchers.

Statistical analysis

Data was analysed using the software package SPSS statistics (V.25.0, SPSS Inc. Chicago. Illinois, USA) and SAS/STAT 9.4 (SAS Institute, Cary NC, USA). Baseline patient level information was summarized by treatment arm. A multilevel regression model with three levels (pharmacies, patients, visits) with a random intercept to account for the clustering by pharmacy and a correlation structure for the visits within patients that accounted for changes in correlation of measurements over time (Toeplitz). A logistic regression model was used with this structure to estimate the odds ratios for the binary outcomes, and a similar linear mixed model was used for continuous outcomes. A likelihood ratio p-value (for the overall effect of the variable across visits) and a Wald p-value for the test of treatment at each time point were estimated. Estimated rates with lower and upper levels were calculated. All patients with data collected from at least two time-points during the study were included in the analysis. Estimated population margins were used to estimate the percentage of patients for binary outcomes and the average value for continuous outcomes, by treatment and time-period. Linear and generalised linear mixed models for the study outcomes were used, allowing for the assumption of 'missing-at-random' (i.e.

missing contingent on values included in the regression model) without requiring imputation for the missing outcomes.

Ethics

This trial follows the Ethical principles for Medical Research involving Human Subjects (Fortaleza, 2013) and Good Clinical Practices (ICH/GCP) and International Council for Harmonisation. It was approved by the Ethics Committee of Research of Granada (CEI-Granada) (Register Number: 0021-N-17).

RESULTS

A total of 98 pharmacies and 138 pharmacists were recruited. Four pharmacies and four pharmacists dropped out from the study before starting patient recruitment and two pharmacies and three pharmacists dropped out during the study (n=4 IG, n=2 CG). Patient recruitment was undertaken by pharmacists between October and November 2017, with 1,186 patients enrolled (Asthma: 385, COPD: 299, hypertension: 502) and 1,038 patients (Asthma: 333, COPD: 249, hypertension: 456) completing the study (87.5%). 218 patients were ineligible due to exclusion criteria (Figure 2). Baseline patient characteristics are described in table 1.

VARIABLES	CONTROL GROUP (n= 553)	INTERVENTION GROUP (n= 633)	TOTAL (n= 1186)
Age, mean +/- SD	64.0 +/- 15.4	63.9 +/- 15.6	**64.0 +/- 15.5**
Gender, n (%)			
- Male	257 (46.5%)	303 (47.9%)	**560 (47.2%)**
- Female	296 (53.5%)	330 (52.1%)	**626 (52.8%)**
Education, n (%)			
- No studies	129 (23.3%)	146 (23.1%)	**275 (23.2%)**
- Primary	201 (36.3%)	258 (40.8%)	**459 (38.7%)**
- High school	125 (22.6%)	151 (23.9%)	**276 (23.3%)**
- Vocational degree	13 (2.4%)	9 (1.4%)	**22 (1.9%)**
- University	85 (15.4%)	69 (10.9%)	**154 (13.0%)**
Working status, n (%)			
- Paid employment	137 (24.8%)	138 (21.8%)	**275 (23.2%)**
- Paid employment but on sick leave	13 (2.4%)	21 (3.3%)	**34 (2.9%)**
- Unemployed	51 (9.2%)	62 (9.8%)	**113 (9.5%)**
- Retired	320 (57.9%)	374 (59.1%)	**694 (58.5%)**
- Student	32 (5.8%)	38 (6.0%)	**70 (5.9%)**
Clinical condition (n, %)			
- Asthma	180 (32.5%)	205 (32.4%)	**385 (32.5%)**

- COPD	154 (27.8%)	145 (22.9%)	**299 (25.2%)**
- Hypertension	219 (39.6%)	283 (44.7%)	**502 (42.3%)**
Medications prescribed for the studied disease*, mean (SD)	1.84 (0.98)	1.91 (1.08)	**1.88 (1.04)**
All prescribed medications, mean (SD)	5.72 (3.48)	5.69 (3.32)	**5.71 (3.39)**
Total number of diseases, mean (SD)**	2.58 (1.45)	2.55 (1.37)	**2.57 (1.41)**

SD: Standard Deviation, COPD: Chronic Obstructive Pulmonary Disease
**Hypertension, asthma or COPD*
***Number of all Chronic diseases per patient*

Table 1. Baseline characteristics of study patients

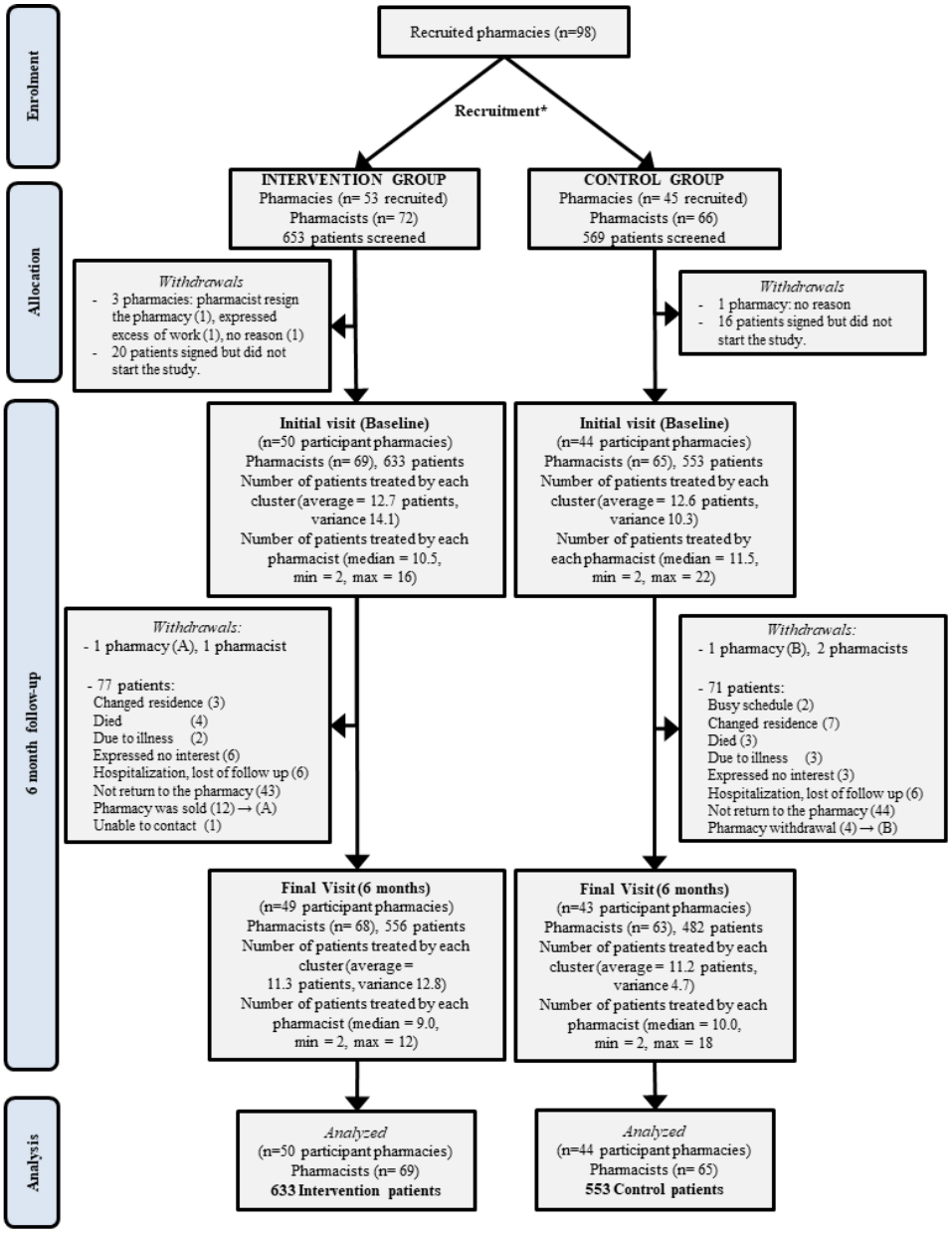

Figure 2. Study flowchart

Medication adherence

At baseline, the percentage of adherent patients was 39.1% (IG) and 44.3% (CG). For individual follow-up periods, significant differences between study groups were observed from visit 3 ($p<0.05$) to visit 6 [OR: 5.12 (95% CI: 3.20-8.20), $p<0.05$] (Appendix 2, Figure 3). Overall, the absolute increase in the percentage of adherent patients during the study was higher in the IG (51.8%) than in the CG (22.2%) ($p<0.05$). Disease-specific results are reported in the Appendix 3.

Clinical Control

Hypertension: Mean baseline BP levels were similar in both study groups. Mean differences (MD) DBP between IG and CG became statistically significant after visit 5 ($p<0.05$). At the end of the study, there was a significant reduction on mean DBP in the IG [MD: -2.88 (95% CI: -5.33--0.43), p=0.02]. Changes on SBP were not statistically significant [MD: -1.10 (95% CI: -4.49-2.29), p=0.53] (Appendix 2). Mean baseline percentages of controlled patients were similar in both groups (IG=55.5%, CG=52.9%). These percentages increased in both groups, with no difference between groups at the end of the study [OR: 1.22 (95% CI: 0.78-1.91), p=0.38] (Appendix 2, Figure 3).

Asthma: Mean baseline ACQ scores were similar in the IG and CG (p=0.98). A gradual decrease was observed in both groups until reaching significant differences in visit 5, favouring the IG ($p<0.05$). Mean scores decreased 0.53 (IG) and 0.26 points (CG) between baseline and visit 6. Only the diminution in the IG was clinically significant. At visit 6, mean ACQ scores were significantly lower in the IG [MD: -0.28 (95%CI: -0.56-0.00), $p<0.05$], indicating a better asthma control (Appendix 2). Percentages of controlled patients at baseline were similar (IG: 37.3%; CG: 43.8%). Statistically significant differences were evident after visit 5. Percentages of controlled patients at the end of the study were significantly higher in the IG (72.0%) when compared to the CG (57.8%) [OR: 1.88 (95% CI: 1.05-3.36), p=0.03] (Appendix 2) (Figure 3).

COPD: Mean baseline CCQ scores were 1.79 (IG) and 2.10 (CG) ($p<0.05$). Mean scores decreased in both groups across study visits, with significant differences being

evident after visit 3 (p<0.05) [MD: -0.50 (95%CI: -0.82—0.18), p<0.05] (Appendix 2). A reduction of 0.39 (CG) and 0.58 (IG) points in the mean scores was observed at the end of the 6-month period, with the latter being clinically significant. At baseline, percentages of patients with low clinical impact of the disease (i.e. low level of symptoms were 20.6% (IG) and 16.3% (CG) at baseline (Figure 3). These percentages increased across study visits in both groups, with significant differences favouring the IG after visit 3 (p<0.05). At the end of the study, the percentage of patients with low clinical impact of COPD was significantly larger in the IG [OR: 2.01 (95% CI: 1.07-3.75), p<0.05] (Appendix 2).

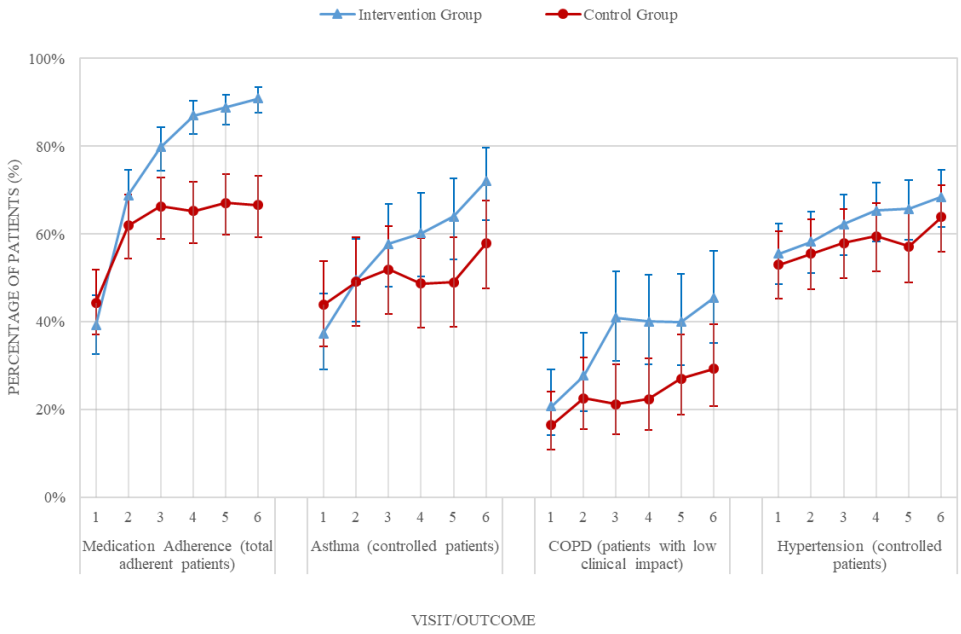

Figure 3. Percentage of patients estimated from multilevel model of categorical outcomes. Intervention vs. Control group. Error bars represent 95% CIs.

DISCUSSION

A community pharmacist-led medication adherence management intervention resulted in improvements in medication adherence and clinical outcomes. Significant increases in the percentage of patients adhering to their dosing regimen and improvements in COPD outcomes were evident after three months of follow-up. In the case of asthma outcomes and DBP significant improvements were observed after five months.

The observed baseline percentage of adherent patients, close to 50%, aligned with the figures previously reported by the WHO.[58] Interestingly, there was a gradual increase in these percentages, reaching statistically significant differences between study groups at visit 3. The percentage of adherent patients in the CG was found to remain constant during the following visits, always below 70%. In the IG, this percentage progressively increased during all study visits. At the end of the study, 90% of patients were adherent to their medications, doubling the baseline percentage in the IG and being nearly 25% more than in the CG. Previous studies assessing the effectiveness of pharmacists' interventions using a similar follow-up period have found between 10% to 40% increase in the percentage of adherent patients.[17,59,60] One study targeted patients using new prescribed medications found a 10% increase in the percentage of adherent patients after 10 weeks of follow-up, but decreased after 26 weeks.[61] This study consisted of one initial consultation and one follow-up consultation 5 weeks later.[61] Our study resulted in a larger increase (51.8%), probably due to the core components of the brief complex intervention, continuous follow-up, and fidelity monitoring of the intervention provision.

These results highlight the importance of continuous follow-up in medication adherence management. Evidence supports that interventions provided on a regular basis are more likely to increase adherence than a single intervention, signalling adherence management interventions are to be maintained as long as the treatment is needed.[28] Similarly, interventions delivered across multiple visits are more effective than those delivered during a single visit.[62] Our results align with these findings, suggesting adherence interventions should be delivered for at least three months to be effective.

There is evidence in the literature indicating that pharmacist-led interventions improve medication adherence in patients with asthma, COPD and hypertension.[32,63] However, limited information exists regarding the description of effective interventions, making it difficult to replicate these in real practice. There has been a call to generate more evidence on the impact of these interventions on disease-specific clinical outcomes.[28] Due to the negative impact medication non-adherence

has on patient's outcomes, adherence management has been considered a key element in the development of quality improvement initiatives.[35] Moreover, monitoring patient outcomes and medication management skills are essential when delivering interventions aiming at improving quality and safe medicines use.[64]

Core components of the intervention were based on evidence-based behaviour change frameworks, to tailor specific patient needs and elicit medication adherence improvement. Including cognitive-based behaviour techniques resulted in adherence improvements.[65] A recent meta-analysis stated the importance of cognitive and behavioural components to effectively change adherence behavior.[25] However, there is no evidence supporting that a single theory should be used.[66] We considered a range of strategies tailored to each patient's individual needs, including educational components or reminders, as they have shown to be effective in chronic conditions,[67,68] such as hypertension.[69] Our findings align with previous studies, which have shown increases in medication adherence and decreases in BP levels.[41,60,70,71] Although our intervention resulted on a larger increase in the proportion of controlled patients in the IG (12.8%) when compared to the CG, differences between study groups were not statistically significant at the end of the study. This could be due to the low mean baseline BP levels of included patients and to uncontrolled hypertension not being a patient inclusion criterion. Additionally, BP changes may also take longer to manifest, as differences in DBP levels started to be significant after five months of follow-up. Consistent with other studies that reported reductions of 3-11mmHg (DBP) and 7-30mmHg (SBP),[41,60,71-74] our study reported a reduction of 3.3mmHg SBP and 2.5mmHg in DBP levels. Non-adherence has been associated with a high DBP, thereby, an improvement of medication adherence can positively impact in DBP and hypertension control.[75-77]

Pharmacists' interventions in patients with respiratory conditions such as counselling and education have also found to be effective at improving clinical outcomes.[33] Our proposed intervention resulted in a larger increase in the percentage of controlled patients (34.7%), when compared to previous studies that reported 13-30%.[17,78] The reduction of 0.53 points in mean ACQ scores was clinically significant[52] and similar to

previous studies.[17,78] Similarly, an improvement on the average score and percentage of patients with low clinical impact of COPD was observed. Unlike previous studies,[40,79] our intervention resulted in clinically[54] and statistically significant differences in mean CCQ scores from visit 3 until the end of the study, indicating the intervention was effective at improving clinical outcomes in patients with COPD.

To the best of our knowledge, this is the first study proposing a medication adherence management intervention in community pharmacies in Spain using complex interventions based on theories and frameworks of behaviour change and reporting clinical outcomes; targeting one of the priority Spanish pharmacy services[37] and one of the key goals of healthcare.[35] The novelty of this study is the proposal of a structured patient-tailored pharmacist intervention based on evidence-based frameworks[25] and assessment of clinical variables in a community pharmacy setting. Although there is some evidence supporting the use of these frameworks in patients suffering from hypertension, it is limited for patients with asthma or COPD.

Practice Implications

Findings of this study provide evidence on the effectiveness of a patient-targeted intervention and support the future implementation of a medication adherence management service in regular practice.

Limitations

Objective adherence measures such as dispensing data could not be used. There was a lack of interoperability between pharmacies hindering the access to dispensing records. Therefore, only implementation adherence through a self-reported method was assessed, which may have been affected by desirability bias. Nonetheless, in the absence of a gold standard,[80] patient self-reported questionnaires have a close correlation with electronic monitoring devices.[81] Due to the nature of the intervention, pharmacists blinding was impossible. This is common in studies evaluating educational interventions. The intervention's design required the collection of data as part of the patient's evaluation and the provision of the intervention. Therefore, it was impossible to include a blinded data collector.

Blinding personnel and intervention providers is often not achievable for studies assessing educational interventions. Potential risk of bias derived from lack of blinding for pharmacists was minimised, as the main study outcomes were either participant-reported outcomes (i.e. patients, who were blinded to the study group) or observer reported outcomes not involving judgement.

Positive effects were also observed in the CG for medication adherence, asthma and COPD control during the first two months of study. Patients often modify their behaviour when feeling observed (i.e. Hawthorne effect). Moreover, data collection could have made patients more conscious of their behaviours and have impacted their health. Finally, control pharmacists may have provided more information than they would provide during usual care, even if they were instructed not to change their regular practice.

CONCLUSION

A structured patient-targeted intervention based on behavioural change frameworks and the assessment of clinical variables proved to be effective at improving medication adherence and disease-specific clinical outcomes in patients with hypertension, asthma and COPD. Overall, intergroup differences were significant after three months of follow-up, highlighting the importance of continuous monitoring in the management of medication adherence. This study proposes an approach to address patient safety and quality of care through adherence management. Integrating prescribing and pharmacy data would increase the potential of the intervention by measuring all dimensions of medication adherence. Future research should explore the implementation of these interventions in routine practice.

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Declaration of Interests

The authors of this paper do not have conflicts of interest in this study.

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Chapter 5

Evaluation of the impact of a community pharmacist-led medication adherence management service on inhaler technique in patients with asthma and COPD

Chapter 5 describes the results of a sub-analysis conducted on patients suffering from asthma and COPD and using inhaled medications (main drug therapy in these conditions). This study evaluates the impact of a medication adherence management service on inhaler technique performance.

This chapter is presented as paper to be submitted to the Journal *Journal of Asthma.*

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ABSTRACT

Background: As inhaled medications continue to be the main treatment for patients suffering from respiratory diseases such as asthma and COPD, it is therefore important to ensure patients use them correctly. However, the literature reports that incorrect inhaler technique is prevalent. Interventions aiming to improve adherence to inhaled medications may also have an impact on inhaler technique.

Methods: A sub-analysis was undertaken of patients with inhaled medication for asthma and COPD recruited during a six-month cluster randomised controlled trial evaluating a medication adherence management service in Spanish community pharmacies. The service was a multi-component intervention based on theoretical frameworks for changing patient behaviour. Inhaler technique (device-specific checklists) and disease-specific outcomes (assessed with Asthma Control Questionnaire and Clinical COPD Questionnaire) were measured. Data was collected through pharmacist observation and self-reporting at each of the six-monthly visits and analysed with a multilevel regression model.

Results: 652 patients (IG: 336, CG: 316) were included in the sub-analysis. Patients in the intervention group had an odds ratio of 4.57 (CI: 2.18-9.60) and 4.01 (CI: 1.89-8.60) times having "total" and "critical" correct inhaler technique at the end of follow-up. Patients in the intervention group also had 1.93 (CI: 1.06-3.52) and 1.92 (CI: 1.03-3.56) times the odds of having asthma control and COPD low clinical impact, respectively.

Conclusions: A medication adherence management service provided by community pharmacists resulted in the improvement of inhaler technique and associated disease outcomes in patients with asthma and COPD. Future research should focus on the implementation of this service.

Keywords: Medication adherence intervention, chronic diseases, inhaler technique, inhaled medication, asthma, COPD.

Background

Chronic respiratory diseases represent a global burden with negative economic implications for health care systems (1). These conditions represent the third cause of death for non-communicable diseases, with Chronic Obstructive Pulmonary Disease (COPD) accounting for 2.93 million and asthma 420,000 deaths in 2016 (2). The global prevalence of COPD is 11.7% in 2010. For asthma, it ranges between 1-18% of the global population as reported in 2012 (3, 4).

While not curable, the long-term goals of asthma and COPD management include the reduction of symptoms, prevention of disease progression, improvement of health status, minimisation of risks of exacerbations and reduction of mortality (3, 4). Pharmacological treatment through inhaled medications in combination with self-management strategies has become the cornerstone of their management, allowing the drug to reach the site of action, maximising its effectiveness and reducing side effects (3, 4). Optimal inhaler technique may aid to improve patient-related outcomes (e.g. asthma control, number of COPD exacerbations and quality of life) (5). Despite inhaler technique training and education for patients being recognised as a key element in the management of respiratory diseases (6, 7), poor inhaler technique is a prevalent problem (7-10). A systematic review analysing 40 years of inhaler technique found that more than 60% of patients fail to use their inhaler device correctly (6). The consequences of poor inhaler technique involve an increased risk of hospitalisation, poor disease control and waste of healthcare resources (7, 11). Optimal inhaler technique is fundamental to achieve therapeutic outcomes and adherence (e.g. implement the prescribed dose) (12). It is now, therefore, recommended that educational strategies to improve symptom control and risk reduction should include the continuous assessment and monitoring of medication adherence and inhaler technique (3, 4).

A Cochrane review analysing interventions to improve inhaler technique reported high variability in the core components of interventions and the method of inhaler technique assessment, making it challenging to assess the evidence on the impact of

these interventions on clinical outcomes (13). These interventions generally involve the provision of information and education (8, 14). However, additional components such as behaviour change strategies based on theoretical frameworks, which may reinforce the patient's empowerment and inhaler technique maintenance over time (15) are often not considered. Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma (GINA) guidelines recommend the assessment of inhaler technique and adherence to medications as part of the management of patients with COPD and asthma (3, 4). The development and evaluation of innovative educational approaches that combine both components seem therefore, appropriate. It has also been recommended that sufficient study duration (at least six months) to monitor clinical outcomes and more useful measures inhaler technique assessment (e.g. proportion of patients with correct inhaler technique, the proportion of patients with correct critical steps) should be considered when developing and evaluating interventions aimed at managing inhaler technique (13).

Among healthcare providers, community pharmacists have the potential to deliver interventions for patients with respiratory conditions (16-18). Previous studies have addressed the impact of community pharmacist-led interventions on inhaler technique (19-23). However, research is needed to identify the optimal frequency of assessment of inhaler technique and provision of interventions (24). A recent systematic review found that community pharmacists-led interventions based on information, motivation and behavioural skills are effective at improving adherence and inhaler technique. Nonetheless, more evidence is required of the validation of these interventions in clinical practice (25) and if there are benefits of the intervention on patient outcomes.

Aim of the study

The aim of this study is to evaluate the effectiveness of a medication adherence management service on inhaler technique performance and disease clinical control in adult patients suffering from asthma and COPD compared to usual care.

Methods

This paper reports a sub-analysis aiming at evaluating the impact of the adherence management service on inhaler technique performance in patients with asthma and COPD (Figure 1).

Methods of the main study

Design and Setting: The main study was a six-month (October/2017-April/2018) cluster randomised controlled trial aiming at assessing the effectiveness of a community pharmacist-led medication adherence management service at improving adherence and disease-specific clinical outcomes on patients with medications for treating hypertension, asthma and COPD (Chapter 4). The trial was undertaken in community pharmacies located in Spain in the provinces of A Coruña, Albacete, Ciudad Real, Guadalajara, Soria and Tenerife.

Pharmacies and Patients: All the pharmacies in the participating provinces received an invitation letter from the College of Pharmacy to enrol in the study. Pharmacies' inclusion criteria were: 1) a counselling area for initial and follow-up visits; 2) at least one pharmacist in a participating pharmacy to deliver the intervention protocol and 3) the attendance of all pharmacists to training. An independent researcher randomly assigned eligible pharmacies to either the intervention group or control group using a computer-generated list of random numbers, with a ratio 1:1. To minimise cross-contamination between study groups, pharmacies were the unit of randomisation. Patients' inclusion criteria were: 1) age ≥18 years; 2) to have signed and returned informed consent; 3) to be able to complete questionnaires to measure the study outcomes; 4) were prescribed a medication for; blood pressure, asthma (group R03) or COPD (group R03). Patients were excluded if they: 1) were collecting someone else's medication; 2) were pregnant or lactating; 3) could not attend the pharmacy on a regular basis; 4) had previously participated in any education program or study related to the improvement of adherence to medications; 5) if the pharmacist judged that the patient had communication limitations or any other

impairment to preclude them from participating in the study. The sample size was estimated for the main study and not for the sub-analysis (post hoc sub-analysis).

All patients attended monthly face to face visits for six months which took place in a counselling area of the pharmacy. Patients in the intervention group (IG) received the medication adherence management service with part of the service being assessment and monitoring of inhaler technique, whereas patients in the control group (CG) received usual care. Usual care was defined at the safe supply of medicines and medication-taking advice.

This trial was approved by the Ethics Committee of Research of Granada, Spain (CEI-Granada) (Register Number: 0021-N-17).

Intervention group - Medication Adherence management service: The service involved the provision of a brief complex intervention based on evidence-based theories of change behaviour aiming at identifying patients' specific barriers to non-adherence and proposing strategies to those barriers. The details of the intervention have been previously described elsewhere (Chapter 4). The inhaler technique educational component had the following elements: 1) During the visit, the pharmacist asked the patient to demonstrate the inhaler technique and assess it against device-specific checklists. All the checklists were stored and displayed in an electronic data collection form (eCRD). Checklists for dry powder inhalers, mist inhalers and pressurised metered-dose inhalers with and without mask were included. If the patient had multiple inhaled medications, they were asked to demonstrate the technique for all inhalers. 2) The patient was then classified as having correct or incorrect inhaler technique. 3) Pharmacist and patient identified barriers for not achieving a correct inhaler technique. 4) Strategies associated with previously identified barriers were offered through eCRD, and the patient and pharmacist agreed on the one(s) to follow. A combination of educational, oral and/or written instructions on the correct performance were available. 5) The patient received follow-up and inhaler technique reassessment on a monthly basis during six-monthly visits.

Control group – Usual care: Patients in the control group followed monthly visits for the six-month visits with the pharmacist, but only data collection and usual care were undertaken.

Training of pharmacists: All pharmacists were trained in the protocol and data collection. Only those assigned to the intervention group received group and individualised training. Group training was delivered by the research team and focused on adherence management, the delivery of professional pharmacy services, theoretical frameworks, clinical knowledge and educational skills needed to intervene with non-adherent patients. Specific training on knowledge on inhaled medication and inhaler technique was provided. These sessions had a combined duration of approximately 10 hours split across two days and included workshops and role-play sessions.

Blinding: Given the nature of the intervention and randomisation, patients were blinded but not pharmacists.

Data Collection and Quality: Pharmacist collected and recorded data for all patients in an electronic data collection form (eCRD) designed specifically for this study and were accessible to the pharmacists prior to and during the monthly visits. Disease outcomes were collected across every visit, whereas inhaler technique was collected on visits 1, 3 and 6. Control and intervention pharmacists had a different program of the eCRD with the control group having no access to the intervention module. Personal patient data registered on the eCRD was protected and exported as dissociated to the statistical analysis and study. The final, clean, data set was available to researchers only. Practice Change Facilitators (PCF) (26) provided ongoing support to pharmacists and monitored quality and fidelity to the intervention.

Methods specific to the sub-analysis

Study Patients: For the sub-analysis conducted in this paper, patients were included if they had asthma or COPD and were using inhaled medications (including at least one preventer/controller inhaler).

Inhaler technique – Primary outcome: Proportion of patients with correct inhaler technique was the primary outcome of the sub-analysis. Checklists and critical steps were identified based on previous literature (11, 27-30). Device-specific inhaler checklists were used to assess the inhaler technique of patients suffering from COPD and asthma during visits 1, 3 and 6. Critical steps were also identified, defined according to Usmani et al., "as those steps that if not performed correctly can become a critical error, an action or inaction that in itself would have a definite detrimental impact on the delivery of the drug to the lung" (11). Those devices where critical steps had not been previously identified were analysed based on other devices and defined as optimal critical steps (Supplementary Material 1). Two researchers (ATR, MVM) conducted the identification of critical steps. A categorical variable 'correct inhaler technique' was defined as the proportion of patients with the correct technique when analysing all the checklist steps (total correct inhaler technique); or only critical steps (critical correct inhaler technique). For patients with more than one inhaler, correct inhaler technique was defined as the total of steps correct for all the inhalers.

Clinical impact – Secondary outcome: Asthma control was assessed using the validated Asthma Control Questionnaire (ACQ) (31), where a value of 0.75 or less was indicative of good control of asthma. The proportion of controlled patients was analysed in both groups as a categorical variable, and the total score as a continuous variable. For COPD, the Clinical COPD Questionnaire (CCQ) (32) was used. A score of <1.0 has been considered a better health status (33). Results were reported as the proportion of patients with CCQ score <1 as a categorical variable, and total score as a continuous variable.

Statistical analysis: Quantitative and qualitative data were analysed by using the software package SPSS statistics (V.25.0, SPSS Inc. Chicago. Illinois, USA), MySQL Workbench 8.0 and SAS/STAT 9.4 (SAS Institute, Cary NC, USA). Baseline pharmacy and patient level information will be summarized by treatment arm. To account for within-cluster correlation, multilevel models were used with a random intercept for pharmacies, and a Toeplitz covariance structure for repeated measurements of

patients within pharmacies. A logistic regression model was used with this structure to estimate the odds ratios for the binary outcomes, and a similar linear mixed model was used for continuous outcomes. A Wald p-value for the test of treatment at each time point was estimated. Estimated rates with lower and upper levels were calculated. All patients with data collected from at least two time-points during the study were included in the analysis. Estimated population margins were used to estimate the proportions of patients for binary outcomes and the average value for continuous outcomes, by treatment and time-period. An analysis of the treatment effect across age groups, the number of inhalers and inhaler type was also conducted.

Results

Ninety-eight pharmacies and 138 pharmacists were recruited across the six Spanish provinces (IG: 53, CG: 45). Four pharmacies and four pharmacists dropped out before the patient recruitment and 2 pharmacies and 3 pharmacists during the study. A total of 1186 patients were recruited in the main study (Chapter 4) and 652 (IG: 336, CG: 316) were part of the corresponded sub-analysis. After the six-month follow-up, 557 patients completed the study (85%) (Figure 1). Baseline patients' characteristics are described in Table 1.

Primary outcome – Inhaler technique

Total correct inhaler technique – all steps: At baseline (visit 1), 38.3% of patients in the CG and 27.5% of patients in the IG had a correct inhaler technique [OR: 0.63 (95% CI: 0.32–1.25), p=0.18]. These proportions increased in both groups at visit 3 (CG: 64.5%, IG: 77.5%, p<0.0001) and visit 6 (CG: 72.1%, IG: 92.2%, p<0.0001). At the end of the study, the odds of having a correct inhaler technique was significantly higher in the IG compared to the CG [OR: 4.57 (95% CI: 2.18-9.60), p<0.05] (Table 2, figure 2). When analysing the results per disease, the odds of having correct inhaler technique in the intervention group was 4.04, p<0.01, (for asthma) and 13.7, p<0.05, (for COPD) times greater than in the control group after the 6-months follow up (Table 2).

Critical correct inhaler technique – only critical steps: When analysing the inhaler technique based on critical steps, 51.2% of patients in the control group and 43.4% in the intervention group had a correct inhaler technique at baseline. These proportions increased in both groups and reached 20.1% difference between groups at visit 6 favouring the IG (CG: 79.9%, IG: 92.2%, p<0.0001) (Figure 3). At the end of the study, the odds of having correct inhaler technique were 4.01 times higher in the IG (95% CI: 1.89 – 8.60, p<0.05) (Table 1). When analysed by asthma and COPD, these odds were to 4.0 (p<0.01 and 5.96 (p<0.05), respectively (Table 1), (Supplementary material 2 – Table 1).

Secondary outcome – Clinical control

Asthma: Baseline proportions of controlled patients were similar in the IG and CG [OR: 0.65 (95% CI: 0.37 - 1.14)]. The probability of patients having their asthma controlled was 1.16 times greater at visit 3, favouring the IG (95% CI: 0.65 - 2.05) and increased to 1.935 at visit 6 (95% CI: 1.06 - 3.52). The mean difference (MD) score for ACQ between groups was not significant at baseline [MD: 0.02 (95% CI: -0.25 - 0.29)]. This difference increased at visit 3 [MD: -0.13 (95% CI: -0.41 - 0.14)] and at visit 6 [MD: -0.29 (95% CI: -0.57 - 0.02)], with this difference being significant at visit 6 and negative values indicating a better clinical control (Table 2).

COPD: At baseline, there were no significant differences in the proportion of patients with low clinical impact [OR: 1.38 (95% CI: 0.72 – 2.62)]. The odds increased and was statistically significant at visit 3 [OR: 2.49 (95% CI: 1.34 – 4.65)] and at visit 6 [OR: 1.92 (95% CI: 1.03 - 3.56)] favouring the IG (Table 2). Mean differences of CCQ scores between control and intervention groups were lesser at baseline [MD: -0.30 (95% CI: -0.61 - 0.01)] and became greater on visits 3 [MD: -0.46 (95% CI: -0.78 - -0.15)] and 6 [MD: -0.45 (95% CI: -0.77 - -0.13)], with these results being statistically significant and favouring the IG (Table 2).

Sub-group analysis

The analysis of the treatment effect across subgroups (age, clinical condition, number of inhalers and type of inhaler) did not show statistically significant effects (Supplementary material 2 – Table 2).

Discussion

The results of this sub-analysis provide evidence on the impact of a medication adherence management service delivered by community pharmacists on inhaler technique performance and specific disease clinical outcomes. The intervention resulted in an increase of approximately 60% in the proportion of patients with total correct inhaler technique (OR=4.57) and 50% in the proportion of patients with critical correct inhaler technique (OR=4.01) from baseline to visit 6, with these being significant when compared to the control group. The multilevel model was adjusted to account for baseline differences. After six monthly face-to-face visits, there was also an improvement on disease-specific clinical outcomes, with the odds of patients having controlled asthma (1.93) and patients having low COPD clinical impact (1.92) favouring the IG when compared to the control group.

Patients in the control group also experimented an initial improvement from baseline to visit 3 of 26.2% (total correct inhaler technique) and 29.4% (critical correct inhaler technique), may be due to patients feeling observed and, therefore, modifying their behaviour (i.e. Hawthorne effect).

The positive effect observed on inhaler technique performance may be related to the components of the intervention, which specifically focused on tailoring the patient's specific barriers. These barriers could be due to intentional or unintentional reasons (34). For incorrect inhaler technique, these may be associated with psychological and practical barriers such as like cognitive impairments, lack of understanding of the inhaler use, lack of coordination, lack of disease awareness, lack of motivation (8, 12, 35, 36). It is likely that multi-component interventions, proven effective at improving long term adherence (37), may also be effective at improving inhaler technique, as inhaler technique and medication adherence are closely related (12). Therefore,

assessment of inhaler technique could be included as part of the medication adherence management service.

Previous research has reported the relationship between clinical control and inhaler technique could depend on the checklist' steps (38). In 2017, Price et al. conducted a cross-sectional multinational study, including data of patients receiving an asthma review service (28). This study identified critical errors, which are related to critical steps, and associated them to poor health outcomes (28). Therefore, it is necessary to identify them when addressing interventions to improve patient outcomes. In our study, we analysed correct inhaler technique in terms of all steps in the process and also the critical steps associated with each inhaler. The intervention resulted in a higher proportion of patients with correct inhaler technique at visit 6 for all steps (OR=4.57) and critical steps only (OR=4.01). These findings could be explained by the continuous training and monitoring of the technique during the intervention (39). Due to the current variability on the definition of critical steps (11), we reported both an analysis of correct inhaler technique based on total steps and critical steps.

In terms of the specific disease, the odds of having a proportion of patients with total and critical correct inhaler technique was higher (13.7 and 5.96) in patients with COPD that with asthma (4.04 and 4.00). These results may be explained as the baseline proportions of patients with incorrect inhaler technique were lower in the COPD group (supplementary material 2), leaving more room for improvement. A further contributing factor could be that as asthma symptoms may be episodic and patients can experience prolonged symptom-free periods in contrast with COPD in which these are progressive and debilitating (12), therefore patients with COPD could have perceived the benefits of improving the technique.

Previous studies involving a community pharmacist-led intervention have reported variable results. Mehuys et al. reported an increase of 40% in the percentage of patients performing correctly after six months of a community pharmacist intervention based on education and counselling (40). Similarly, increases ranging from 40 to 50% (19, 23) were also observed after a six-month intervention focused on medication knowledge and adherence. This is lower than the 60% found in our

study. These differences could be related to the continuous follow-up provided in our study (six-monthly visits) when compared to 1-month and 6-month compulsory visits in a previous study (23). Garcia-Cardenas et al. found an increase of 60% after six months of intervention (22), similar to our study. However, the inhaler technique was only measured for one type of inhaler, opposite to our study, which measured the inhaler technique of the whole inhaled therapy. A 3-month intervention based on disease, medicines education and self-management in COPD patients, resulted on an increase of nearly 50% from baseline after 3 months of (41), comparable to the 50% increase observed in our study at 3 months (visit 3). A 3-month study evaluating an inhaler technique service reported the proportion of patients with optimal (all steps) and acceptable (all critical steps) technique after three months (27). They found an increase from baseline to month 3 of about 50% on both proportions (27), which is similar to the findings in the present study.

The improvement observed on disease-specific clinical outcomes was probably driven by the association of an appropriate inhaler technique with an optimal deposition of the drug in the lungs, as reported by previous literature (42). The effect may also be attributed to the continuous follow-up providing education and assessment of inhaler technique and medication adherence, suggested to be necessary when aiming to improve health outcomes (20, 43, 44).

Our study resulted in better asthma control and a decrease in mean ACQ scores, with a magnitude of the effect similar to previous studies (22). A cRCT reporting a community pharmacist-led intervention found an increase in the proportion of asthma-controlled patients after six-months (OR=3.06) and this result is similar to our study (OR=1.93) (22). In terms of COPD, a study reported mean difference scores between groups of -0.08 between groups after 3 months of follow-up, and this was not significant, measured by the CAT (COPD Assessment Test) questionnaire (41). This is lower than our results, which found significant mean differences at visit 3 (-0.46) and visit 6 (-0.45), may be due to the components of the medication adherence management service allowing the identification of patient's barriers associated to intentional and unintentional reasons.

It has been suggested more evidence is needed on effective interventions to improve inhaler technique in patients with respiratory conditions (45). The findings of this study provide evidence on an effective community pharmacist-led medication adherence management service on inhaler technique performance. Compared to previous randomised controlled trials (22, 40, 41), we also measured the impact of the intervention on inhaler technique when assessing critical steps. As highlighted by a Cochrane review (13) missing these critical steps have been found to be associated to poor health outcomes (11); therefore, it is important to consider them when analysing inhaler technique.

Some limitations in this study include the missing data associated with patients who forgot to bring their inhalers when attending to the monthly visits with pharmacists. In these cases, the assessment of inhaler technique was not possible. Variability associated with pharmacists observing the patient inhaler technique performance could have caused bias on data collection. However, this bias was reduced by providing the same device-specific checklists to all participating pharmacists, who were unaware of which steps were considered critical.

Conclusion

The findings reported in the present study provide evidence on the impact of a medication adherence management service in a community pharmacy setting at improving inhaler technique, measured in terms of total and critical steps, and associated disease-specific outcomes. Future research should include the implementation of this service in routine practice. As inhaled medications continue to be the backbone therapy for patients with asthma and COPD, effective interventions are needed to improve inhaler technique and clinical outcomes. Continuous technique checking and training is necessary to maintain the results.

Declaration of Interests

The authors of this protocol deny having any competing interest on this study.

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TABLES and FIGURES

Table 2. Patients' baseline characteristics

CHARACTERISTIC	CONTROL GROUP (n= 308)	INTERVENTION GROUP (n= 331)	P-value
Age, mean +/- SD	62.07 +/- 16.69	61.87 +/- 17.55	0.889
Gender, n (%)			0.538
• Male	160 (51.95%)	180 (54.38%)	
• Female	148 (48.05%)	151 (45.62%)	
Education, n (%)			0.787
• No studies	65 (21.10%)	68 (20.54%)	
• Primary	115 (37.34%)	137 (41.39%)	
• High school	76 (24.68%)	79 (23.87%)	
• Vocational degree	6 (1.95%)	4 (1.21%)	
• University	46 (14.94%)	43 (12.99%)	
Working status, n (%)			0.876
• Paid employment	78 (25.32%)	75 (22.66%)	
• Paid employment but on sick leave	9 (2.92%)	12 (3.63%)	
• Unemployed	29 (9.42%)	37 (11.18%)	
• Retired	168 (54.55%)	182 (54.98%)	
• Student	24 (7.79%)	25 (7.55%)	
Indication (n, %)			0.251
• Asthma	161 (53.28%)	188 (57.61%)	
• COPD	147 (46.72%)	143 (42.39%)	
Duration of the disease			0.478
• < 3 months	1 (0.33%)	3 (0.91%)	
• 3-6 months	3 (0.98%)	3 (0.91%)	
• 6-12 months	6 (1.96%)	3 (0.91%)	
• 1-5 years	63 (20.59%)	54 (16.36%)	
• >5 years	233 (76.14%)	267 (80.91%)	
Number of oral medications, mean +/- SD (135 patients)	1.02 +/- 0.13	1.04 +/- 0.19	0.470
Number of relievers, mean (SD) (646 patients)	1.05 +/- 0.22	1.08 +/- 0.29	0.399
Number of inhaled medications, mean (SD)	1.69 +/- 0.68	1.70 +/- 0.67	0.943
Number patients with controller inhaled medication (n, %)			0.405
• 1 inhaler	231 (75%)	244 (73.72%)	
• >1 inhaler	77 (25%)	87 (26.28%)	
Number of controller inhalers (n, %)			
• Dry powder inhaler (capsule)	84 (17.7%)	84 (14.5%)	
• Dry powder inhaler (multi-dose_	217 (45.6%)	238 (42.2%)	
• Mist inhaler	32 (6.7%)	47 (8.3%)	
• Presurised metered-dose inhaler (pMDIs)	20 (4.2%)	37 (6.6%)	
• Conventional pMDIs	52 (10.9%)	58 (10.3%)	

Figure 1. Study Flowchart

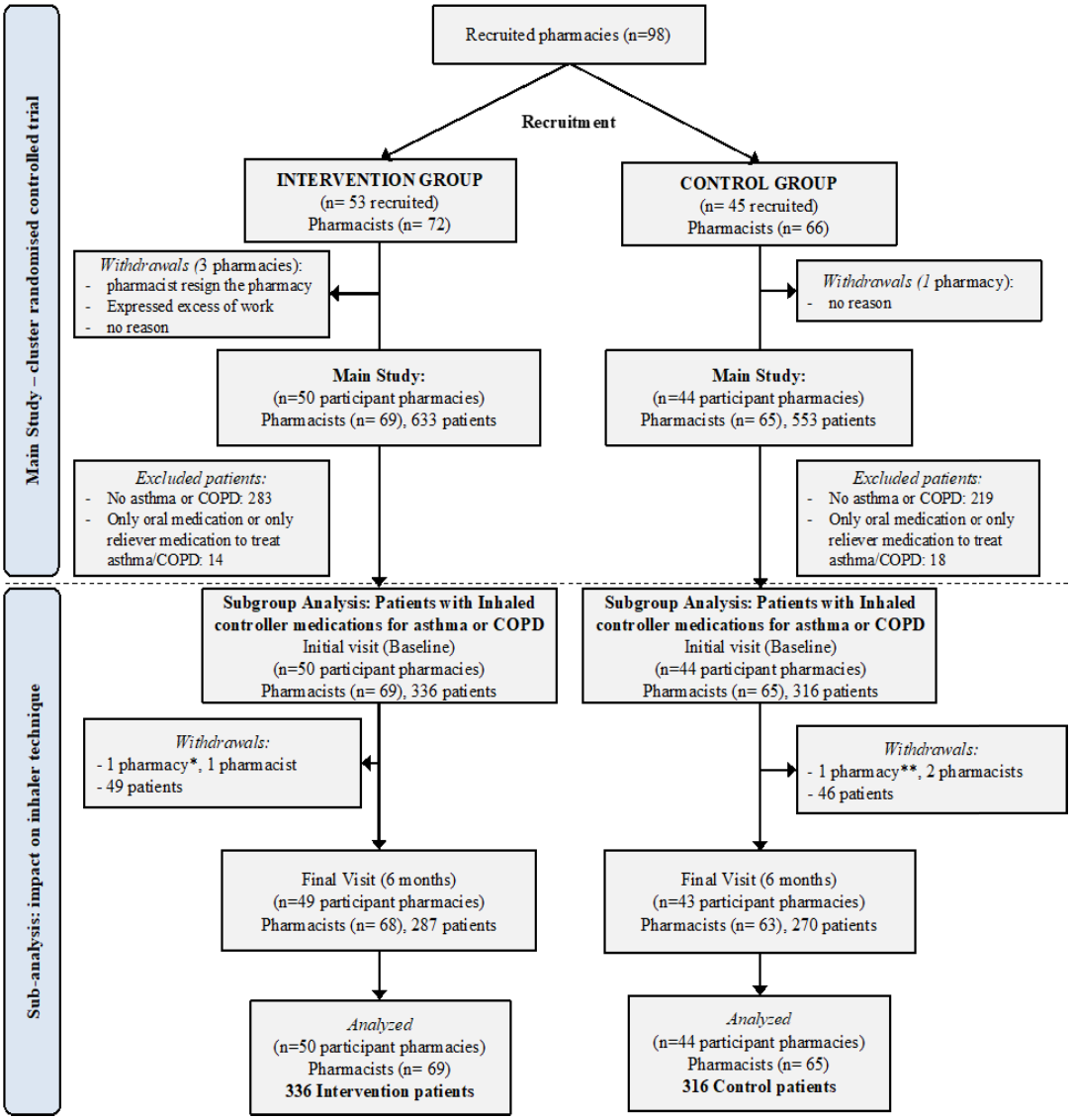


Table 3. Comparison of treatment vs control (reference) groups for main and secondary outcomes

VARIABLE	*ASTHMA*		*COPD*		*ALL PATIENTS*	
	Odds Ratio (95% CI)	**p-value**	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
1. Primary outcome – Inhaler technique						
Proportion of patients with correct inhaler technique						
Baseline	0.87 (0.40 - 1.89)	0.73	0.22 (0.03 - 1.43)	0.11	0.63 (0.32 - 1.25)	0.18
3 Months	2.41 (1.09 - 5.35)	0.03	1.49 (0.42 - 5.23)	0.54	1.91 (0.96 - 3.78)	0.06
6 months	4.04 (1.64 - 9.95)	<0.01	13.7 (4.39 - 42.5)	<0.001	4.57 (2.18 - 9.60)	<0.001
Proportion of patients with optimal inhaler technique (only critical steps)						
Baseline	0.88 (0.39 - 1.98)	0.76	0.60 (0.28 – 1.29)	0.19	0.74 (0.38 - 1.43)	0.37
3 Months	2.46 (0.99 – 6.11)	0.05	1.39 (0.64 – 3.02)	0.41	1.65 (0.83 - 3.29)	0.15
6 months	4.00 (1.46 – 11.00)	<0.01	5.96 (2.31 – 15.4)	<0.001	4.01 (1.89 - 8.60)	<0.001
2. Disease-specific clinical control						
Categorical variable - Proportion of controlled patients (ACQ or CCQ)						
Baseline	0.67 (0.38 - 1.16)	0.15	1.38 (0.72 - 2.62)	0.33	NA	NA
3 Months	1.16 (0.65 - 2.05)	0.62	2.49 (1.34 - 4.65)	<0.01	NA	NA
6 months	1.93 (1.06 - 3.52)	0.03	1.92 (1.03 - 3.56)	0.04	NA	NA
Continuous variable – Total score						
	Mean Difference (95% CI)	**p-value**	**Mean Difference (95% CI)**	**p-value**	**Mean Difference (95% CI)**	**p-value**
	ACQ score		***CCQ score***			
Baseline	0.02 (-0.25 - 0.29)	0.90	-0.30 (-0.61 - 0.01)	0.06	NA	NA
3 Months	-0.13 (-0.41 - 0.14)	0.34	-0.46 (-0.78 - -0.15)	<0.01	NA	NA
6 months	-0.29 (-0.57 - -0.02)	0.04	-0.45 (-0.77 - -0.13)	<0.01	NA	NA

Figure 2. Proportion of patients with Total correct inhaler technique estimated from multilevel model of categorical outcomes. Intervention vs. Control group. Error bars represent 95% CIs. (Visit 1 is equivalent to Baseline)

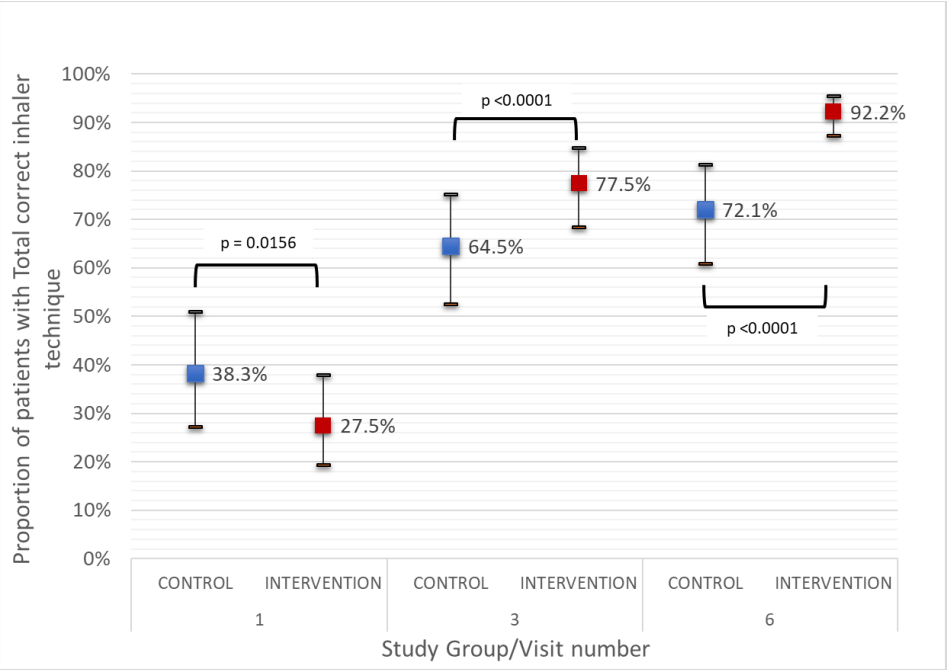
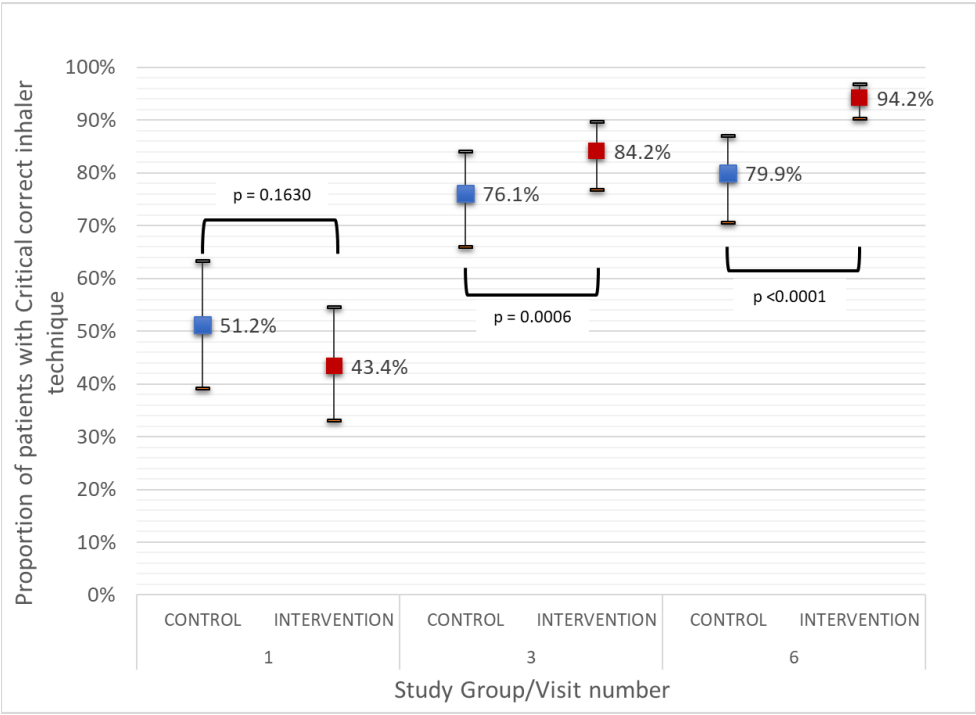


Figure 3. Proportion of patients with Critical correct inhaler technique estimated from multilevel model of categorical outcomes. Intervention vs. Control group. Error bars represent 95% CIs. (Visit 1 is equivalent to Baseline)



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Chapter 6

Evaluation of a medication adherence management service in a community pharmacy setting: an effectiveness-implementation hybrid trial

Chapter 6 evaluates the effectiveness of an intervention (with proven efficacy under the clinical trial described on chapter 4) when translated to a real-world setting.

This chapter is presented as paper submitted to the Journal *BMC Health Services Research.*

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ABSTRACT

Background

Research on medication adherence interventions is mainly focused on the evaluation of the efficacy of interventions through clinical trials. Due to the complexity of the implementation process of adherence interventions, it is unclear if these benefits translate to routine-practice. Therefore, this study aims to evaluate the impact of a. medication adherence management service, which improved patient's outcomes under controlled settings, once implemented into routine practice.

Methods

This was Phase 2 of a two-phase medication adherence management program delivered to patients suffering from hypertension, asthma and COPD. An effectiveness-implementation hybrid design was undertaken in Spanish community pharmacies. Patients coming from the Phase 1 (Groups A and B) and new patients (Group C) in Phase 2 received the intervention. Medication adherence (MGL Medication adherence questionnaire), asthma (ACQ questionnaire), COPD (CCQ questionnaire) and hypertension (Blood pressure levels) outcomes were measured at each one of the six visits. SPSS was used to analyse the data. Categorical (frequencies and proportions) and continuous (means and standard deviations) variables were reported.

Results

Pharmacies (n=90), pharmacists (n=127) and 850 patients participated in Phase 2, with 780 patients completing the six months. The study outcomes improved for all groups after the six-month study: Proportion of adherent patients (Group A: 92.4%, Group B: 86.3% and Group C: 85.7%), hypertension-controlled patients (Group A: 74.1%, Group B: 71.1% and Group C: 71.3%), asthma-controlled patients (Group A: 70.2%, Group B: 67.3% and Group C: 63.6%) and patients with low COPD clinical impact (Group A: 60.4%, Group B: 37.3% and Group C: 38.6%).

Conclusions

A medication adherence management service provided by community pharmacists was effective at improving medication adherence and disease-specific outcomes during its implementation into routine-practice. The sustainability of the service should be explored in future research.

Trial registration none

Keywords: Medication adherence interventions, implementation science, real-practice, asthma, COPD, hypertension, effectiveness.

Background

Implementation of innovations such as new interventions and services in health care settings can be a complex process (1). Numerous theories and frameworks have been described to guide and evaluate the process of implementing an innovation into routine practice (2). While randomised controlled trials continue to be the gold standard to assess the efficacy of interventions, alternative approaches adopted by implementation science can facilitate the uptake of innovations, providing valuable evidence on how the intervention works in real-world environments (3). Different approaches such as pragmatic trials (which aim to assess an intervention's effectiveness in real-world settings) or effectiveness-implementation hybrid designs (which aim to assess the clinical effectiveness and implementation efforts) (3) are increasingly being used. The use of these research designs is key to understand how effective interventions behave in routine practice and to test whether expected benefits are achieved and sustained once integrated into a given setting.

Medicines are the core treatment modality for most chronic diseases. However, patients often discontinue their treatments or fail to follow them as prescribed. There is extensive evidence highlighting suboptimal adherence rates to chronic treatments, with high rates of treatment discontinuation and non-initiation (4-6). The level of low adherence rates continues to be consistent over time, with nearly 50% of patients failing to adhere to their chronic medications (7-10). There is evidence between 4% and 30% of patients with chronic conditions fail to initiate their treatment (4, 11). Moreover, medication non-adherence represents a significant

global burden, linked to disease progression, deterioration of quality of life (12, 13) and higher costs for the health care system (14). To overcome this prevalent problem, a range of interventions have been designed and tested in different settings including pharmacy (15). Community pharmacists are accessible healthcare providers, who often have regular interactions with patients with chronic conditions (16, 17). They are ideally placed to target medication non-adherence by delivering evidence-based adherence management interventions. In addition, there is evidence that these interventions have the potential to improve disease-specific clinical outcomes (18). However, the benefits of these interventions, which are often evaluated in randomised controlled trials (RCTs), appear to be rarely translated into usual practice (19). Moreover, it is often unknown if an intervention's efficacy observed in controlled randomised studies will be achieved once the intervention is implemented into routine practice (20). Unless an intervention is implemented effectively, neither patients nor healthcare systems will receive its full benefits (21).

In Spain, the provision of adherence management interventions (i.e. medication adherence management services) in community pharmacy has been described as a priority for the pharmacy profession (22). A cluster randomised controlled trial evaluated the impact of this service, providing evidence of its efficacy in patients with asthma, COPD and hypertension (Chapter 4). However, the impact of this service once implemented into routine practice remains unknown.

Aim of the Study

This study aimed to evaluate the clinical effectiveness of an evidence-based community pharmacist-led medication adherence management service during an effectiveness-implementation hybrid study. It was hypothesised that the effectiveness of the service would be similar to its efficacy, tested during a previous cluster randomised controlled trial.

METHODS

This trial followed the Standard for Reporting Implementation Studies (StaRI) checklist (23). Only clinical outcomes of the intervention are reported in this paper.

Design and Setting

This study was part of the AdherenciaMED program, which was conducted in two phases. Phase 1 aimed to evaluate the efficacy of a medication adherence management service using a cluster randomised controlled trial design (Chapter 4). Phase 2, which is reported in this paper, aimed to evaluate the effectiveness of the service adopting an effectiveness - implementation hybrid design (3). The study was conducted in community pharmacies in six Spanish provinces (A Coruña, Albacete, Ciudad Real, Guadalajara, Soria and Tenerife).

Pharmacy Recruitment

As AdherenciaMED was a two-phase study, community pharmacists who participated in phase 1 were offered to continue their participation in phase 2. New community pharmacists in each province were also invited to participate in the study by the local Colleges of Pharmacy. Pharmacies were eligible if they met the following inclusion criteria: 1) availability of a counselling area for initial and follow-up interviews; 2) availability of at least one participating pharmacist per pharmacy to deliver the intervention and 3) the attendance of all pharmacists involved in the project to the training programs delivered before the beginning of the study.

Patient Recruitment

Patients who had participated in phase 1 could continue their participation in phase 2. New patients could also be recruited during phase 2. Therefore, there were three patient groups: *Group A:* Patients who had been allocated to the intervention group during phase 1 and continued their involvement in the study during phase 2, *Group B*: Patients who had been allocated to the control group during phase 1 and continued their involvement in the study during phase 2; or *Group C:* New patients recruited during phase 2. (Figure 1).

Patients were recruited consecutively between May and June 2018 in the participant community pharmacies when filling a prescription. As in phase 1, to be eligible, patients had to meet the following inclusion criteria: 1) age 18 years or older; 2) have

signed and returned informed consent; 3) to be able to complete the questionnaires EuroQol-5D (24), Morisky-Green-Levine medication adherence questionnaire (MGL MAQ) (25), Asthma Control Questionnaire (ACQ) (26) or Clinical COPD Questionnaire (CCQ) (27); 4) were currently prescribed a medication for; blood pressure (groups CO2, CO3, C07, C08 or C09), asthma (group R03), or COPD (group R03). Groups of medication defined as per the Anatomical Therapeutical Chemical (ATC) classification system (28). Patients were excluded if they: 1) were collecting someone else's medication; 2) were pregnant or lactating; 3) could not attend the pharmacy on a regular basis; 4) had previously participated, or were participating at the moment of recruitment, in any education program or study related to the improvement of adherence to medications (except those participating in phase 1 of the AdherenciaMED program).

Intervention to be implemented: Medication Adherence management service

The adherence management service was a brief complex intervention based on theoretical models for changing patient behaviour. It involved monthly visits during a 6-months follow-up. During each visit, the pharmacist identified patient's barriers to adhere to his/her medications and agreed with the patient on strategies to address these barriers. The complete intervention has been described elsewhere (Chapter 4).

Implementation strategy

The framework for the implementation of pharmacy services (FISpH) was derived from the Consolidated Framework for Implementation Research (CFIR) by Damschroder et al. (29) but made specific to the community pharmacy setting. FISpH involves five different stages pharmacies can go through during the implementation effort: exploration, preparation, testing, implementation and sustainability (1). Each stage has associated implementation factors (i.e. communication, time, recruitment, methodology of the service, complexity, adaptability) which moderate the implementation effort. Tailored implementation strategies were developed.

The exploration stage involved the communication of the implementation study to pharmacy stakeholders external to community pharmacy (e.g. Pharmacy Official

Body (COF) of each province and the General Pharmaceutical Council of Spain (CGOF)). Pharmacies which had participated in phase 1 and new pharmacies were informed about the new study and were invited to participate by these organisations.

The preparation stage referred to the preparation of participating pharmacies and pharmacists to provide the service (e.g. pharmacists' training, initial evaluation of barriers and facilitators in each pharmacy). Pharmacy owners, who were responsible for the management of the pharmacy, received training by the research team during a 4-hour session. The content included issues regarding national health policy, business and implementation models, staffing requirements and the implications and needs of the participating pharmacists. All the pharmacists delivering the intervention received specific training on adherence, clinical management and implementation science during 15 hours divided in three sessions.

The testing stage included trialling the service in a limited number of patients in each community pharmacy. Finally, the implementation stage involved the delivery of the service to the target number of patients and promoted its integration into routine practice.

A detailed description of the implementation strategies used can be found in Supplementary Material.

Practice Change facilitators (PCF)

Practice change facilitators provided support to community pharmacists during the study, facilitating internal and external communication between pharmacists and the research team (30).

They provided a tailored support provided on a monthly basis focussed on each pharmacy particular needs. Besides providing support to pharmacists, they contributed to ensuring the quality of the processes by assessing implementation barriers and facilitators in each pharmacy to improve the provision of the service.

PCF also worked with pharmacists to successfully implement the service. This was conducted through the "Plan, Do, Study, Act (PDSA) cycles and model for

improvement", a model for developing, testing and implementing changes in practice (31).

All data were collected in a specific electronic data collection form specially designed for the PCF.

Service Outcomes

This paper reports medication adherence and disease-specific clinical outcomes described in Table 1 (located at the end of this manuscript).

Data Collection and Quality

Patient demographic and clinical data and were collected by the pharmacist for all patients at every visit for 6 months and recorded all study variables in an electronic data collection program ("eCRD").

Data analysis

Data was analysed by using the software package SPSS statistics, version 25.0 (SPSS Inc. Chicago. Illinois, USA) and Microsoft Excel (2016). Frequencies and proportions were used for describing categorical variables whereas means and standard deviations were used for continuous variables.

Results

Ninety pharmacies and 127 pharmacists participated in Phase 2. Six pharmacies and 9 pharmacists withdrew during the study. A total of 850 patients were included in phase 2 (Figure 1, located at the end of this manuscript) and 780 completed the 6 months study. Patients' baseline characteristics are described in Table 2 (located at the end of this manuscript).

Medication adherence

At baseline, 64.9% of patients were adherent. Group A had the largest proportion, with 86.1% of adherent patients. Group B and Group C had the lowest proportion of adherent patients (62.5% and 55.7% respectively). Medication adherence improved

for all groups across study visits, with 87.6% of patients being adherent by the end of the six months. Proportions of adherent patients in the study groups were 92.4% (Group A), 86.3% (Group B) and 85.7% (Group C). The largest increase in the proportion of adherent patients from baseline to visit 6 was observed in Group C (30%), followed by Group B (23.8%) and Group A (6.3%) (Figure 2).

Hypertension Control

At baseline, the proportion of patients with controlled hypertension was very similar in all study groups. The lowest proportion of controlled patients was observed in Group B (63%), followed by Group A (67.3%) and Group C (67.6%). These proportions increased in all study groups, reaching 74.1% (Group A), 71.1% (Group B) and 71.3% (Group C) at visit 6, with the largest increment observed in the Group B (8%) (Figure 2). In terms of systolic (SBP) and diastolic blood pressure (DBP), patients in Group B had the highest mean SBP values (135.49mmHg, SD: 19.19), followed by Group C (133.86mmHg, SD: 18.23) and Group A (133.45mmHg, SD: 14.45) at baseline. DBP at baseline were 77.14mmHg (SD; 12.67), 77.10mmHg (SD: 9.4) and 78.67mmHg (SD: 11.00), for Group A, B and C respectively. At visit 6, mean SBP was 130.67 (SD: 12.11), 132.83mmHg (SD: 15.22) and 131.06mmHg (SD: 14.53) and DBP was 75.15mmHg (SD: 8.30), 75.63mmHg (SD: 11.40) and 76.8mmHg (SD: 9.26) for Groups A, B and C respectively. The largest decreases in SBP and DBP, 2.80mmHg and 1.87mmHg respectively were observed in Group C (Figure 3) by the end of the study.

Asthma Control

At baseline, proportions of controlled asthma patients were 59.1% (Group A), 47.2% (Group B), and 35.4% (Group C). This proportion increased for all study groups, with the largest increase (28.2%) being observed in Group C at visit 6 [70.2% (Group A), 67.3% (Group B), 63.6% (Group C)] (Figure 2). Regarding mean ACQ scores at baseline, these were 0.79 (SD: 1.01) (Group A), 1.14 (SD: 1.10) (Group B), 1.29 (SD: 1.19) (Group C). These scores decreased across at the end of the follow-up reaching values of 0.67 (SD: 0.97) (Group A), 0.66 (SD: 0.90) (Group B) and 0.67 (SD: 0.81)

(Group C), indicating a better clinical control (Figure 3). The decrease of 0.62 points in Group C is considered clinically significant (>0.5).

COPD clinical impact

At baseline, the proportion of patients with low clinical impact of their COPD was 39.1% (Group A), 24.5% (Group B) and 21.7% (Group C). There was an increment in the proportion of patients, reaching 60.4%, 37.3%, and 38.6% at visit 6 for Group A, B and C respectively (Figure 2). Mean CCQ scores were 1.22 (SD: 0.72) (Group A), 1.98 (SD: 1.32) (Group B), and 2.15 (SD: 1.19) (Group C) at the beginning of the study. These scores decreased to 1.13 (SD: 1.01) (Group A), 1.60 (SD: 1.33) (Group B), and 1.45 (SD: 1.04) (Group C) at visit 6, indicating a better clinical control (Figure 3). The decrease from baseline to visit 6 was clinically significant (>0.4) in Group C (0.7).

Discussion

A medication adherence management service provided in a community pharmacy setting was effective at improving patient's outcomes (medication adherence and disease-specific clinical control) during an effectiveness-implementation study.

Despite the negative health impact of medication non-adherence, only few medication adherence interventions that have proven effective under very controlled environments (RCTs) have been implemented and sustained in healthcare settings (19), highlighting an important gap in medication adherence research. Translating evidence into real practice may have a critical role in policymaking and the sustainability of pharmacy services. The need for implementation research in pharmacy has already been underlined (32). This study provides insight into how adherence interventions that have proved to be effective under controlled study designs continue to demonstrate benefits when implemented into routine practice environments.

The results obtained in this effectiveness-implementation study followed a similar trend to those obtained during the impact phase (Chapter 4), with improvements observed on medication adherence and clinical outcomes after six months of follow-

up. This could have been expected, as the intervention being implemented was the same as the one provided in phase 1. It might be that the intervention was more adapted (33) into the daily pharmacy practice as a result of the experience during phase 1. In comparison to the previous phase (cRCT), the schedule of visits was more flexible and based on patient's improvement and the professional judgement of the pharmacists, as it would be in real practice.

For those groups receiving the intervention for the first time during phase 2 (i.e. Groups B and C), the proportion of adherent patients increased approximately 30% at the end of the study (from 55.7% to 85.7% for Group C and from 62.5% to 86.3% for Group B). The magnitude of the effect in the proportion of adherent patients was smaller when compared to the efficacy of the service observed during phase 1 (51.8% increase, from 39.1% to 90.9%) (Chapter 4). This could be explained by baseline proportions of adherent patients being considerably higher in phase 2 (Group B: 55.7%, Group C: 62.5%) compared to phase 1 (39.1%). It should be noted medication adherence was maintained over time in those patients who had already received the intervention during phase 1 (Group A). During this trial, the proportion of adherent patients increased by 6.3% at the end of the study, reaching 92.4%. The proportion of adherent patients in this group was already high (86.1%), as a result of the intervention received during phase 1. Obviously, the potential to improve adherence when an optimal rate has been achieved is limited (34). Nonetheless, this underlines that the benefits observed during the cluster randomised controlled trial were sustained during the implementation study. As medication adherence is a dynamic behaviour that changes over time (35), it is crucial to provide regular follow up. This provides an opportunity to reassess if the patient's determinants of adherence changed and provide tailored interventions that prevent a possible relapse. It is also logical to think that those groups of patients showing high adherence rates (Group A) would not require the same level of intensity than those showing poorer adherence rates (Groups B and C) (36).

The effectiveness of the service on clinical outcomes was also evident during the phase 2 of the program. Opposite to medication adherence, baseline proportions of

controlled hypertension patients during phase 2 were similar for all groups (nearly 65%). These proportions were higher than the ones observed during phase 1, which were close to 50% (Chapter 4). All study groups showed a similar increase, reaching approximately 72% of controlled patients at the end of the study. Mean blood pressure levels were also similar at baseline, decreasing at the end of the study for all study groups. Among all diseases targeted by the service being tested, hypertension had the smallest changes by the end of the study. This might be explained by the fact the proportion of patients with controlled hypertension at baseline was higher than the proportion of patients with controlled asthma or low clinical impact of COPD. Uncontrolled hypertension was not an inclusion criterion for this study. Previous evidence has shown increases of 50% of controlled patients after a community pharmacist intervention (37, 38). In these studies, contrary to our study, uncontrolled hypertension was an inclusion criteria and therefore, improvements are more evident. Nevertheless, the intervention was effective at improving disease control by tailoring patients and addressing medication non-adherence, proven to be related to uncontrolled blood pressure (39). Regarding average blood pressure levels, SBP decreased between 2.7 and 2.8 mmHg and DBP decreased between 1.51 and 1.95mmHg across all the three groups from baseline to the last visit. As mean baseline values already fell within recommended values (<140mHg/90mmHg), changes could not be noticeable. When comparing the effectiveness during Phase 2 (Group B and C), with the efficacy observed during Phase 1 (-3.3mmHg SBP/-2.5mmHg DBP), the magnitude of the effect was smaller (Chapter 4). It could be hypothesised that BPL had reached the minimum possible levels for patients with hypertension. Decreases ranging from 12.2-12.62mmHg SBP and 4.92-8.63mmHg DBP have been reported in previous studies, where non BP control was an inclusion criteria (37, 40).

Trends on the proportion of patients with controlled asthma were similar to the trends observed in the main study outcome (medication adherence), with the lowest value (35.4%) corresponding to Group C. It is important to note that differences in the proportion of controlled patients between Group A and the other groups at

baseline were greater than at the end of the study, highlighting that patients no exposed to the intervention reached similar levels of control to those who had already received the intervention in the previous clinical trial. The increase in the proportion of controlled patients during Phase 2 on Groups B and C was lower than the increase of 34.7% observed during the clinical trial (Phase 1) (Chapter 4). During the clinical trial (Phase 1), the intervention resulted in a decrease of 0.53 points on the ACQ score (Chapter 4), similar to the decrease observed in Groups B (0.48points) and Group C (0.62points) during Phase 2. The decrease in Group C was clinically significant. These results reinforces the effectiveness of the intervention in improving clinical outcomes in asthma patients. Previous evidence has shown average ACQ decreases of 0.4points after the provision of an intervention focused on asthma education (41). Our intervention resulted on higher decreases, highlighting the potential of the medication adherence management service at improving asthma outcomes.

The proportion of patients with low clinical impact of COPD almost doubled after six months. However, for these patients, the largest change was observed in Group C (21.3%). Average CCQ scores decreased for all patients, with the largest reduction being observed in the Group C (0.7 points). This difference was considered clinically significant. These results reinforce the role of pharmacists in the management of patients with COPD, highlighted in the literature (42).

For respiratory diseases, it is also worth considering the change of seasons while the phases of the study were occurring, which could have affected the improvement of symptoms of these patients.

As expected, the improvement in clinical outcomes during phase 1 (Chapter 4) was greater than on phase 2. There is evidence showing the loss of effectiveness of evidence-based interventions once implemented into routine practice. Efficacy is usually evaluated under optimal conditions, which cannot be replicated or sustained over time. Also, from the provider's perspective, additional factors needed to be taken into consideration when delivering the intervention during the implementation phase. Factors such as time, recruitment, service methodology,

complexity of the service, adaptation of the service of pharmacy characteristics represented a challenge as they can impact on the integration of the intervention in routine practice. Some of these factors have already been identified as important barriers in literature (43, 44). Despite the challenges associated with the implementation phase, the intervention was still effective at improving all the outcomes assessed.

There is some evidence on interventions provided by community pharmacists improving medication adherence and clinical outcomes on hypertension, COPD or asthma (18). Nonetheless, limited evidence exists regarding the impact of these interventions applying implementation science approaches. Previous evidence has highlighted interventions involving attitudinal components (i.e. behaviour change models) are effective at long term (>12 months) (45, 46), components which were considered in the medicating adherence management service. The adherence service also involved the provision of a tailored intervention where the patient was part of the decision-making process, a critical element highlighted in the literature (47).

Specifically for asthma and COPD, where there is limited research on the impact of community pharmacy interventions on clinical outcomes (18), this paper adds evidence on the impact of these interventions and the translation of these benefits into routine practice.

To the best of our knowledge, this study provides novel insight on the effectiveness of the implementation of a medication adherence service in community pharmacy for patients with hypertension, asthma or COPD and compared if the efficacy observed during the clinical trial translates into benefits being maintained in real practice.

Limitations

A limitation of this study was the unavailability of additional resources such as dispensing records to assess medication adherence. Pharmacists providing the intervention to new patients (Group C) could have participated in the previous phase

of the program or be new to the study, which could have affected the experience to provide the intervention and its fidelity.

Conclusion

A community pharmacist-led medication adherence management service was proven to be effective at improving medication adherence and disease-specific clinical outcomes on patients with asthma, COPD and hypertension. These findings suggest similar results in terms of the efficacy vs the effectiveness of the service. Further research should analyse the implementation outcomes and sustainability of the intervention.

List of abbreviations

ACQ: Asthma Control Questionnaire, CCQ: Clinical COPD Questionnaire, PCF: Practice Change Facilitator, SBP: Systolic blood pressure. DBP: Diastolic blood pressure, FISpH: Framework for the Implementation of Services in Pharmacy

Declarations

Ethics approval and consent to participate

This protocol follows the Ethical principles for Medical Research involving Human Subjects (Fortaleza, 2013) and Good Clinical Practices (ICH/GCP) and International Council for Harmonisation. It has been approved by the Ethics Committee of Research of Granada (CEI-Granada) (Approval number 13/C-11).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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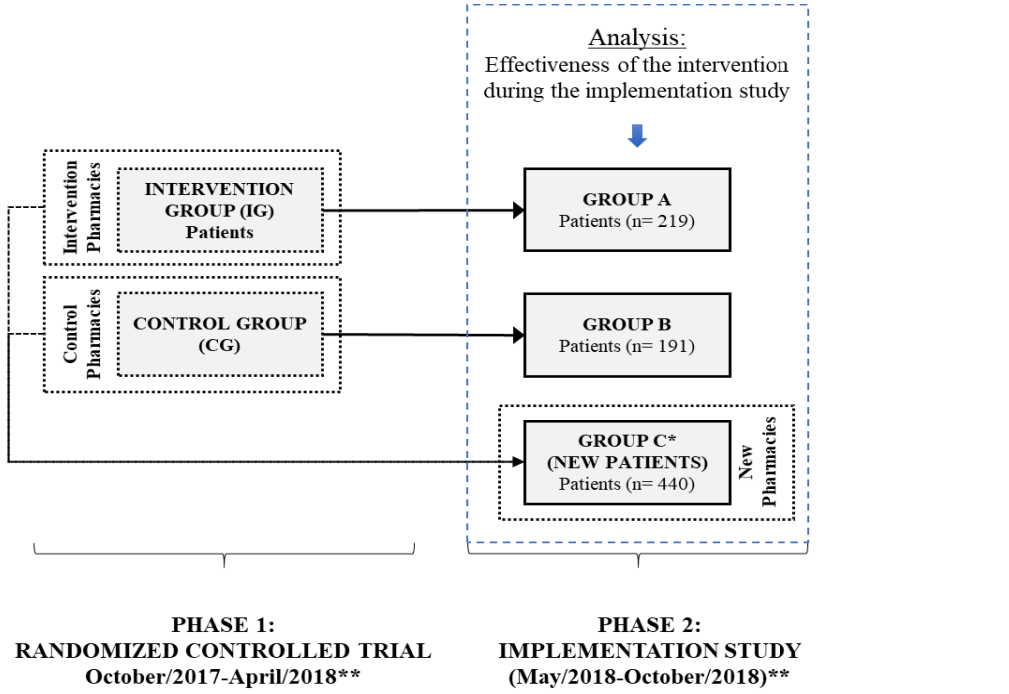
TABLES and FIGURES

Table 1. Service Outcomes

Outcome	Type of variable	Definition	Data Source
Medication adherence	Categorical	Proportion of adherent patients	MLG Medication adherence questionnaire (25)
Hypertension control	Continuous	Blood pressure levels: Systolic and Diastolic Blood pressure	Systolic and Diastolic blood pressure levels
	Categorical	Proportion of controlled patients (BPL < 140mmHg/90mmHg) (48)	
Asthma control	Continuous	ACQ score*	Asthma Control Questionnaire (ACQ) (26)
	Categorical	Proportion of controlled (ACQ score <=0.75) patients.	
COPD clinical impact	Continuous	CCQ score**	Clinical COPD Questionnaire (CCQ) (27)
	Categorical	Proportion of patients with low clinical impact (ACQ score <1.0) (49)	

* A difference of 0.5 or more between the average scores on the visits was considered clinically significant (50).
****** A difference of 0.4 or more between the average scores across the study visits was considered clinically significant (51).

Figure 1. Flow of patients and pharmacies across Phases 1 and 2



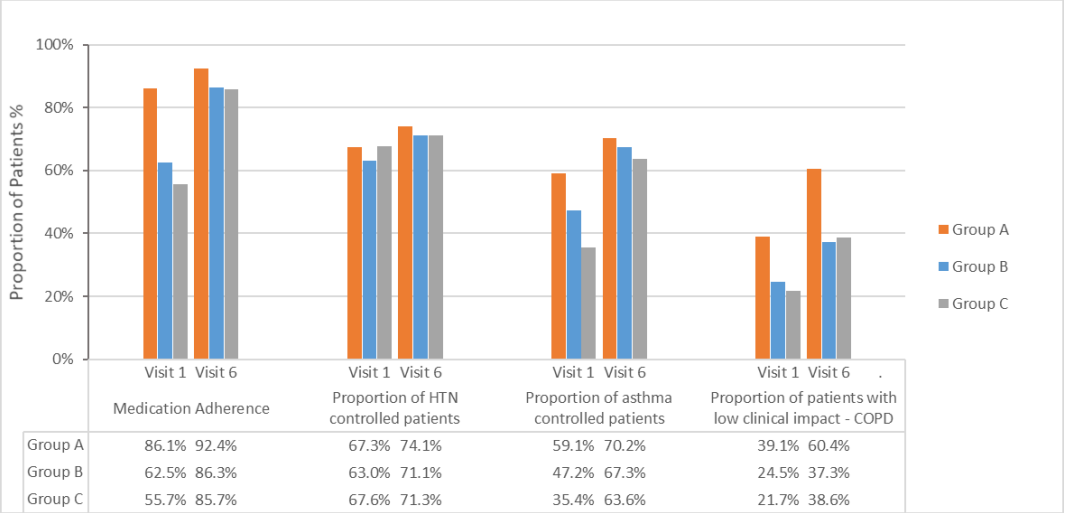
*Patients in Group C could have been recruited by either Intervention and Control Pharmacies from Phase 1, or new pharmacies participating on Phase 2.
**Two months for patient recruitment

Table 2. Patients' baseline Characteristics

Variables	Group A (n= 219)	Group B (n= 191)	Group C (n= 440)
Age, mean +/- SD	66.94 (14.55)	65.89 (14.20)	63.45 (14.34)
Gender (female), n (%)	107 (48.86%)	98 (51.31%)	263 (59.77%)
Education, n (%)			
- No studies	50 (22.83%)	51 (26.70%)	71 (16.14%)
- Primary	90 (41.10%)	61 (31.94%)	194 (44.09%)
- High school	48 (21.92%)	50 (26.18%)	114 (25.91%)
- Vocational degree	5 (2.28%)	8 (4.19%)	7 (1.59%)
- University	26 (11.87%)	21 (10.99%)	54 (12.27%
Working status, n (%)			
- Paid employment	36 (16.44%)	44 (23.04%)	121 (27.50%)
- Paid employment but on sick leave	5 (2.28%)	4 (2.09%	9 (2.05%)
- Unemployed	23 (10.50%)	20 (10.47%)	49 (11.14%)
- Retired	141 (64.38%)	115 (60.21%)	227 (51.59%)
- Student	14 (6.39%)	8 (4.19%)	34 (7.73%)
Clinical condition (n, %)			
- Asthma	49 (22.37%)	60 (31.41%)	118 (26.82%)
- COPD	50 (22.83%)	53 (27.75%)	84 (19.09%)
- Hypertension	120 (54.79%)	78 (40.84%)	238 (54.09%)
Medications associated to the studied clinical condition*, mean (SD)	1.73 (0.84)	1.81 (0.84)	1.74 (0.94)
All prescribed medications, mean (SD)	6.02 (3.38)	6.29 (3.69)	5.30 (3.15)

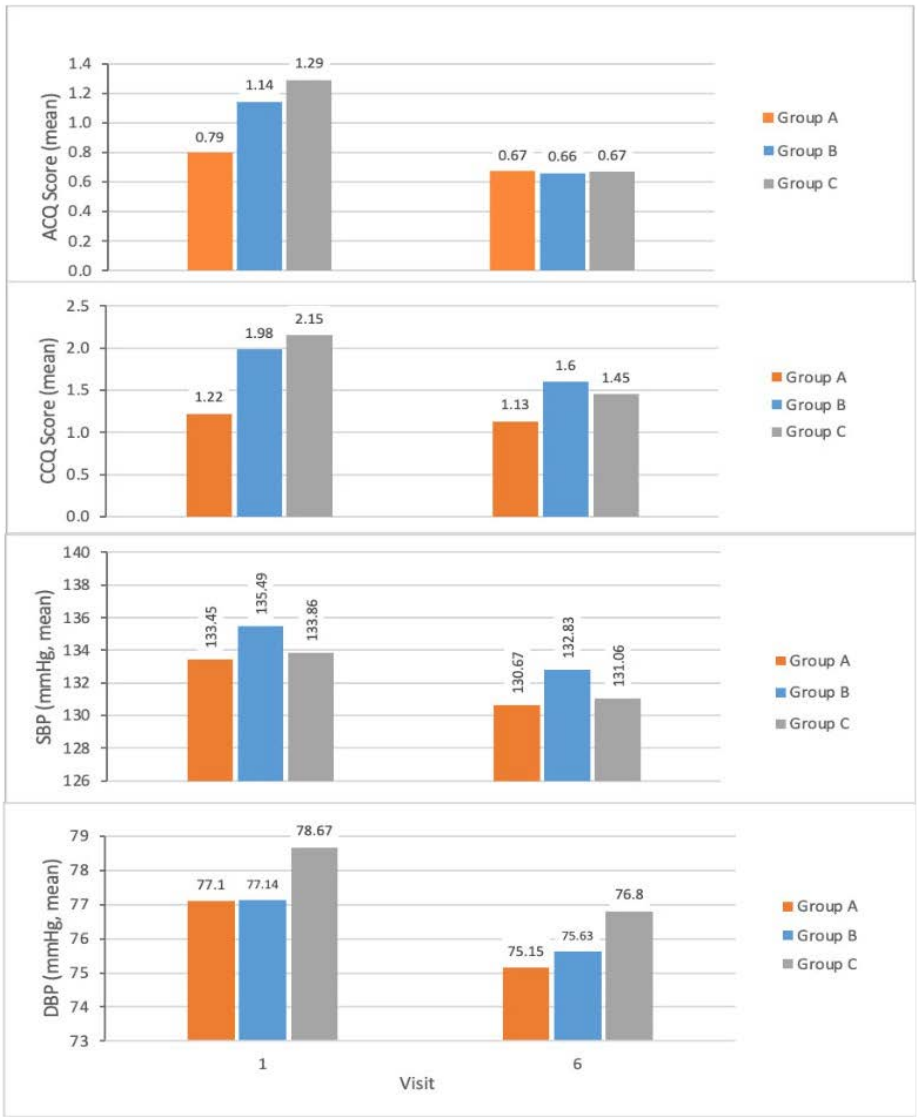
[a] Effectiveness of the intervention during Phase 2
[b] Analysis of the effect of the intervention across Phase 1 and 2

Figure 2. Categorical outcomes for all groups during the phase 2.



	Medication Adherence		Proportion of HTN controlled patients		Proportion of asthma controlled patients		Proportion of patients with low clinical impact - COPD	
	Visit 1	Visit 6	Visit 1	Visit 6	Visit 1	Visit 6	Visit 1	Visit 6
Group A	86.1%	92.4%	67.3%	74.1%	59.1%	70.2%	39.1%	60.4%
Group B	62.5%	86.3%	63.0%	71.1%	47.2%	67.3%	24.5%	37.3%
Group C	55.7%	85.7%	67.6%	71.3%	35.4%	63.6%	21.7%	38.6%

Figure 3. Continuous outcomes for all groups during the phase 2.



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Chapter 7

Discussion

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The research conducted in this thesis involved the exploration and analysis of the impact of medication adherence interventions in the community pharmacy setting. This chapter discusses these findings, methodological considerations and the research implications for future practice.

The growth in the aging population and the increase in the prevalence of chronic diseases worldwide has resulted in greater prescribing of medications. Different factors such as lack of knowledge, lack of skills, physical impairments, health beliefs and lack of motivation (Kardas, Lewek & Matyjaszczyk 2013) impact on patients taking their chronic medications as prescribed, a process defined as medication non-adherence (Sabate 2003). Adherence to medications is necessary to achieve clinical goals and improve quality of care. As non-adherence is a public health matter with significant implications for health costs and patient safety, interventions need to be developed, evaluated and implemented to address this problem effectively.

A systematic review and network meta-analysis (Chapter 2) was undertaken to generate evidence on the comparison of different medication adherence interventions across various chronic disease groups (Torres-Robles et al. 2018). Interventions were classified in four categories: Attitudinal (i.e. those aiming to modify patient's attitudes or beliefs towards their medications or disease); Educational (i.e.those aiming at increasing patient's knowledge or skills through the provision of information about the medication, disease or adherence); Technical (i.e. those providing a gadget or system to facilitate medication intake); and Rewards (i.e. those that focus on the provision of incentives or awards to facilitate adherence) (Tonin et al. 2019). Network meta-analysis was selected as it allows the comparison of direct and indirect evidence (Tonin et al. 2017), unlike pairwise meta-analysis. This approach allowed the comparison of various adherence interventions to provide more robust evidence on their impact and subsequent selection of an intervention. The Network meta-analysis found that multi-component interventions were more effective at improving long-term (>=10months) medication adherence on patients suffering from chronic diseases. Interventions including Educational + Technical components were the most effective in "circulatory system and metabolic diseases"

and “infectious diseases”. These results agreed with previous published research by Kanters et al. (Kanters et al. 2017) and Conn et al. (Conn et al. 2015). This emphasises the importance of the provision of adequate information, medication/disease knowledge (DiMatteo, Haskard-Zolnierek & Martin 2012) and tools or gadgets that help patients adopt routines for medication taking (Vervloet et al. 2012) to overcome those barriers associated to non-intentional non-adherence. Attitudinal interventions were the most effective for “musculoskeletal diseases”. Patients suffering from these conditions may have a higher prevalence of intentional non-adherence (Horne & Weinman 1999) influenced by perceived susceptibility and barriers towards the disease (Glanz, Rimer & Viswanath 2015). For the group of “mental, behavioural or neurodevelopmental disorders” there was not a most effective intervention, perhaps indicative of the complexity and dynamic nature of adherence in these patients. However, compared to usual care, the combination of Educational + Attitudinal resulted in significant differences favouring the combination, supporting previous research (Bond & Anderson 2015; Hartung et al. 2017). Some diseases, such as asthma and COPD, could not be included in the analysis due to the lack of studies reporting long-term outcomes. Therefore, further research on the impact or effect of different adherence interventions on these diseases is necessary.

Overall, components of effective interventions varied between disease groups, and this may be explained by the characteristics intrinsic to the disease (Conn et al. 2016). Clinical status, presence of symptoms, perception of the severity of the disease are characteristics associated to the condition which have an impact on patients and therefore, on adherence (Kardas, Lewek & Matyjaszczyk 2013). The network meta-analysis allows the selection of effective interventions in chronic diseases that should be considered when designing and developing medication adherence management programs.

Community pharmacists’ capacity, professional competency, knowledge on medications and disease management, accessibility and proximity to the patients and focus on the quality and safe use of medications, makes them ideal healthcare

professionals to deliver interventions that effectively improve medication adherence and positively impact on health outcomes (Tsuyuki et al. 2018). Commonly, patients with chronic conditions need to attend to pharmacies to collect their medications at least every month, and once dispensed, this data, in most countries, is recorded in the pharmacy system. Therefore, community pharmacies are a promising setting to provide services focused on adherence management. Furthermore, there is current evidence from the meta-analysis that suggests that targeted interventions delivered face-to-face by pharmacists may be effective at improving adherence (Conn & Ruppar 2017). As the role of community pharmacists is evolving as providers of services aiming to improve patient care (Crespo-Gonzalez, Garcia-Cardenas & Benrimoj 2017), it was pivotal to build evidence on interventions that can be effectively implemented in practice. In Australia and Spain, the proposed model for community pharmacy is patient-oriented. Both countries are actively involved in the design and implementation of innovative professional services. Therefore, they represent ideal countries to explore the potential of community pharmacists at managing medication adherence.

The first part of this research's fieldwork involved the retrospective analysis of dispensing pharmacy data to identify changes in adherence rates one year before and after a community pharmacist educational-based adherence intervention in real-life practice. The MedScreen Compliance Program had been developed by GuildLink Pty, a subsidiary of the Pharmacy Guild of Australia, and implemented in more than 3000 Australian community pharmacies to target non-adherent patients with chronic conditions. The economic impact of this intervention has been measured, reporting estimated savings for the Australian healthcare system of $1.9 billion annually following the intervention (Cutler et al. 2019). Three medications, which were existing part of the MedScreen Compliance program, were analysed: rosuvastatin, irbesartan and desvenlafaxine. Non-adherence was defined as MPR <70% (calculated from dispensing pharmacy data).

The results of this study found that the intervention was effective at improving medication adherence. Mean adherence rates increased to 70% three months after

the delivery of the intervention and declined to 60% average adherence rate for all medications after 12 months afther the provision of the intervention. A similar study, evaluating a real-world long-scale community pharmacist brief intervention based on adherence screening and education, found an increase on mean adherence rates ranging from 2%-7% (from 64% to 70% average PDC) after the intervention (Pringle et al. 2014). Our study resulted in greater increases of PDC after the intervention (between 9% and 18%), maybe due to characteristics of the MedScreen Compliance program (e.g. setting, delivery of the intervention). Adherence rates depicted a gradual decrease overtime of almost 8% after one year of the MedScreen compliance program, a trend reported in previous research (Ogundipe et al. 2020), highlighting the dynamic nature of medication adherence (Blaschke et al. 2012; Demonceau et al. 2013) and the need of continuous interventions to maintain adherence. An important aspect to take into account is the components of the intervention. As the basis was purely educational (e.g. provision of verbal or printed information about the medications), it might be that other reasons for non-adherence such as lack of motivation or forgetfulness, were not addressed. Therefore, the MedScreen intervention could be enhanced by the inclusion of multiple components (e.g. behavioural theories, technical gadgets to facilitate medication taking), proven to be long-term effective at improving adherence (Wiecek et al. 2019). Follow-up was not clearly defined as this was a real-life intervention and fidelity data was not available. A previous study found that pharmacies with low compliance to the protocol resulted in lower medication adherence rates (Blackburn et al. 2016). These results underline the importance of fidelity to the intervention to maintain a positive impact on real-world settings. Patients may need continuous follow-up to maintain adherence (Jimmy & Jose 2011).

Another implication of this research is the relevance of using innovative data analysis techniques to address medication adherence. Pharmacy data might provide an important strategy to measure and improve medication adherence in community pharmacies as they are a cost-effective resource already available in pharmacies and can be used to measure refill adherence patterns through objective measures such

as Proportion of Days Covered or Medication Possession Ratio. These measures have some limitations, such as not reflecting the patient actually taking the medication (Osterberg & Blaschke 2005). As there is no gold standard to measure adherence, it is essential to understand the variety of measurements available, so they can be effectively used (Whalley Buono et al. 2017).

The analysis of real-life interventions not only reinforces the potential of community pharmacists to improve adherence as part of their usual practice but also highlights the necessity to improve the design of interventions so they can be implemented, after proven efficacy in clinical trials. Furthermore, the impact on medication adherence and its associated outcomes (e.g. disease-specific clinical outcomes) should be addressed as highlighted in previous research (Nieuwlaat et al. 2014; Zullig et al. 2018).

The second part of this research was focused on exploring the efficacy and effectiveness of community pharmacists at managing medication adherence in a two-phase study (a cluster randomised controlled trial; and a hybrid effectiveness-implementation study) in Spain. This study addressed adherence management, one of the six professional services with national priority for their implementation in Spain (Sexto 2016). Phase 1 was a clustered randomised controlled trial to evaluate the efficacy of the medication adherence management service across community pharmacies in Spain. Provinces were selected due to their expression of interest to participate in the trial. The intervention included frameworks and models for behaviour change targeting specific barriers and proposing strategies to improve adherence on patients suffering from hypertension, asthma and COPD. Educational, technical and attitudinal components highlighted in the network meta-analysis of interventions (Torres-Robles et al. 2018) were accounted in the development of this intervention. The three diseases were selected due to their increasing prevalence and high non-adherence rates (Blaschke et al. 2012; Mueller et al. 2017). Although there was an option for mixing patients in initiation and implementation phase, the statistical analysis model included those patients with adherence data at baseline, which means that only implementation adherence was assessed. The clinical

outcomes were selected due to their validity and common utilisation in the daily pharmacy practice. These were Spanish validated questionnaires (i.e. Asthma Control Questionnaire for asthma, Clinical COPD Questionnaire for COPD) and validated measures (i.e. blood pressure levels for hypertension). The estimated duration of this complex intervention was 104.32 ± 45.29 min per patient over the six months of the cRCT (Informe 2019).

The results of this study found an improvement on medication adherence and disease-specific clinical outcomes at the end of the follow-up (6 months) and the differences were significant for most of the outcomes when compared to the control group (usual care) (paper described on chapter 4). Only the differences on the baseline mean CCQ scores, the continuous variable for COPD, were statistically significant. The statistical analysis accounted for the baseline differences. Significant improvements in the proportion of adherent patients were not evident until visit 3, suggesting that it may take some time for patients and pharmacists to adapt to the intervention. The proportion of adherent patients in the intervention group increased by 50% from baseline to visit 6, larger than in previously published studies also utilising a self-report measurement of medication adherence (Armour et al. 2007; Stewart et al. 2014). This could be attributed to the strong theoretical basis of the intervention, continuous patient follow-up (monthly visits) and the incorporation of Pharmacists Change Facilitators (PCF), who supported the quality and fidelity of participant pharmacists to the study protocol.

In both the Spanish (chapter 4) and Australian (chapter 3) studies, community pharmacist-led interventions resulted in an increase in the proportion of adherent patients three months after the provision of the intervention (40% and 20% average respectively). However, this proportion decreased over time in the MedScreen Compliance Program (post-intervention) but continually increased in the medication adherence management service during the six months of study. These differences could be probably due to the continuous follow-up (monthly visits for six months) in the cRCT when compared to not continuous follow-up in the Australian intervention. As adherence behaviour changes over time, patient's barriers and strategies may

need to be constantly reviewed to improve, maintain and prevent a decline of adherence, as suggested in literature (van Dalem, Krass & Aslani 2012). Also, the components of both interventions are different. While the Australian MedScreen Compliance program is mainly based on an educational intervention, the medication adherence management service in Spain adopts different educational, attitudinal and technical components that have been proven to be effective in the long-term improvement of adherence (Wiecek et al. 2019). Finally, while there were no fidelity measures available from the real-life intervention, the cRCT included the participation of PCF, pharmacists, external to the intervention, who monitored the quality and fidelity of the intervention delivery.

Due to the nature of the intervention, the MedScreen Compliance Program did not include data on disease-specific outcomes preventing the measurement of the clinical impact of the intervention. However, the cRCT in Spain provided evidence on this. In terms of the proportion of patients with better health status (i.e. hypertension control, asthma control, low clinical impact – low level of symptoms - on COPD) the intervention resulted on increases of 12.8% in hypertension controlled patients, 34.7% asthma controlled patients and 24.9% of patients with low clinical impact on COPD by the end of the study. The baseline proportion of controlled patients in hypertension was higher than for the other two diseases, leaving less room for improvement. The positive effect of the intervention on patients with asthma and COPD may also be justified by the assessment of inhaler technique, a component of the medication adherence management service.

The sub-analysis conducted in patients suffering from asthma and COPD and using long-term controller inhaled medications resulted on improvements on the proportion of patients with correct inhaler technique and significant differences on patients receiving the intervention (medication adherence management service) when compared to usual care. This provides supporting evidence on the effect of adherence interventions delivered in a community pharmacy setting. Therefore, integrating inhaler technique as part of medication adherence management for patients using inhaled medications is essential. Incorrect inhaler technique can be

caused by the patient not understanding the steps involved in the use of their device (i.e. unintentional non-adherence) or the patient not being motivated or willing to use the inhaled medication (i.e. intentional non-adherence). Addressing different causes of non-adherence, as suggested in the medication adherence management service, may not only impact medication adherence but also inhaler technique.

The second part of the Spanish (phase 2) study was a hybrid effectiveness-implementation study (Curran et al. 2012) as research on medication adherence is usually limited to determine the efficacy of interventions in clinical trials, with just a few interventions being tested in routine practice (Zullig et al. 2019). Evidence is needed on interventions that can be effectively implemented in practice. In contrast to the previous phase (cRCT), all participant pharmacies delivered the intervention with follow-up visits. The schedule was more flexible, allowing pharmacists to organise the next follow-up visit based on the patient's improvement and their professional judgement. The findings of this research (chapter 6) provide evidence on the effectiveness during an implementation study, of an intervention after its proven efficacy in the randomised controlled trial. Patients were grouped in three groups: those who were in the intervention group during Phase 1 (Group A), those in the control group during Phase 1 (Group B) and new patients in Phase 2 (Group C). Baseline proportion of adherent patients was lower in Group C (55.7%) as these patients were new to the program and had not received an adherence intervention before. Proportions of adherent patietns in Group B was slightly higher (62.5%), as these patients had participated in the control group during the previous phase (cRCT). They showed a slight improvement on adherence after the trial probably as a result of the monthly adherence and health data collection, which was inherent to the study design. Group A had the highest proportion of adherent patients at baseline (86.1%) resulting from the improvement observed after receiving a monthly face-to-face intervention in the cRCT during six months. The three groups experienced an improvement in the proportion of adherent patients at the end of the study, with the lowest observed in Group A, as the baseline values were already high, leaving less improvement options. The proportions of adherent patients in

Groups B and C increased close to 86%, indicative of the impact of the intervention during the implementation study.

With regards to the clinical outcomes, those in the Group C had an overall better improvement on disease-specific outcomes (hypertension control, asthma control, COPD low clinical impact) when compared to the other groups, as they had lowest control baseline values and, therefore, most likely to benefit from the intervention. Those in Group A and B, who had participated in the previous phase, had an improvement on outcomes with the lowest observed in group A, as these patients had already been receiving the intervention during 6 months and their baseline values on the second Phase were higher as an indicative of good health control. The utilisation of implementation factors to facilitate the integration of the intervention in daily practice, the preparation of the pharmacists to deliver the intervention and the continuation of the fidelity monitoring by the PCF may have contributed to these positive results during the Phase 2.

When observing those patients who received the intervention during both phases (patients in Group A), results indicate an improvement across both phases, with this being higher during Phase 1, as patients were less controlled/adherent. The results from Phase 2 highlight the importance of follow-up to maintain adherence, as adherence behaviour can always change.

The comparison of the impact of the intervention in both phases resulting from comparing patients who received the intervention on Phase 1 and those new to the intervention on Phase 2 (Group C), resulted on greater improvements during the cRCT (Phase 1). This is probably due to patients being more controlled/adherent at baseline in the Phase 2 than Phase 1. For instance, the baseline proportion of adherent patients in Phase 1 was 39.1%, lower than the baseline proportion on Phase 2 (55.7%). Also, the scheduling of the visits was more flexible during Phase 2, as part of the adaptation of the service into routine practice, and this may impact on the overall effect.

This thesis provides further evidence on the role of community pharmacists in managing medication adherence, with adherence rates increasing after an educational-based intervention in real-life in Australia and the efficacy and effectiveness of a multi-component intervention in Spain.

Methodological reflections and limitations

The strengths and limitations of the research included in this thesis have already been discussed in detail in the relevant chapters (3-6). In summary, multiple methodologies were employed to evaluate the impact of community pharmacist interventions to manage medication adherence. A retrospective observational study was undertaken to determine the impact of a real-life community pharmacy intervention in Australia through the analysis of pharmacy dispensing data. The novelty and strength of this study was the utilisation of big data analysis techniques of medication adherence rates from a real-life intervention that was already being provided in Australian community pharmacies. Limitations associated to the information recorded in the databases were identified in this research, including that patient dispensing data was only limited to the pharmacy where he/she received the intervention. Therefore, if the patient collected medications in other pharmacies this information was not recorded. To overcome this limitation, a sensitivity analysis with data from patients claiming prescriptions in the same pharmacy was performed. Indicators for the fidelity of the intervention were unavailable in the databases. However, this is maybe a limitation when analysing real-life interventions.

Regarding the cluster randomised controlled trial, the study design allowed the randomisation of pharmacies as clusters to minimise the contamination of patients between groups, reduce the bias and evaluate the impact of the intervention. Due to the nature of the intervention, blinding of pharmacists could not be possible with this identified as a risk of bias. This is a common limitation on this type of studies, assessing educational interventions in healthcare settings. However, training on data collection for intervention and control groups and fidelity monitoring by PCF were performed to overcome this limitation. Another limitation of the study was related

to the adherence measurement as only self-report was considered in the protocol. The lack of communication between pharmacy data recording systems in Spain prevented the utilisation of objective measures such as the proportion of days covered. Nonetheless, in the absence of a gold standard for adherence measurements, self-report may be considered as a valid measure proven to provide similar results when compared against objective measures (Shi et al. 2010). When patients had more than one of the studied diseases, the pharmacists selected the one, on the basis of the number of patients to be recruited per disease. Althouh this could have presented a classification bias, the selection method guaranteed the maintenance of a similar sample size for all diseases.

The relevance of the sub-analysis of patients suffering from asthma or COPD and being prescribed with inhaled medications relies on the possibility of exploring the impact of the medication adherence management service on inhaler technique performance. The main limitation was some missing data associated to patients forgetting to bring their inhalers when being interviewed by pharmacists and, therefore, the assessment of inhaler technique not being possible. Variability associated with pharmacists observing the patient inhaler technique performance could cause bias on data collection. However, this bias was reduced by providing the same device-specific checklists to pharmacists. Also, they were unaware of which steps were considered as critical during the study.

The final research study described a hybrid effectiveness-implementation study design. The strength of this study was the analysis of the effectiveness of the intervention during its implementation on routine practice and observe if the efficacy of the clinical trial was maintained during the real trial. A complex intervention based on behaviour change frameworks targeted individual patient's barriers and developed strategies. Characteristics of groups of patients included during the Phase 2 were diverse, with some patients already having good health control due to the intervention received in the previous Phase (Group A) and others receiving the intervention for the first time (Group C). The results of the intervention indicate that the intervention can be effective at improving and maintaining positive health

outcomes. Because of their participation during phase 1, pharmacists (providers of the intervention) who continued during the phase 2 (implementation study) had more experience at providing the intervention than new pharmacists with this causing difference on performance and data collection. Similarly, as identified during the RCT, self-report as a measure of adherence might also be a source of some desirability bias.

Implications and recommendations for future research

The role of community pharmacists is evolving towards the provision of professional pharmacy services, including medication adherence management services. As a result, the development of these services should consider current and comparable evidence on interventions that have proven efficacy under controlled trials and if possible, effectiveness studies when implemented in real practice. As medication non-adherence continues to be a topic of public health interest with significant repercussion on patients' outcomes and healthcare, more research is needed on interventions that can be implemented and sustained over time.

The body of work described in this thesis provides evidence on the impact of community pharmacist-led interventions to improve adherence, a real-life intervention in Australian community pharmacies and a controlled trial in Spain with two phases including the effectiveness of an intervention when implemented into routine practice.

Recommendation 1: Improvement of the real-life community pharmacists' intervention.

The intervention provided in Australian community pharmacies (MedScreen Compliance Program) underlines the potential of real-life interventions commercial to improve patient care. The inclusion of components that have proven to be effective to improve adherence based on current evidence and the enhancement of data collection processes and fidelity monitoring may be of benefit for the intervention to be improved and greater impact to be achieved. As some non-

adherent patients may require changes in the medication therapy (e.g. simplification of drug regimen) as a strategy to improve adherence, extensive collaboration and communication between pharmacists and other healthcare providers are pivotal.

The integration of the intervention in more Australian pharmacies could guide the adherence management on a national level.

Recommendation 2: Including pharmacy data as a method to measure non-adherence in community pharmacies

The increasing amount of healthcare data in community pharmacies can be utilised to identify patients' patterns of adherence behaviour. Incorporating big data analysis techniques to retrieve adherence rates from dispensing data using validated measures of adherence (e.g. PDC) may improve the assessment of non-adherence and therefore, patient's health outcomes.

Policy and decision-makers should also consider moving towards the digitalisation of data in community pharmacies to improve traceability and facilitate the adaptation of pharmacy services, to the ultimate goal of enhancing patient care. Strategies should be taking into account to overcome the challenges associated with pharmacy data (Galozy et al. 2020). It would also be interesting to explore the linkage of pharmacy data with other healthcare data (such as hospitalisations and emergency visits) to provide a broader perspective of the impact of adherence.

Recommendation 3: Adoption of the medication adherence pharmacy service on a national level in Spain.

The findings of the randomised controlled trial provide evidence on a brief yet complex community pharmacist-led intervention based on theories and frameworks of change behaviour effective at improving medication adherence, disease-specific clinical outcomes and inhaler technique. These results highlight the importance of follow-up, identification of patient's barriers and targeted strategies as fundamental characteristics when developing an intervention. Specifically, in patients suffering from asthma and COPD, it is critical to consider the assessment of inhaler technique

as part of the development of adherence intervention. The medication adherence management service can be replicated to a national level in Spain and work as a guide on the development of services on a global scale.

The implementation study focused on the effectiveness of a medication adherence management service when integrated into real practice. These findings pave the way on the integration of implementation science in medication adherence research. Further exploration of the implementation factors associated with the medication adherence management service is necessary to strengthen the opportunity to accelerate the implementation of the current service results.

These results may also guide the future negotiation between the national pharmacy body representative and government of the financial remuneration of adherence management services as an integral part of the community pharmacy practice.

Conclusions

This thesis has included multiple approaches, methodologies and collaborations to synthesise evidence on the impact of interventions delivered by community pharmacists in controlled settings and real-life practice.

Multiple conclusions have arisen as a result of the research work described in this thesis:

- Network meta-analysis techniques are useful to compare the effectiveness of medication adherence interventions across different chronic conditions.
- An education-based real-life practice intervention in Australia was effective at improving medication adherence when measured with the Proportion of Days Covered from dispensing pharmacy data. As adherence rates declined over time (≥12 months), enhancing the intervention should be considered in the future.
- The integration of big data analysis techniques was effective at measuring adherence rates and determine the impact of a real-life intervention delivered in community pharmacies in Australia.

- A pharmacist-led medication adherence management service in Spain was effective at improving medication adherence, disease-specific clinical outcomes and inhaler technique. This highlights the potential of community pharmacists at managing patient care and provides a basis for the development of medication adherence pharmacy services.
- The clinical benefits observed during the clinical trial (cRCT) of a medication adherence management service in Spain continued during the implementation study (routine-practice).

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Appendices

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Contribution: Conception or design of the work (CD), Data collection (DC), data analysis (DA), Data interpretation (DI), manuscript preparation (MP), revision of the manuscript (RM).

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Chapter 2

1. **Complete search strategy**

PubMed	**#1** ("drug therapy"[Mesh Terms] OR "medication[Title/Abstract]) AND ("patient compliance"[Mesh Terms] OR "medication adherence"[Mesh Terms] OR "medication adherence"[Title/Abstract]) **#2** "systematic review"[Title/Abstract] OR "meta-analysis"[Publication type] OR "meta-analysis"[Title/Abstract] **#1 AND #2**

2. **Complete inclusion and exclusion criteria**

Meta-analyses

We are looking for meta-analyses focused on medication adherence interventions with adherence outcomes including: pill count, refill data, self-report, or electronic monitoring.

Excluded

1. Meta-Analysis not performed or studies in meta-analysis not listed
2. Only paediatric studies included (<18 years)
3. No medication adherence intervention studies included (i.e. only medication efficacy studies)
4. No medication adherence data reported
5. No outcomes of adherence reported including: pill count, refill data, self-report, and electronic monitoring (i.e. clinical outcomes only) or only includes outcomes that are not assessable (i.e. drug levels/depot medications/etc.)
6. Only provider/healthcare professional targeted interventions and outcomes

Primary studies

We are looking for experimental studies with interventions aimed at adult patients on prescription medications with adherence outcomes including: pill count, refill data, self-report, or electronic monitoring.

Exclusion criteria

1. Publications not subject to peer-review, conference posters/abstracts, dissertations, or unpublished data sets
2. Expert opinion pieces, economic analyses, single case reports, cross-sectional studies (i.e. retrospective data on once vs twice daily), medication efficacy studies with no adherence intervention, or cohort studies
3. Children < 18 years included in study or studies aimed at physicians/healthcare professionals
4. Over-the-counter medications, depot medications, vaccines, any medication without instructions or with "as needed" instructions where the patient decides the dose
5. Studies only measuring clinical outcomes, drug levels, undefined adherence outcomes, or initiation or discontinuation adherence
6. Treatment follow-up less than 10 months.

3. Category definitions

Category	**Definition**
Educational	Interventions providing information regarding the medication, disease state or importance of adherence, in any form (e.g. written, oral, in group, by telephone), to a patient with the aim of increasing a patient's knowledge or skills that facilitate adherence.
Attitudinal	Interventions aiming to modify behavioral intention based on modifying patient's attitudes, beliefs or subjective norm related to their disease state or medication (e.g. motivational interviewing, cognitive behavioral therapy, etc.), delivered in any form (e.g. written, oral, in group, by telephone).
Technical	Interventions providing any gadget, instrument, or system that facilitate the medication intake or increase convenience of the medication taking process, such as reminders, regime simplifications, telephone follow-ups, direction observation therapy, self-monitoring, cue-dose training, electronic monitoring feedback etc.
Rewards	Interventions that provide incentives, awards or penalties to facilitate medication adherence.

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c. Excluded primary studies

Meta-analysis	**Original studies**
Easthall C, Song F, Bhattacharya D. A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. BMJ Open. 2013;3(8).	
	Berger, 2005
	Brown, 2009
	George, 2010
	Hovell, 2003
	Maneesriwongul, 2012
	Put, 2003
	Sheeran, 1999
	Smith, 2003
	Solomon, 2012
	Van Es, 2001
	Williams, 2012
Tao D, Xie L, Wang T, Wang T. A meta-analysis of the use of electronic reminders for patient adherence to medication in chronic disease care. J Telemed Telecare. 2015;21(1):3-13.	
	Andrade, 2005
	Charles, 2007
	Christensen, 2010
	Chung, 2011
	Franklin, 2006
	Ho, 2008
	Petrie, 2012

	Simoni, 2009
Sakakibara BM, Kim AJ, Eng JJ. A Systematic Review and Meta-Analysis on Self-Management for Improving Risk Factor Control in Stroke Patients. Int J Behav Med. 2017;24(1):42-53.	
	Evans-Hudnall, 2014
	Kim, 2013
	Kronish, 2014
	Mackenzie, 2013
	O'Carroll, 2013
Rash JA, Campbell DJ, Tonelli M, Campbell TS. A systematic review of interventions to improve adherence to statin medication: What do we know about what works? Prev Med. 2016;90:155-69.	
	Aslani, 2011
	Evans, 2010
	Flemming, 2013
	Jarab, 2012
	Kardas, 2012
	Mols, 2015
	Patel, 2015
	van Bruggen, 2009
Kassavou A, Sutton S. Automated telecommunication interventions to promote adherence to cardio-metabolic medications: meta-analysis of effectiveness and meta-regression of behaviour change techniques. Health Psychol Rev. 2018;12(1):25-42.	
	Arora, 2014
	Gatwood, 2016
	Kamal, 2015
	Sherrard, 2015
	Stacy, 2009
Parienti JJ, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: a meta-analysis. Clin Infect Dis. 2009;48(4):484-8.	
	Benson, 2004
	Kubota, 2006
	Parienti, 2007
	Portsmouth, 2005
	Rode, 2008
	Ruane, 2006
Falagas ME, Karagiannis AK, Nakouti T, Tansarli GS. Compliance with once-daily versus twice or thrice-daily administration of antibiotic regimens: a meta-analysis of randomized controlled trials. PLoS One. 2015;10(1):e0116207.	
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	Ballantyne, 1985
	Behre, 1997
	Cheung, 1988

	Clegg, 2006
	Cohen, 1996
	Cook, 1996
	Damrikarnlert, 2000
	Disney, 1990
	Edelstein, 1993
	Fyllingen, 1991
	Garcia Callejo, 1998
	Gehanno, 1994
	Gerber, 1985
	Gooch, 1993
	Gooch, 1997
	Hosie, 1995
	Kardas, 2007
	Lennon, 2008
	Linder, 1993
	Martinot, 2001
	Mita, 2003
	Owen, 1993
	Pichichero, 1999
	Richard, 1981
	Venuta, 1998
Conn VS, Enriquez M, Ruppar TM, Chan KC. Cultural relevance in medication adherence interventions with underrepresented adults: systematic review and meta-analysis of outcomes. Prev Med. 2014;69:239-47.	
	Anderson, 2004
	Austin, 1986
	Babamoto, 2009
	Bogart, 2012
	Bogner, 2008
	Chaisson, 2001
	Cordasco, 2009
	Fernandez, 2008
	Fisher, 2011
	Freedman, 2007
	Gazmararian, 2010
	Harper, 1984
	Laine, 1996
	Mann, 2001
	Martin, 2011
	McKenney, 1973
	McKenney, 1978

	Moitra, 2011
	Muir, 2012
	Mundy, 2009
	Newsome, 1995
	Powell, 2002
	Tagliacozzo, 1974
	Vivian, 2002
	Walker, 2000
	Webel, 2010
	Werner, 1979
	Wyatt, 2004
Hart JE, Jeon CY, Ivers LC, Behforouz HL, Caldas A, Drobac PC, et al. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. J Acquir Immune Defic Syndr. 2010;54(2):167-79.	
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Mutasa-Apollo T, Ford N, Wiens M, Socias ME, Negussie E, Wu P, et al. Effect of frequency of clinic visits and medication pick-up on antiretroviral treatment outcomes: a systematic literature review and meta-analysis. J Int AIDS Soc. 2017;20(Suppl 4):21647.	
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	Jaffar, 2009
Readdean KC, Heuer AJ, Scott Parrott J. Effect of pharmacist intervention on improving antidepressant medication adherence and depression symptomology: A systematic review and meta-analysis. Res Social Adm Pharm. 2017.	
	Aljumah, 2015
	Al-Saffar, 2005
	Finley, 2002
	Klang, 2015
	Rubio-Valera, 2013
Morrissey EC, Durand H, Nieuwlaat R, Navarro T, Haynes RB, Walsh JC, et al. Effectiveness and content analysis of interventions to enhance medication adherence and blood pressure control in hypertension: A systematic review and meta-analysis. Psychol Health. 2017;32(10):1195-232.	
	Dusing, 2009
	Girvin, 1999
	Greer, 2014
	Margolius, 2012
	Matsumura, 2012
	Sackett, 1975
	Stewart, 2014
Zomahoun HTV, Guenette L, Gregoire JP, Lauzier S, Lawani AM, Ferdynus C, et al. Effectiveness of motivational interviewing interventions on medication adherence in adults with chronic diseases: a systematic review and meta-analysis. Int J Epidemiol.	
	DiIorio, 2009

	Kender, 2010
	Martino, 2006
	Williams-a, 2012
Rubio-Valera M, Serrano-Blanco A, Magdalena-Belio J, Fernandez A, Garcia-Campayo J, Pujol MM, et al. Effectiveness of pharmacist care in the improvement of adherence to antidepressants: a systematic review and meta-analysis. Ann Pharmacother. 2011;45(1):39-48.	
	Adler, 2004
	Brook, 2005
	Crockett, 2006
	Finley, 2003
	Rickles, 2005
Vignon Zomahoun HT, de Bruin M, Guillaumie L, Moisan J, Gregoire JP, Perez N, et al. Effectiveness and Content Analysis of Interventions to Enhance Oral Antidiabetic Drug Adherence in Adults with Type 2 Diabetes: Systematic Review and Meta-Analysis. Value Health. 2015;18(4):530-40.	
	Bogner, 2010
	Bogner, 2012
	Farmer, 2012
	Heisler, 2010
	Rothschild, 2014
	Walker, 2011
	Zolfaghari, 2012
Zhu Y, Zhou Y, Zhang L, Zhang J, Lin J. Efficacy of interventions for adherence to the immunosuppressive therapy in kidney transplant recipients: a meta-analysis and systematic review. J Investig Med. 2017;65(7):1049-56.	
	Bessa, 2016
	Chisholm-Burns, 2013
	Fennell, 1994
	Garcia, 2015
Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials. J Acquir Immune Defic Syndr. 2006;43 Suppl 1:S23-35.	
	Jones, 2003
	Knobel, 1999
	Margolin, 2003
	Rawlings, 2003
	Rotheram-Borus, 2004
Langebeek N, Nieuwkerk P. Electronic medication monitoring-informed counseling to improve adherence to combination anti-retroviral therapy and virologic treatment outcomes: a meta-analysis. Front Public Health. 2015;3:139.	
	Davies, 2010
	Engelbrecht, 2010

	Sabin, 2014
	Wilson, 2010
Petry NM, Rash CJ, Byrne S, Ashraf S, White WB. Financial reinforcers for improving medication adherence: findings from a meta-analysis. Am J Med. 2012;125(9):888-96.	
	Bock, 2001
	Carroll, 2001
	Carroll, 2002
	Claassen, 2007
	Grabowski, 1979
	Jakubowiak, 2007
	Martins, 2009
	Morisky, 2001
	Nunes, 2006
	Preston, 1999
	Rigsby, 2000
	Seal, 2003
	Stitzer, 2010
	Tulsky, 2000
	Volpp, 2008
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	Kardas, 2004
	Kozuki, 2006
	Onyirimba, 2003
	Qureshi, 2007
	Rapoff, 2002

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	Lai, 2010
	Montori, 2011
	Moss, 2010
	Shu, 2009
	Stockl, 2010
	Stockl, 2010b
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	Cochran, 1984
	Colom, 2003
	Dogan, 2003
	Eker, 2012
	Elixhauser, 1990
	Lam, 2000
	Lenz, 2010
	Miklowitz, 2000
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Kauppi K, Valimaki M, Hatonen HM, Kuosmanen LM, Warwick-Smith K, Adams CE. Information and communication technology based prompting for treatment compliance for people with serious mental illness. Cochrane Database Syst Rev. 2014(6):CD009960.	
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Kanters S, Park JJ, Chan K, Socias ME, Ford N, Forrest JI, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. Lancet HIV. 2017;4(1):e31-e40.	
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	Garcia, 2005
	Hersch, 2013
	Kurth, 2014
	Levin, 2006

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	Orrell, 2015
	Peltzer, 2012
	Safren, 2012
	Wagner, 2013
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Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. Cochrane Database Syst Rev. 2017;4:CD012226.	
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	Chatkin, 2006
	Duncan, 2013
	Foster, 2014
	Hederos, 2005
	Mehuys, 2008
	Otsuki, 2009
van Driel ML, Morledge MD, Ulep R, Shaffer JP, Davies P, Deichmann R. Interventions to improve adherence to lipid-lowering medication. Cochrane Database Syst Rev. 2016;12:CD004371.	
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	Brun, 1994
	Edworthy, 1999
	Gabriel, 1977
	Grant, 2003
	Halfmann, 2000
	Jennings, 1992
	Klein, 2006
	Lipton, 1994
	Lourens, 1994
	Pullar, 1988
	Raynor, 1993
	Rimer, 1987
	Roden, 1985
	Rozenfeld, 1999
	Schectman, 1994
	Simkins, 1986
	Solomon, 1998
	Wood, 1989

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	Castellano, 2014
	Gould, 2011
	Gould, 2011
	Jiang, 2007
	Lourenco, 2014
	Ostbring, 2014
	Polack, 2008
Conn VS, Ruppar TM, Chase JA, Enriquez M, Cooper PS. Interventions to Improve Medication Adherence in Hypertensive Patients: Systematic Review and Meta-analysis. Curr Hypertens Rep. 2015;17(12):94.	
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	Aguwa, 2008
	Al Owaish, 1985
	Avanzini, 2002
	Beeson, 1977
	Beune, 2014
	Carter, 2010
	Cooper, 2011
	Erickson, 2003
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	Fletcher, 1975
	Friedberg, 2015
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	Gonzalez-Fernandez, 1990
	Hacihasanoglu, 2011
	Harowski, 1983
	Harper, 1984
	Hess, 2007
	Inui, 1976
	Jafar, 2009
	Kauric-Klein, 2012
	Kobalava, 2010
	Leung, 2012
	Levine, 1979
	Logan, 1982
	Ma, 2014
	Magadza, 2009
	Marquez-Contreras, 2005
	Martin, 2011
	McGillicuddy, 2013

	McKinstry, 2013
	Moore, 2013
	Morgado, 2011
	Muhlhauser, 1988
	Murray, 2004
	Oliver, 2011
	Oparah, 2006
	Park, 1996
	Park, 2013
	Patel, 2013
	Pertusa Martinez, 1998
	Pierce, 1984
	Pippalla, 1994
	Pladevall, 2010
	Planas, 2003
	Resnick, 2009
	Roca-Cusachs, 1991
	Rodriguez, 2011
	Roumie, 2006
	Saleem, 2013
	Santschi, 2008
	Schroeder, 2005
	Sicras-Mainar, 2013
	Sookaneknun, 2004
	Stewart, 2005
	Stewart, 2008
	Svarstad, 2013
	van de Steeg-van Gompel, 2010
	Wentzlaff, 2011
	Wong, 2013
	Zang, 2010
Hollands GJ, McDermott MS, Lindson-Hawley N, Vogt F, Farley A, Aveyard P. Interventions to increase adherence to medications for tobacco dependence. Cochrane Database Syst Rev. 2015(2):CD009164.	
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	Mooney, 2005
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Manias E, Williams A. Medication adherence in people of culturally and linguistically diverse backgrounds: a meta-analysis. Ann Pharmacother. 2010;44(6):964-82.	
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	Berrien, 2004
	Bonner, 2002
	Canino, 2008
	Krier, 1999
	Morisky, 2001
	Rich, 1995
	Schaffer and Tian, 2004
	Schwartz-Lookinland, 1989
	van Servellen, 2003
	Yin, 2008
Ruppar TM, Dunbar-Jacob JM, Mehr DR, Lewis L, Conn VS. Medication adherence interventions among hypertensive black adults: a systematic review and meta-analysis. J Hypertens. 2017;35(6):1145-54.	
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Ruppar TM, Delgado JM, Temple J. Medication adherence interventions for heart failure patients: A meta-analysis. Eur J Cardiovasc Nurs. 2015;14(5):395-404.	
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	Goodyer, 1995
	Jerant, 2003
	Nimpitakpong, 2002
	Nucifora, 2006
	Powell, 2010
	Rich, 1996
	Tierney, 2003
	Udelson, 2009
	Wakefield, 2009
	Wu, 2012
Conn VS, Ruppar TM, Enriquez M, Cooper P. Medication adherence interventions that target subjects with adherence problems: Systematic review and meta-analysis. Res Social Adm Pharm. 2016;12(2):218-46.	
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	Austin, 1986
	Cook, 2010
	De Geest, 2006
	Freedman, 2007

	Harper, 1984
	Haynes, 1976
	Kogos, 2004
	Matterson, 2011
	Mitchell, 1992
	Moitra, 2011
	Murphy, 2002
	Murphy, 2007
	Nietert, 2009
	Okeke, 2009
	Oser, 2008
	Ramirez-Garcia & Cote, 2012
	Remien, 2005
	Rosen, 2007
	Ruppar, 2010
	Russell, 2010
	Safren, 2003
	Sorensen, 2007
	Stewart, 2008
	Van Servellen, 2005
	Wall, 1995
	Watakakasol, 2010
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	Leenen, 1997
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	Nessman, 1980
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	Saunders, 1991
	Sclar, 1991
Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. Am J Health Syst Pharm. 2003;60(7):657-65.	
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	Cole, 1971
	Cramer, 1995
	Ellison, 1982
	Eriksson, 1998

	Finney, 1985
	Garnett, 1981
	Gibbs, 1989
	Jameson, 1995
	Katon, 1996
	Kelly, 1990
	Kruse, 1991
	Levesque, 1983
	Linszen, 1996
	McCrindle, 1997
	Mengze, 1994
	Murray, 1993
	Powell, 1995
	Sanmarti, 1993
	Sellors, 1997
	Sharpe, 1974
	Smith, 1986
	Spriet, 1980
	Taggart, 1981
	Tinkelman, 1980
	Williams, 1986
Miller L, Schuz B, Walters J, Walters EH. Mobile Technology Interventions for Asthma Self-Management: Systematic Review and Meta-Analysis. JMIR Mhealth Uhealth. 2017;5(5):e57.	
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	Khonsari, 2015
	Lua and Neni, 2013
	Lv, 2012
	Maduka and Tobin-West, 2013
	Marquez Contreras, 2004
	Mbuagbaw, 2012
	Park, 2014
	Quilici, 2013
	Quilici, 2013
	Strandbygaard, 2010
	Vervloet, 2012
	Wald, 2014

	Wang, 2014
Palacio A, Garay D, Langer B, Taylor J, Wood BA, Tamariz L. Motivational Interviewing Improves Medication Adherence: a Systematic Review and Meta-analysis. J Gen Intern Med. 2016;31(8):929-40.	
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	DiIorio, 2008
	Golin, 2006
	Holstad, 2011
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	Ingersoll, 2011
	Interian, 2013
	Konkle-Parker, 2012
	Parsons, 2007
	Pradier, 2003
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Wald DS, Butt S, Bestwick JP. One-way versus two-way text messaging on improving medication adherence: meta-analysis of randomized trials. Am J Med. 2015;128(10):1139 e1-5.	
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Conn VS, Ruppar TM, Chan KC, Dunbar-Jacob J, Pepper GA, De Geest S. Packaging interventions to increase medication adherence: systematic review and meta-analysis. Curr Med Res Opin. 2015;31(1):145-60.	
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	Becker, 1986
	Bosworth, 2008
	Burelle, 1986
	Crome, 1982
	Eshelman, 1976
	Henry, 1999
	Kalichman, 2011
	Kennedy, 1990
	Laramee, 2003
	Lee, 1999
	Levensky, 2006
	Linkewich, 1974
	MacDonald, 1977
	MacIntosh, 2007
	McPherson-Baker, 2000

	Nazareth, 2001
	Park, 1992
	Peterson, 1984
	Qingjun, 1998a
	Revankar, 1993
	Safren, 2001
	Spriet, 1980
	Suarez-Varela, 2009
	Sweeney, 1989
	Traiger, 1997
	Tsuyuki, 2004
	Wang, 2010
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Rocha BS, Silveira MP, Moraes CG, Kuchenbecker RS, Dal-Pizzol TS. Pharmaceutical interventions in antiretroviral therapy: systematic review and meta-analysis of randomized clinical trials. J Clin Pharm Ther. 2015;40(3):251-8.	
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	Detry, 1995
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	Fujii, 1985
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	Winland-Brown, 2000
Zou H, Li Z, Nolan MT, Arthur D, Wang H, Hu L. Self-management education interventions for persons with schizophrenia: a meta-analysis. Int J Ment Health Nurs. 2013;22(3):256-71.	
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de Bruin M, Viechtbauer W, Schaalma HP, Kok G, Abraham C, Hospers HJ. Standard care impact on effects of highly active antiretroviral therapy adherence interventions: A meta-analysis of randomized controlled trials. Arch Intern Med. 2010;170(3):240-50.	
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Iglay K, Cao X, Mavros P, Joshi K, Yu S, Tunceli K. Systematic Literature Review and Meta-analysis of Medication Adherence With Once-weekly Versus Once-daily Therapy. Clin Ther. 2015;37(8):1813-21 e1.	
	Downey, 2006
Finitsis DJ, Pellowski JA, Johnson BT. Text message intervention designs to promote adherence to antiretroviral therapy (ART): a meta-analysis of randomized controlled trials. PLoS One. 2014;9(2):e88166.	
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Fenerty SD, West C, Davis SA, Kaplan SG, Feldman SR. The effect of reminder systems on patients' adherence to treatment. Patient Prefer Adherence. 2012;6:127-35.	
	Armstrong, 2009
	Bender, 2010
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	Fulmer, 1999
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Fletcher BR, Hartmann-Boyce J, Hinton L, McManus RJ. The Effect of Self-Monitoring of Blood Pressure on Medication Adherence and Lifestyle Factors: A Systematic Review and Meta-Analysis. Am J Hypertens. 2015;28(10):1209-21.	
	Bailey, 1999
	Bove, 2013
	Green, 2014
	Hosseininasab, 2014
	Johnson, 1978
	Magid, 2011
	McKenney, 1992
	Rudd, 2004
	Stewart, 2014a
	Zarnke, 1997
van Galen KA, Nellen JF, Nieuwkerk PT. The Effect on Treatment Adherence of Administering Drugs as Fixed-Dose Combinations versus as Separate Pills: Systematic Review and Meta-Analysis. AIDS Res Treat. 2014;2014:967073.	
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	RCTAI, 1989

Chase JA, Bogener JL, Ruppar TM, Conn VS. The Effectiveness of Medication Adherence Interventions Among Patients With Coronary Artery Disease: A Meta-analysis. J Cardiovasc Nurs. 2016;31(4):357-66.	
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	Costa, 2008
	Faulkner, 2000
	Gould, 2011
	Guthrie, 2007
	Kelly, 1988
	Kotowycz, 2010
	Lehr, 1986
	Lourenco, 2011
	Miller, 1990
	Muniz, 2010
	Nicoleau, 1985
	Shemesh, 2006
	Shemesh, 2006
	Sherrard, 2009
	Smith, 2008
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	Zhao, 2004
Caldeira D, Vaz-Carneiro A, Costa J. The impact of dosing frequency on medication adherence in chronic cardiovascular disease: systematic review and meta-analysis. Rev Port Cardiol. 2014;33(7-8):431-7.	
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De Simoni A, Hardeman W, Mant J, Farmer AJ, Kinmonth AL. Trials to improve blood pressure through adherence to antihypertensives in stroke/TIA: systematic review and meta-analysis. J Am Heart Assoc. 2013;2(4):e000251.	
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Kanters S, Park JJ, Chan K, Ford N, Forrest J, Thorlund K, et al. Use of peers to improve adherence to antiretroviral therapy: a global network meta-analysis. J Int AIDS Soc. 2016;19(1):21141.	
	Altice, 2007
	Berg, 2011
	Gross, 2009
	Gross, 2015
	Macalino, 2007
	Nachega, 2010
	Ruiz, 2010

5. Risk of bias assessment:

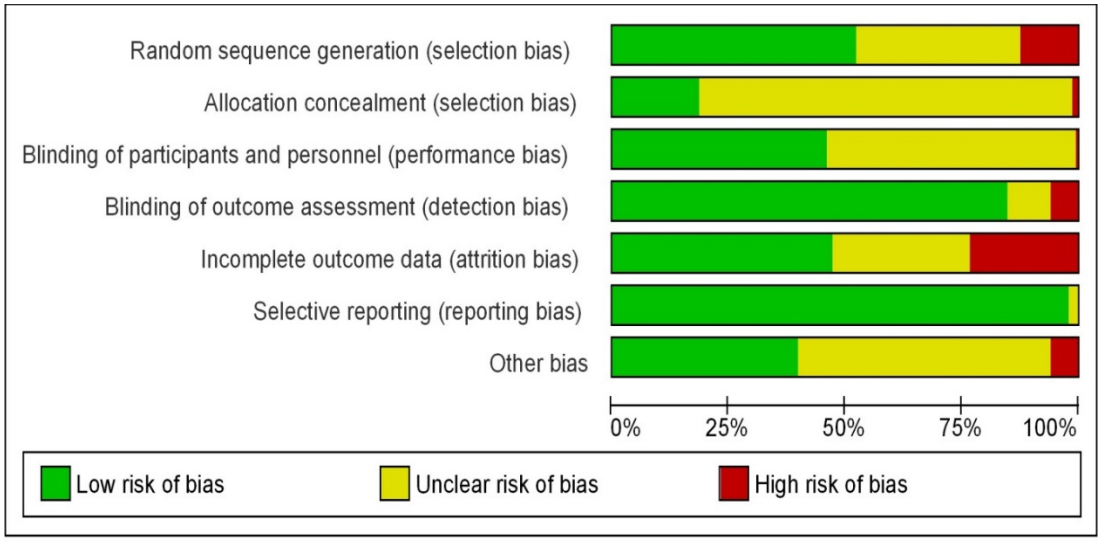
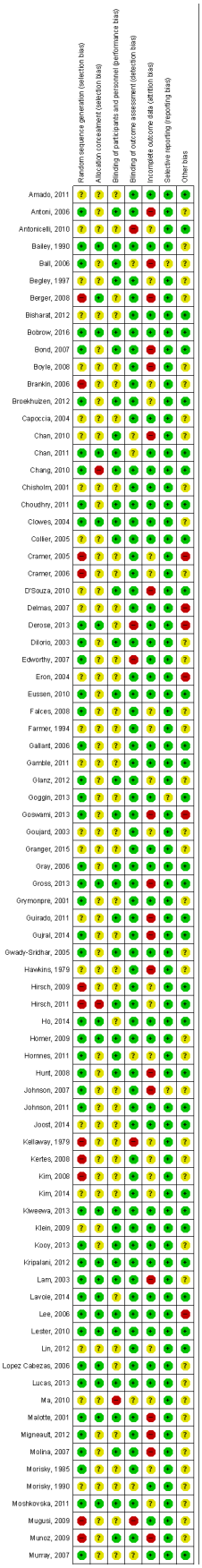


Figure 1. Risk of bias assessment.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Amado, 2011
Antoni, 2006
Antonicelli, 2010
Bailey, 1990
Ball, 2006
Begley, 1997
Berger, 2008
Bisharat, 2012
Bobrow, 2016
Bond, 2007
Boyle, 2008
Brankin, 2006
Broekhuizen, 2012
Capoccia, 2004
Chan, 2010
Chan, 2011
Chang, 2010
Chisholm, 2001
Choudhry, 2011
Clowes, 2004
Collier, 2005
Cramer, 2005
Cramer, 2006
D'Souza, 2010
Delmas, 2007
Derose, 2013
Dilorio, 2003
Edworthy, 2007
Eron, 2004
Eussen, 2010
Falces, 2008
Farmer, 1994
Gallant, 2006
Gamble, 2011
Glanz, 2012
Goggin, 2013
Goswami, 2013
Goujard, 2003
Granger, 2015
Gray, 2006
Gross, 2013
Grymonpre, 2001
Guirado, 2011
Gujral, 2014
Gwady-Sridhar, 2005
Hawkins, 1979
Hirsch, 2009
Hirsch, 2011
Ho, 2014
Horner, 2009
Hommes, 2011
Hunt, 2008
Johnson, 2007
Johnson, 2011
Joost, 2014
Kellaway, 1979
Kertes, 2008
Kim, 2008
Kim, 2014
Kweeva, 2013
Klein, 2009
Kooy, 2013
Kripalani, 2012
Lam, 2003
Lavole, 2014
Lee, 2006
Lester, 2010
Lin, 2012
Lopez Cabezas, 2006
Lucas, 2013
Ma, 2010
Malotte, 2001
Migneault, 2012
Molina, 2007
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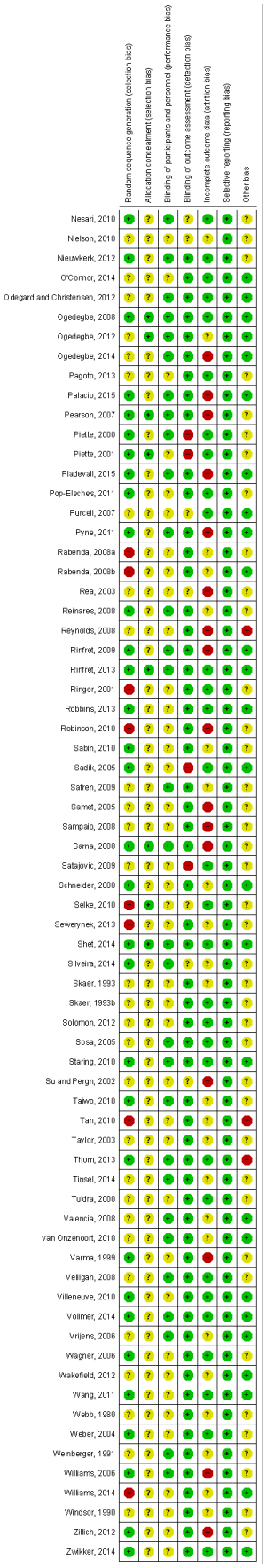
Munoz, 2009
Murray, 2007


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Nesari, 2010
Nielson, 2010
Nieuwkerk, 2012
O'Connor, 2014
Odegard and Christensen, 2012
Ogedegbe, 2008
Ogedegbe, 2012
Ogedegbe, 2014
Pagoto, 2013
Palacio, 2015
Pearson, 2007
Piette, 2000
Piette, 2001
Pladevall, 2015
Pop-Eleches, 2011
Purcell, 2007
Pyne, 2011
Rabenda, 2008a
Rabenda, 2008b
Rea, 2003
Reinares, 2008
Reynolds, 2008
Rinfret, 2009
Rinfret, 2013
Ringer, 2001
Robbins, 2013
Robinson, 2010
Sabin, 2010
Sadik, 2005
Safren, 2009
Samet, 2005
Sampalo, 2008
Sarna, 2008
Satajovic, 2009
Schneider, 2008
Selke, 2010
Sewerynek, 2013
Shet, 2014
Silveira, 2014
Skaer, 1993
Skaer, 1993b
Solomon, 2012
Sosa, 2005
Staring, 2010
Su and Pergn, 2002
Taiwo, 2010
Tan, 2010
Taylor, 2003
Thom, 2013
Tinsel, 2014
Tuldra, 2000
Valencia, 2008
van Onzenoort, 2010
Varma, 1999
Velligan, 2008
Villeneuve, 2010
Vollmer, 2014
Vrijens, 2006
Wagner, 2006
Wakefield, 2012
Wang, 2011
Webb, 1980
Weber, 2004
Weinberger, 1991
Williams, 2006
Williams, 2014
Windsor, 1990
Zillich, 2012
Zwikker, 2014

6. Studies included in the network meta-analysis

a) Cardiovascular and metabolic diseases

Study ID	Title	Study size	Interventions
Antonicelli, 2010	Impact of Home Patient Telemonitoring on Use of ß-Blockers in Congestive Heart Failure	57	Educational + Technical 4th, Standard care 4th
Broekhuizen, 2012	Can Multiple Lifestyle Behaviours Be Improved in People with Familial Hypercholesterolemia? Results of a Parallel Randomised Controlled Trial	224	Educational + Attitudinal 4th, Standard care 4th
Choudhry, 2011	Full Coverage for Preventive Medications after Myocardial Infarction	5855	Rewards 4th, Standard care 4th
Derose, 2013	Automated Outreach to Increase Primary Adherence to Cholesterol-Lowering Medications	5216	Educational + Technical 4th, Standard care 4th
Edworthy, 2007	Effects of an enhanced secondary prevention program for patients with heart disease: A prospective randomized trial	2643	Educational 4th, Standard care 4th
Eussen, 2010	A Pharmaceutical Care Program to Improve Adherence to Statin Therapy: A Randomized Controlled Trial	899	Educational 4th, Standard care 4th
Falces, 2008	[An educative intervention to improve treatment compliance and to prevent readmissions of elderly patients with heart failure]	103	Educational 4th, Standard care 4th
Goswami, 2013	Impact of an integrated intervention program on atorvastatin adherence: a randomized controlled trial	208	Educational 4th, Standard care 4th
Gurjal, 2014	Impact of community pharmacist intervention discussing patients' beliefs to improve medication adherence	200	Attitudinal 4th, Standard care 4th
Hawkins, 1979	Evaluation of a clinical pharmacist in caring for hypertensive and diabetic patients	137	Educational 4th, Standard care 4th
Ho, 2014	Multifaceted Intervention to Improve Medication Adherence and Secondary Prevention	241	Educational + Technical 4th, Standard care 4th

	Measures After Acute Coronary Syndrome Hospital Discharge A Randomized Clinical Trial		
Hornnes, 2011	Blood Pressure 1 Year after Stroke: The Need to Optimize Secondary Prevention	293	Educational + Technical 4th, Standard care 4th
Hunt, 2008	A Randomized Controlled Trial of Team-Based Care: Impact of Physician-Pharmacist Collaboration on Uncontrolled Hypertension	272	Educational + Technical 4th, Standard care 4th
Kooy, 2013	Does the use of an electronic reminder device with or without counseling improve adherence to lipid-lowering treatment? The results of a randomized controlled trial	381	Technical 4th, Attitudinal + Technical 4th, Standard care 4th
Lopez Cabezas, 2006	Randomized clinical trial of a postdischarge pharmaceutical care program vs. regular follow-up in patients with heart failure	63	Educational 4th, Standard care 4th
Morisky, 1985	Evaluation of family health education to build social support for long-term control of high blood pressure.	290	Educational 4th, Standard care 4th
Ogedegbe, 2008	A Practice-based Trial of Motivational Interviewing and Adherence in Hypertensive 065African Americans	160	Attitudinal 4th, Standard care 4th
Ogedegbe, 2012	A Randomized Controlled Trial of Positive-Affect Intervention and Medication Adherence in Hypertensive African Americans	256	Educational 4th, Educational + Attitudinal 4th
Pagoto, 2013	Can attention control conditions have detrimental effects in behavioral medicine randomized trials?	235	Educational 4th, Standard care 4th
Palacio, 2015	Can Phone-Based Motivational Interviewing Improve Medication Adherence to Antiplatelet Medications After a Coronary Stent Among Racial Minorities? A Randomized Trial	339	Attitudinal 4th, Educational 4th
Piette, 2000	Do Automated Calls with Nurse Follow-up Improve Self-Care and Glycemic Control among Vulnerable Patients with Diabetes?	248	Educational + Technical 4th, Standard care 4th

Piette, 2001	Impact of Automated Calls With Nurse Follow-Up on Diabetes Treatment Outcomes in a Department of Veterans Affairs Health Care System A randomized controlled trial	272	Educational + Technical 4th, Standard care 4th
Rinfret, 2013	Telephone contact to improve adherence to dual antiplatelet therapy after drug-eluting stent implantation	300	Educational 4th, Standard care 4th
Sadik, 2005	Pharmaceutical care of patients with heart failure	208	Educational + Technical 4th, Standard care 4th
Taylor, 2003	Improving primary care in rural Alabama with a pharmacy initiative	69	Educational + Technical 4th, Standard care 4th
Thom, 2013	Effects of a Fixed-Dose Combination Strategy on Adherence and Risk Factors in Patients With or at High Risk of CVD The UMPIRE Randomized Clinical Trial	1860	Technical 4th, Standard care 4th
Varma, 1999	Pharmaceutical Care of Patients with Congestive Heart Failure: Interventions and Outcomes	49	Educational + Technical 4th, Standard care 4th
Villeneuve, 2010	A cluster randomized controlled Trial to Evaluate an Ambulatory primary care Management program for patients with dyslipidemia: the TEAM study	225	Educational 4th, Standard care 4th
Vollmer, 2014	Improving Adherence to Cardiovascular Disease Medications With Information Technology	21752	Technical 4th, Educational + Technical 4th, Standard care 4th
Wang, 2011	Effects of pharmaceutical care interventions on blood pressure and medication adherence of patients with primary hypertension in China	59	Educational + Technical 4th, Standard care 4th
Zillich, 2012	Evaluation of Specialized Medication Packaging Combined With Medication Therapy Management: Adherence, Outcomes, and Costs Among Medicaid Patients	14621	Educational 4th, Standard care 4th

b) HIV

Study ID	Title	Study size	Interventions
Boyle, 2008	Randomization to Once-Daily Stavudine Extended Release/Lamivudine/Efavirenz Versus a More Frequent Regimen Improves Adherence While Maintaining Viral Suppression	300	Technical 4th, Standard care 4th
Chang, 2010	Effect of Peer Health Workers on AIDS Care in Rakai, Uganda: A Cluster-Randomized Trial	1203	Educational + Technical 4th, Standard care 4th
Collier, 2005	A Randomized Study of Serial Telephone Call Support to Increase Adherence and Thereby Improve Virologic Outcome in Persons Initiating Antiretroviral Therapy	101	Educational + Attitudinal 4th, Standard care 4th
Eron, 2004	Once-Daily versus Twice-Daily Lopinavir/Ritonavir in Antiretroviral-Naive HIV-Positive Patients: A 48-Week Randomized Clinical Trial	38	Technical 4th, Standard care 4th
Gallant, 2006	Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV	509	Technical 4th, Standard care 4th
Gross, 2013	Managed Problem Solving for Antiretroviral Therapy Adherence: A Randomized Trial	180	Educational + Attitudinal + Technical 4th, Standard care 4th
Hirsch, 2009	Evaluation of the First Year of a Pilot Program in Community Pharmacy: HIV/AIDS Medication Therapy Management for Medi-Cal Beneficiaries	7018	Educational 4th, Standard care 4th
Hirsch, 2011	Antiretroviral Therapy Adherence, Medication Use, and Health Care Costs During 3 Years of a Community Pharmacy Medication Therapy Management Program for Medi-Cal Beneficiaries with HIV/AIDS	2234	Educational + Technical 4th, Standard care 4th
Johnson, 2011	Improving Coping Skills for Self-management of Treatment Side Effects Can Reduce Antiretroviral Medication Nonadherence among People Living with HIV	249	Educational + Attitudinal 4th, Standard care 4th
Kiweewa, 2013	Noninferiority of a Task-Shifting HIV Care and Treatment Model Using Peer Counselors and Nurses Among Ugandan Women Initiated on ART: Evidence From a Randomized Trial	85	Educational 4th, Standard care 4th

Lester, 2010	Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial	538	Technical 4th, Standard care 4th
Lucas, 2013	Directly Administered Antiretroviral Therapy for HIVInfected Individuals in Opioid Treatment Programs: Results from a Randomized Clinical Trial	107	Technical 4th, Standard care 4th
Molina, 2007	A Lopinavir/Ritonavir-Based Once-Daily Regimen Results in Better Compliance and Is Non-inferior to a Twice-Daily Regimen Through 96 Weeks	190	Technical 4th, Standard care 4th
Mugusi, 2009	Enhancing adherence to antiretroviral therapy at the HIV clinic in resource constrained countries; the Tanzanian experience	621	Technical 4th, Educational + Technical 4th, Standard care 4th
Munoz, 2009	Community-based DOT-HAART Accompaniment in an Urban Resource-Poor Setting	120	Educational + Technical 4th, Standard care 4th
Pearson, 2007	Randomized Control Trial of Peer-Delivered, Modified Directly Observed Therapy for HAART in Mozambique	350	Educational + Technical 4th, Standard care 4th
Pop-Eleches, 2011	Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders	428	Technical 4th, Standard care 4th
Purcell, 2007	Results From a Randomized Controlled Trial of a Peer-Mentoring Intervention to Reduce HIV Transmission and Increase Access to Care and Adherence	408	Attitudinal 4th, Educational 4th
Pyne, 2011	Effectiveness of Collaborative Care for Depression in Human Immunodeficiency Virus Clinics	178	Educational + Technical 4th, Standard care 4th
Reynolds, 2008	Telephone Support to Improve Antiretroviral Medication Adherence	109	Educational 4th, Educational + Attitudinal 4th
Sabin, 2010	Using Electronic Drug Monitor Feedback to Improve Adherence to Antiretroviral Therapy Among HIV-Positive Patients in China	64	Educational + Technical 4th, Standard care 4th
Samet, 2005	A randomized controlled trial to enhance antiretroviral therapy adherence in patients with a history of alcohol problems	94	Educational + Attitudinal + Technical 4th, Standard care 4th
Selke, 2010	Task-Shifting of Antiretroviral Delivery From Health Care Workers to Persons	208	Educational 4th, Standard care 4th

	Living With HIV/AIDS: Clinical Outcomes of a Community-Based Program in Kenya		
Shet, 2014	Effect of mobile telephone reminders on treatment outcome in HIV: evidence from a randomised controlled trial in India	631	Technical 4th, Standard care 4th
Silveira, 2014	Randomized Controlled Trial to Evaluate the Impact of Pharmaceutical Care on Therapeutic Success in HIV-Infected Patients in Southern Brazil	332	Educational 4th, Standard care 4th
Sosa, 2005	Abacavir and Lamivudine Fixed-Dose Combination Tablet	236	Technical 4th, Standard care 4th
Taiwo, 2010	Assessing the Viorologic and Adherence Benefits of Patient-Selected HIV Treatment Partners in a Resource-limited Setting	499	Technical 4th, Standard care 4th
Tuldra, 2000	Prospective Randomized Two-Arm Controlled Study To Determine the Efficacy of a Specific Intervention To Improve Long-Term Adherence to Highly Active Antiretroviral Therapy	116	Attitudinal 4th, Standard care 4th
Wagner, 2006	Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CCTG 578)	199	Attitudinal 4th, Standard care 4th
Weber, 2004	Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial	60	Attitudinal 4th, Standard care 4th
Williams, 2006	Home Visits to Improve Adherence to Highly Active Antiretroviral Therapy: A Randomized Controlled Trial	171	Educational + Attitudinal 4th, Standard care 4th
Williams, 2014	Efficacy of an Evidence-Based ARV Adherence Intervention in China	110	Educational + Attitudinal 4th, Standard care 4th

c) Musculoskeletal diseases

Study ID	**Title**	**Study size**	**Interventions**
Brankin, 2006	The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from three databases	15330	Technical 4th, Standard care 4th
Clowes, 2004	The Impact of Monitoring on Adherence and Persistence with Antiresorptive Treatment for Postmenopausal	48	Technical 4th, Standard care 4th

	Osteoporosis: A Randomized Controlled Trial		
Cramer, 2005	Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis	2741	Technical 4th, Standard care 4th
Cramer, 2006	The Effect of Dosing Frequency on Compliance and Persistence with Bisphosphonate Therapy in Postmenopausal Women: A Comparison of Studies in the United States, the United Kingdom, and France	15640	Technical 4th, Standard care 4th
Delmas, 2007	Effect of Monitoring Bone Turnover Markers on Persistence with Risedronate Treatment of Postmenopausal Osteoporosis	2302	Technical 4th, Standard care 4th
Homer, 2009	Providing patients with information about disease-modifying antirheumatic drugs: Individually or in groups? A pilot randomized controlled trial comparing adherence and satisfaction	62	Educational 4th, Educational + Technical 4th
Nielson, 2010	Patient education in groups increases knowledge of osteoporosis and adherence to treatment: A two-year randomized controlled trial	300	Educational 4th, Standard care 4th
Rabenda, 2008a	Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women	29157	Technical 4th, Standard care 4th
Rabenda, 2008b	Low Incidence of Anti-Osteoporosis Treatment After Hip Fracture	306	Technical 4th, Standard care 4th
Soloman, 2012	Osteoporosis Telephonic Intervention to Improve Medication Adherence (OPTIMA): A Large Pragmatic Randomized Controlled Trial	2087	Attitudinal 4th, Educational 4th
Zwikker, 2014	Effectiveness of a group-based intervention to change medication beliefs and improve medication adherence in patients with rheumatoid arthritis: A randomized controlled trial	123	Attitudinal 4th, Educational 4th

d) Psychological diseases

Study ID	**Title**	**Study size**	**Interventions**
Ball, 2006	A Randomized Controlled Trial of Cognitive Therapy for Bipolar Disorder: Focus on Long-Term Change	52	Attitudinal 4th, Standard care 4th
Capoccia, 2004	Randomized trial of pharmacist interventions to improve depression care and outcomes in primary care	74	Educational + Technical 4th, Standard care 4th

Lam, 2003	A Randomized Controlled Study of Cognitive Therapy for Relapse Prevention for Bipolar Affective Disorder	103	Attitudinal 4th, Standard care 4th
Pyne, 2011	Effectiveness of Collaborative Care for Depression in Human Immunodeficiency Virus Clinics	178	Educational + Technical 4th, Standard care 4th
Reinares, 2008	Impact of caregiver group psychoeducation on the course and outcome of bipolar patients in remission: a randomized controlled trial	113	Educational + Attitudinal 4th, Standard care 4th
Silveira, 2014	Randomized Controlled Trial to Evaluate the Impact of Pharmaceutical Care on Therapeutic Success in HIV-Infected Patients in Southern Brazil	332	Educational 4th, Standard care 4th
Valencia, 2008	A psychosocial skills training approach in Mexican out-patients with schizophrenia	82	Educational 4th, Standard care 4th
Velligan, 2008	The Use of Individually Tailored Environmental Supports to Improve Medication Adherence and Outcomes in Schizophrenia	61	Attitudinal 4th, Standard care 4th
Williams, 2014	Efficacy of an Evidence-Based ARV Adherence Intervention in China	110	Educational + Attitudinal 4th, Standard care 4th
Zillich, 2012	Evaluation of Specialized Medication Packaging Combined With Medication Therapy Management: Adherence, Outcomes, and Costs Among Medicaid Patients	14621	Educational 4th, Standard care 4th

7. Node-splitting analyses per disease group (Musculoskeletal and Psychological conditions do not have node-splitting analysis as this is only possible when there are close-loops in the networks)

a) Cardiovascular and metabolic diseases

Name	Direct Effect	Indirect Effect	Overall	P-Value
Attitudinal, Educational	-0.61 (-2.22, 1.01)	0.87 (-0.40, 2.19)	0.29 (-0.77, 1.34)	0.19
Attitudinal, Standard care	0.30 (-0.91, 1.49)	-1.15 (-2.87, 0.60)	-0.17 (-1.19, 0.87)	0.19
Educational, Educational + Attitudinal	0.25 (-1.51, 1.93)	-0.60 (-2.44, 1.18)	-0.16 (-1.40, 1.06)	0.6
Educational, Standard care	-0.61 (-1.14, -0.08)	0.68 (-0.86, 2.17)	-0.46 (-0.98, 0.06)	0.9
Educational + Attitudinal, Standard care	0.10 (-1.64, 1.87)	-0.74 (-2.61, 1.02)	-0.31 (-1.56, 0.95)	0.5
Educational + Technical, Technical	-0.01 (-1.68, 1.60)	0.57 (-1.21, 2.29)	0.03 (-1.12, 1.16)	0.6

b) HIV

Name	Direct Effect	Indirect Effect	Overall	P-Value
Attitudinal, Educational	-0.28 (-1.44, 0.89)	0.04 (-0.97, 0.97)	-0.09 (-0.84, 0.60)	0.66
Attitudinal, Standard care	-0.32 (-1.07, 0.38)	-0.62 (-1.93, 0.71)	-0.40 (-1.00, 0.22)	0.67
Educational, Educational + Attitudinal	0.53 (-1.71, 2.89)	0.16 (-0.66, 1.02)	0.17 (-0.56, 1.00)	0.75
Educational, Standard care	-0.37 (-1.00, 0.32)	-0.05 (-1.18, 1.12)	-0.31 (-0.84, 0.28)	0.63
Educational + Attitudinal, Standard care	-0.47 (-1.11, 0.15)	-0.77 (-3.30, 1.50)	-0.48 (-1.10, 0.11)	0.8
Educational + Technical, Technical	0.76 (-0.96, 2.88)	-0.15 (-0.72, 0.42)	-0.10 (-0.64, 0.45)	0.32

8. SUCRA analyses per disease group

a) Circulatory system and metabolic diseases

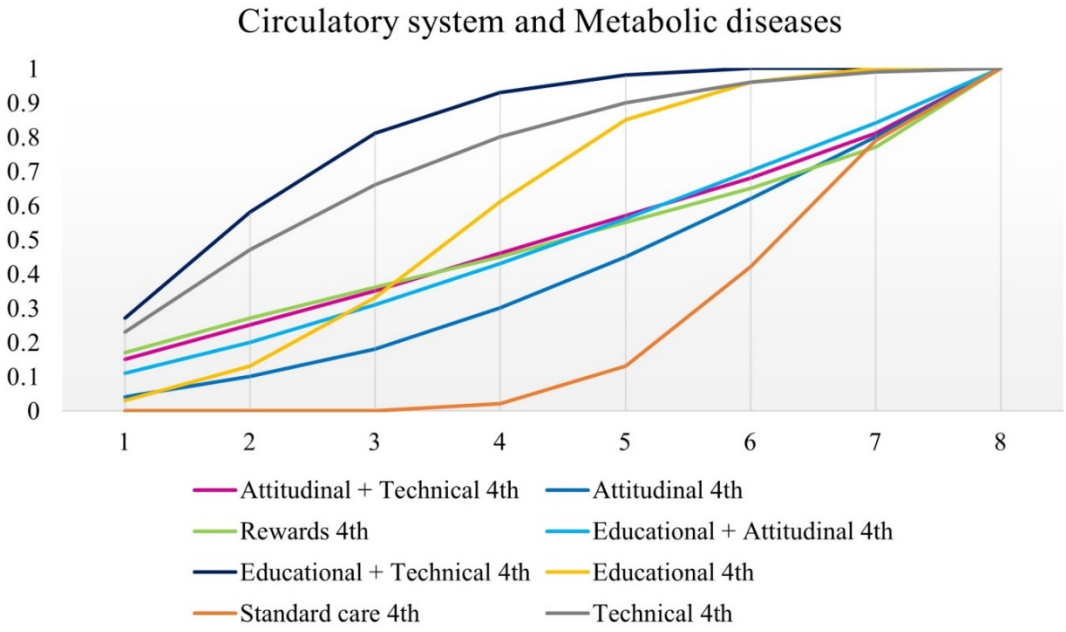


Figure 2. SUCRA values for interventions in Circulatory system and metabolic diseases

b) Infectious diseases (HIV)

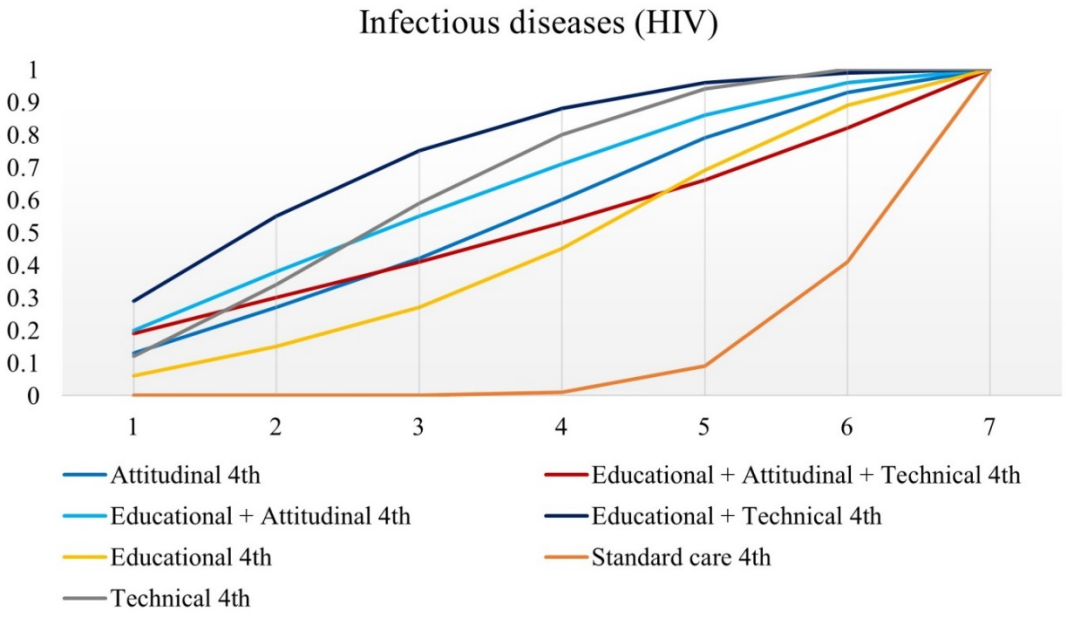


Figure 3. SUCRA values for interventions in infectious (HIV) diseases

c) Musculoskeletal diseases

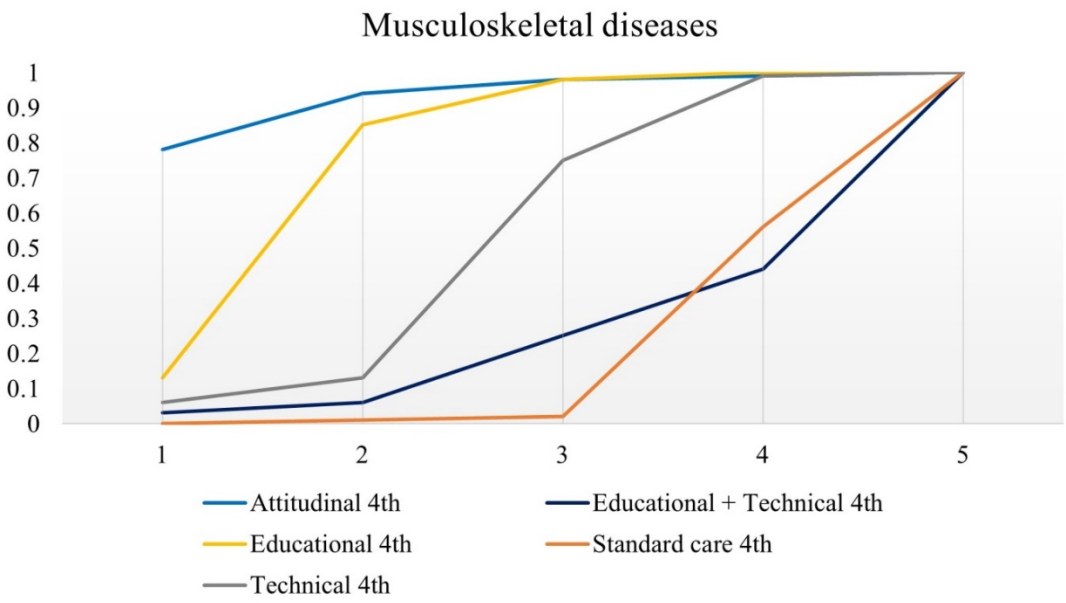


Figure 4. SUCRA values for interventions in musculoskeletal diseases

d) Mental, behavioural or neurodevelopmental disorders

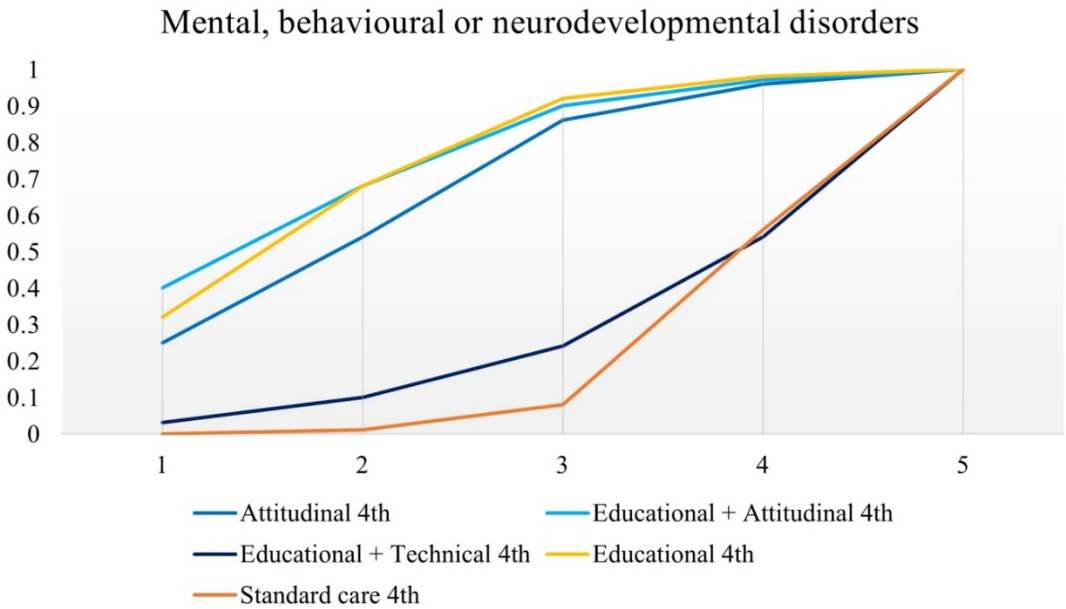


Figure 5. SUCRA values for interventions in mental, behavioural or neurodevelopmental disorders

Chapter 3

1. Negligible Risk Ethics Approval

Dear Applicant

Project title: Analysis of retrospective medication adherence data

You have declared your research as Nil/Negligible Risk and that it DOES NOT include any of the following:
* Establishment of a register or databank for possible use in future research projects
* Collection, transfer and/or banking of human biospecimens
* Any significant alteration to routine care or health service provided to participants
* Interventions and therapies, including clinical and non-clinical trials, and innovations
* Targeted recruitment or analysis of data from any of the participant groups listed in Chapter 4 of the National Statement (or where any of these participants are likely to be significantly over-represented in the group being studied) including:
  - Women who are pregnant and the human fetus
  - Children and young people (under 18 years)
  - People in dependent or unequal relationships
  - People highly dependent on medical care who may be unable to give consent
  - People with a cognitive impairment, an intellectual disability, or a mental illness
  - People who may be involved in illegal activities (including those affected)
  - Aboriginal and Torres Strait Islander Peoples
* Collection, use or disclosure of personal information (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* Collection, use or disclosure of health information
* Collection, use or disclosure of sensitive information
* Covert observation, active concealment, or planned deception of participants
* Activity that potentially infringes the privacy or professional reputation of participants, providers or organisations (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* Potential for participants to experience harm (e.g. physical, psychological, social, economic and/or legal)
* Direct contact with UTS staff/students, patients, consumers or members of the public (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* Participants who have a pre-existing relationship with the researcher (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* People unable to give free informed consent due to difficulties in understanding the Information Sheet or Consent Form
* People in other countries

PLEASE NOTE: If at any time, the scope of your research changes to include one or more of the above categories, you are immediately required to submit a new application.
To access the National Statement on Ethical Conduct in Human Research, visit the NHMRC webpage: https://www.nhmrc.gov.au/guidelines-publications/e72

Please keep a copy of your Declaration form on file to show you have considered the risks associated with your research. You should consider this your official letter of approval.
For tracking purposes, you have been provided with an ethics application number, which is UTS HREC ETH18-2312N.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

Instructions for saving the declaration form can be downloaded from: https://staff.uts.edu.au/howdoi/Pages/Researching/Research%20ethics%20and%20Integrity/Human%20research%20ethics/submit-my-human-research-ethics-application.aspx

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://vpn.uts.edu.au, and click on ""RM6 - Production"" after logging in.

If you have any queries about this approval, please do not hesitate to contact your local research office or Research.Ethics@uts.edu.au.

Kind regards

UTS HREC Ethics Secretariat
C/- Research & Innovation Office
University of Technology Sydney
E: Research.Ethics@uts.edu.au
https://staff.uts.edu.au/topichub/Pages/Researching/Research%20Ethics%20and%20Integrity/Human%20research%20ethics/human-research-ethics.aspx
PO Box 123, BROADWAY NSW 2007
[Level 14, Building 1, Broadway Campus]

REF: Ethics 2 -Neg Risk approved (c)

Chapter 4

1. **Appendix 1:** Checklist of barriers and/or strategies prompted by the eCRD (electronic data collection program) to guide pharmacists during the provision of the intervention.

a. Barriers and strategies to target non-adherent patients

Practical barrier (Non-intentional non-adherence)	Strategy to increase capacity
Lack of information or understanding (about prescribed medications, instructions and consequences of non-adherence)	Provide verbal and written information about health problem and medications (including what they are for and how to take them)
Cognitive barriers (e.g. confusion, lack of attention, mental agility, psychomotor speed)	Prepare medicine list
	Organize Dose Administration Aid (DAA)
Physical barriers (e.g. difficulties swallowing, body trembling, difficulties using correctly the inhaler)	Contact GP to simplify or modify medication regimen
	Suggest and/or contact GP to prescribe DAA
Complexity of treatment	Prepare medicine list
	(DAA
	Contact GP to simplify medication regimen
Forgetfulness (Patients' difficulty to remember dose or schedule times of their medications)	Set up medication reminder system (SMS reminders
	Link medication taking to daily activity
	Set up a medication management application for smartphone
Lack of family support	Reinforcement responsible self-medication Involve family on rational use of medications
Perceptual barrier (Intentional non-adherence)	**How to intervene**
Beliefs of health problem (COPD, asthma, hypertension)	Provide specific information regarding health problem and medications.
Beliefs of medications: • **Perceived necessity of taking the medication** • **Concerns about taking the medication**	Give specific information about the health problem and its management to increase the perceived severity and susceptibility to disease Explain the necessity of taking medication on a regular basis Explain how the medication is helping to control the health problem/symptoms and preventing future events Explain the risks of not taking the medications as prescribed

	Address misunderstandings regarding the medications Explain the probability of suffering a side effects and explain how to deal with them if they occur
Perception/Social stigma (Wanting to avoid taking the medications in public places, work place, between family and friends)	Motivation related to the necessity of taking the medication at the right time. Education on beliefs about perception and social stigma related to the use of medication.
Absence of symptoms (asymptomatic nature of the disease, clinical improvement)	Provide specific information regarding health care condition, emphasizing on the need of taking the medication even on absence of symptoms Highlight the importance of taking the medication in order to achieve clinical outcomes.
Lack of motivation (Depression, lack of perception of clinical improvement)	Reinforcement of knowledge regarding health condition, enquiring for factors that cause lack of motivation on patients. Highlight importance of taking medications and associate it with improvement on clinical goals.
Communication patient-health care provider (lack of confidence on health care provider, inaccurate communication)	Reinforcement of prescriber criteria Work on relation health care provider-patient.

b. Strategies to target adherent patients

Strategy	Description
Education on medication	Education on medications, assessing doubts regarding management of schedules and medications. Verbal and written information when needed.
Education on health problem	Reinforcement of knowledge on health problem. Verbal and written information when needed.
Education on adherence	Verbal and written information regarding concept of adherence and its impact on health and quality of life. Review and reinforcement of adherence behavior.
Motivation/Recognition of accomplishments	Pharmacist-patient review of clinical outcomes and adherence, recognition of achievements; goal setting and motivation to persist adherent.
Education and reinforcement of clinical	Written or verbal information regarding clinical outcomes.
Solving other questions	Treatment changes, alcohol/smoking use

2. **Appendix 2:** Study outcomes

8. CATEGORICAL VARIABLES								
Comparison	**Percentage of Patients (95%CI)**		**Odds Ratio (95% CI)**	**p-value**	**Percentage of Patients (95%CI)**		**Odds Ratio (95% CI)**	**p-value**
	CG	**IG**			**CG**	**IG**		
a) Medication Adherence: Adherent patients n: Control=553, Intervention=633					b) Hypertension control n: Control=219, Intervention=283			
At visit 1	44.3% (37.0-51.8)	39.1% (32.6-46.0)	0.82 (0.54 - 1.24)	0.34	52.9% (45.2%-60.5%)	55.5% (48.5%-62.3%)	1.11 (0.73 - 1.68)	0.63
At visit 2	61.9% (54.3-68.9)	68.7% (62.2-74.6)	1.39 (0.91 - 2.13)	0.13	55.4% (47.3%-63.2%)	58.2% (51.1%-65.0%)	1.12 (0.73 - 1.73)	0.61
At visit 3	66.2% (58.9-72.8)	79.8% (74.4-84.3)	2.06 (1.33 - 3.19)	0.0012*	57.9% (49.9%-65.5%)	62.2% (55.0%-68.8%)	1.20 (0.77 - 1.85)	0.42
At visit 4	65.1% (57.7-71.9)	86.9% (82.7-90.2)	3.60 (2.28 - 5.67)	<0.0001*	59.5% (51.5%-67.0%)	65.3% (58.2%-71.7%)	1.28 (0.82 - 1.99)	0.27
At visit 5	67.0% (59.7-73.6)	88.7% (84.8-91.7)	3.97 (2.49 - 6.33)	<0.0001*	57.1% (49.0%-64.8%)	65.7% (58.6%-72.1%)	1.44 (0.92 - 2.24)	0.11
At visit 6	66.5% (59.2-73.1)	90.9% (87.5-93.4)	5.12 (3.20 - 8.20)	<0.0001*	63.8% (56.0%-71.0%)	68.3% (61.5%-74.5%)	1.22 (0.78 - 1.91)	0.38
Overall			**1.86 (1.24 - 2.81)**	**0.0030*[a]**			**1.21 (0.87 - 1.70)**	**0.26[a]**
c) Asthma control n: Control=180, Intervention=205					d) COPD low clinical impact n: Control=154, Intervention=145			
At visit 1	43.8% (34.3%-53.8%)	37.3% (29.0%-46.4%)	0.76 (0.44 - 1.32)	0.33	16.3% (10.7%-24.1%)	20.6% (14.1%-29.1%)	1.33 (0.68 - 2.60)	0.40
At visit 2	49.0% (38.9%-59.2%)	49.4% (40.0%-58.8%)	1.01 (0.58 - 1.77)	0.96	22.5% (15.4%-31.8%)	27.7% (19.6%-37.5%)	1.31 (0.69 - 2.52)	0.41
At visit 3	51.8% (41.6%-61.8%)	57.7% (48.0%-66.8%)	1.27 (0.72 - 2.23)	0.41	21.2% (14.3%-30.2%)	40.8% (31.0%-51.4%)	2.57 (1.35 - 4.87)	0.0039*
At visit 4	48.6% (38.5%-58.9%)	60.1% (50.3%-69.2%)	1.59 (0.90 - 2.83)	0.11	22.4% (15.2%-31.6%)	40.0% (30.1%-50.7%)	2.31 (1.22 - 4.40)	0.0106*
At visit 5	48.9% (38.7%-59.2%)	63.9% (54.2%-72.6%)	1.85 (1.04 - 3.31)	0.0369*	27.0% (18.8%-37.1%)	39.9% (29.9%-50.8%)	1.80 (0.95 - 3.42)	0.07
At visit 6	57.8% (47.5%-67.5%)	72.0% (63.1%-79.5%)	1.88 (1.05 - 3.36)	0.0339*	29.2% (20.8%-39.4%)	45.3% (35.0%-56.0%)	2.01 (1.07 - 3.75)	0.0294*
Overall			**1.28 (0.81 - 2.03)**	**0.29[a]**			**1.92 (1.13 - 3.25)**	**0.0151*[a]**

3. Appendix 2: Predicted proportion of adherent patients per clinical condition

Comparison	Predicted Proportion of adherent Patients (95%CI)		Odds Ratio (95% CI)	p-value
	Control Group (CG)	Intervention Group (IG)		
COPD				
At visit 1	47.6% (37.6%-57.9%)	40.6% (31.1%-50.8%)	0.75 (0.42 - 1.35)	0.34
At visit 2	62.3% (51.6%-71.9%)	71.6% (61.7%-79.8%)	1.53 (0.82 - 2.85)	0.18
At visit 3	66.6% (56.2%-75.6%)	80.5% (71.8%-87.0%)	2.07 (1.07 - 4.00)	0.0297*
At visit 4	65.3% (54.7%-74.6%)	87.9% (80.7%-92.7%)	3.88 (1.90 - 7.90)	0.0002*
At visit 5	66.4% (55.6%-75.8%)	91.4% (84.9%-95.2%)	5.36 (2.46 - 11.7)	<0.0001*
At visit 6	72.5% (62.3%-80.7%)	92.9% (87.0%-96.2%)	4.93 (2.20 - 11.1)	0.0001*
Overall			**1.71 (1.01 - 2.91)**	**0.0465[a]***
ASTHMA				
At visit 1	31.5% (23.5%-40.8%)	26.8% (20.0%-34.9%)	0.79 (0.46 - 1.38)	0.42
At visit 2	60.1% (50.1%-69.3%)	54.3% (45.1%-63.2%)	0.79 (0.46 - 1.37)	0.42
At visit 3	56.7% (46.7%-66.2%)	69.2% (60.2%-76.8%)	1.71 (0.98 - 3.00)	0.40
At visit 4	54.1% (44.0%-63.8%)	81.7% (74.2%-87.5%)	3.80 (2.09 - 6.93)	0.06
At visit 5	57.2% (47.0%-66.8%)	83.7% (76.5%-89.0%)	3.85 (2.09 - 7.09)	<0.0001*
At visit 6	55.2% (45.1%-64.8%)	85.% (78.2%-89.9%)	4.59 (2.50 - 8.41)	<0.0001*
Overall			**1.86 (1.17 - 2.96)**	**0.0085[a]***
HYPERTENSION				
At visit 1	54.5% (44.0%-64.6%)	45.7% (36.4%-55.2%)	0.70 (0.40 - 1.24)	0.22
At visit 2	65.1% (54.5%-74.4%)	77.8% (69.9%-84.2%)	1.88 (1.02 - 3.46)	0.0416*
At visit 3	75.8% (66.4%-83.2%)	87.3% (81.3%-91.6%)	2.20 (1.15 - 4.20)	0.0171*
At visit 4	76.1% (66.8%-83.4%)	91.1% (86.3%-94.4%)	3.24 (1.65 - 6.34)	0.0006*
At visit 5	77.7% (68.5%-84.8%)	92.1% (87.5%-95.1%)	3.34 (1.67 - 6.67)	0.0006*
At visit 6	74.4% (64.9%-82.1%)	94.8% (91.3%-96.9%)	6.24 (3.05 - 12.7)	<0.0001*
Overall			**1.67 (0.98 - 2.85)**	**0.06[a]**

[a] LR P-value: Likelihood ratio p-value for the overall effect of the outcome.

*Statistically significant

RESULTS: The trends in the three conditions were similar, with an increase on the proportion of adherent patients at the end of the study. Statistically significant differences between intervention and control groups were observed earlier in COPD (starting at visit 3) and hypertension (starting at visit 2).

4. **Appendix 3:** Number of participants each outcome was collected from and rate (%) of missingness in follow-up visits by treatment group

Outcome	Number of eligible participants	Visit number	Control	Intervention
Adherence	n: Control=553, Intervention=633	1	0%	0%
		2	14%	9%
		3	11%	12%
		4	13%	15%
		5	17%	17%
		6	13%	12%
Systolic Blood Pressure (mmHG)	n: Control=217, Intervention=283	1	0%	1%
		2	15%	7%
		3	11%	11%
		4	10%	11%
		5	14%	13%
		6	9%	8%
Diastolic Blood Pressure (mmHG)	n: Control=217, Intervention=283	1	0%	1%
		2	15%	7%
		3	11%	11%
		4	10%	11%
		5	14%	13%
		6	9%	8%
Hypertension control	n: Control=217, Intervention=283	1	0%	1%
		2	15%	7%
		3	11%	11%
		4	10%	11%
		5	14%	13%
		6	9%	8%
CCQ score	n: Control=154, Intervention=145	1	0%	0%
		2	14%	11%
		3	12%	11%
		4	16%	14%
		5	23%	20%

Outcome	Number of eligible participants	Visit number	Control	Intervention
		6	19%	14%
CCQ binary (COPD low clinical impact)	n: Control=154, Intervention=145	1	0%	0%
		2	14%	11%
		3	12%	11%
		4	16%	14%
		5	23%	20%
		6	19%	14%
ACQ score	n: Control=180, Intervention=205	1	1%	0%
		2	12%	10%
		3	10%	15%
		4	13%	20%
		5	15%	20%
		6	11%	16%
ACQ binary (asthma control)	n: Control=180, Intervention=205	1	1%	0%
		2	12%	10%
		3	10%	15%
		4	13%	20%
		5	15%	20%
		6	11%	16%

Observation: Linear and generalised linear mixed models for the study outcomes were used, allowing for the assumption of 'missing-at-random' (i.e. missing contingent on values included in the regression model) without requiring imputation for the missing outcomes.

Chapter 5

1. Supplementary Material 1:

Table 1. List of specific-device checklists and critical steps.

Dry powder inhaler (capsule)	**CRITICAL STEP**
Breezhaler	
1. Remove cap	x
2. Tilt mouthpiece to open the inhaler	x
3. Remove capsule from the blister	x
4. Place the capsule in chamber	x
5. Close mouthpiece until it clicks	x
6. Hold the inhaler upright with the mouthpiece pointing up	x
7. Press side buttons in once	x
8. Release side buttons (do not shake)	x
9. Breath out gently, away from inhaler	x
10. Put mouthpiece in mouth and close lips to form a good seal	x
11. Breathe in quickly and steadily, so capsule vibrates.	x
12. Take inhaler away.	
13. Hold breath for about 5 seconds, or as long as comfortable and breathe out away from the inhaler.	x
14. Close mouthpiece and cap	
Handihaler	
1. Remove capsule from blister	x
2. Open cap and mouthpiece and place the capsule in the chamber	x
3. Close the mouthpiece until you hear a click	x
4. Press the piercing button once and release it again.	x
5. Breath out fully, away from the inhaler.	x
6. Put mouthpiece in mouth and close lips to form a good seal	x
7. Breathe in slowly and deeply through the mouth, fast enough to hear the capsule rattle	x
8. Put the inhaler aside, maintain breath hold 8-10 seconds and breathe out away from the inhaler	x
9. Open the inhaler and extract empty capsule. If there is still powder, repeat from step 5.	x
10. If more than one dose is needed, repeat from step 1	x
11. Rinse your mouth with water.	
12. Close mouthpiece and cap	
Zonda	
1. Remove one capsule from the bottle, inmediately before use and close the bottle tightly	x
2. Pull the cap upwards. Hold the base of the inhaler firmly and open the mouthpiece by pulling it upwards.	x
3. Place the capsule in the chamber in the inhaler.	x
4. Close the mouthpiece until you hear a click, leaving the cap open	x

5. Hold the inhaler with the mouthpiece upright, press the piercing button once as far as it will go then release.	x
6. Breathe out as far as comfortable, away from the inhaler.	
7. Place the mouthpiece in your mouth; closing your lips around it to form a good seal.	x
8. Breathe in strongly and deeply through the mouthpiece, you should hear or feel the capsulse vibrate	x
9. Removing the inhaler from your mouth, hold your breath for about 10 seconds and then breathe out gently away from your inhaler mouthpiece	x
10. To empty the capsule completely, repeat steps 6-9	x
11. Open the mouthpiece and tip out the used capsule and dispose.	
12. Rinse your mouth with water.	
13. Close mouthpiece and dust cap	
Aerolizer	
1. Remove capsule from blister	x
2. Remove cap, hold base and twist mouthpiece to open and place capsule in chamber. Close mouthpiece	x
3. Press side buttons in together once and release	x
4. Breathe out gently, away from the inhaler.	
5. Place mouthpiece in mouth and close lips to form a good seal.	x
6. Breathe in quickly and deeply	x
7. Remove inhaler from mouth	
8. Hold breath for about 8-10 seconds with the inhaler away.	x
9. Open mouthpiece to check if capsule is empty. If powder remains repeat from step 4. If not, remove capsule.	x
10. If an extra dose is needed, wait 30 seconds and repeat from step 1	x
11. Rinse your mouth with water.	
12. Close mouthpiece and cap	
Dry powder inhaler (multi-dose)	**CRITICAL STEP**
Accuhaler	
1. Open cover using thumb grip	x
2. Load dose by sliding lever until it clicks	x
3. Breathe out gently, away from the inhaler.	
4. Place mouthpiece in mouth and close lips to form a good seal	x
5. Breathe in steadily and deeply	x
6. Remove inhaler from mouth, hold breath for about 8-10 seconds and breath out gently, away from the inhaler	x
7. If an extra dose is prescribed, wait minimum 30 seconds and repeat from step 2	x
8. Rinse mouth with water	
9. Close cover to click shut	
Easyhaler	
1. Remove the dust cap and hold uprithg ("L" shape)	x
2. Press the top of the inhaler down until you hear a click, and let it click back again	x
3. Breathe out gently, away from the inhaler.	
4. Place the mouthpiece in mouth and for a good seal with your lips	x

5. Breathe in through your mouth as fast, forcefully and deeply as you can.	x
6. Remove inhaler from mouth, hold breath for about 8-10 seconds and breath out gently, away from the inhaler	x
7. If an extra dose is prescribed, wait minimum 30 seconds and repeat from step 2	x
8. Rinse mouth with water	
9. Close the inhaler	
Ellipta	
1. Open cap. Do not shake	x
2. Slide the cover down until you hear a click	x
3. Breathe out gently, away from the inhaler.	x
4. Place mouthpiece in mouth and close lips to form a good seal	x
5. Breathe in steadily and deeply	x
6. Remove inhaler from mouth.	
7. Hold breath for 8-10 seconds and breathe out gently, away from inhaler	x
8. Slide the cover upwards as far as it will go, to cover the mouthpiece.	
9. Rinse mouth with water	
Forspiro	
1. Open the transparent side chamber door of the inhaler and remove the foil strip from the side chamber by carefully tearing away the full elnght of strip against the 'teeth' of the side chamber. Do not pull or tug on the strip.	
2. Open the protective cap downwards to reveal the mouthpiece	x
3. Make sure the side chamber is closed	
4. Prepare the dose by lifting up the edge of the with lever until it clicks	x
5. Fully close the white lever so it clicks back into its original position.	x
6. Breathe out gently, away from the inhaler	x
7. Hold the inhaler level with the protective cap pointing downwards and place the mouthpiece in your mouth to form a good seal with your lips	x
8. Breathe in steadily and deeply through the inhaler.	x
9. Remove the inhaler from your mouth and hold your breath 8-10 seconds, then breathe out slowly, away from the inhaler.	x
10. Rinse mouth with water	
11. Close the protective cap over the mouthpiece	
Genuair	
1. Remove cap from mouthpiece.	x
2. Hold inhaler horizontal so the green button is facing straight up	
3. Without titling inhaler, press and release the button	x
4. Check control window has changed to green	x
5. Breath out gently, away from inhaler	x
6. Place mouthpiece in mouth and close lips to form a good seal. Keep inhaler horizontal.	x
7. Breathe in strongly and deeply. Keep breathing in after click is heard	x
8. Remove inhaler from mouth	
9. Hold breath for about 8-10 seconds and breath out gently, away from inhaler	x
10. Close cap	
Nexthaler	

1. Open the protective cap and check remaining doses	x
2. Hold the inhaler in the upright position. Do not cover the air vent when holding the NEXThaler	x
3. Breathe out gently as far as is comfortable away from mouthpiece	
4. Place the mouthpiece between your teeth without biting and form a good seal around it with your lips.	x
5. Breathe in quickly and deeply through your mouth.	x
6. Remove the NEXThaler from your mouth after inhaling and hold your breath for 8-10 seconds or as long as is comfortable, then breathe out slowly.	x
7. Replace the cover over the mouthpiece. Check the dose counter has reduced by one.	
8. If another dose is prescribed, wait minimum 30 seconds and repeat from step 1	x
9. Rinse mouth with water	
10. Close cap	
Novolizer	
1. Remove the protective cap.	x
2. Completely depress the coloured dosage button.	x
3. The control window will change to green, indicating the dose is loaded.	x
4. Breathe out gently, away from the inhaler.	
5. Place mouthpiece in mouth and close lips to form a good seal.	x
6. Breathe in quickly and deeply until a click is heard, indicating correct inhalation.	x
7. Remove inhaler from mouth. Hold breath for 8-10 seconds and breathe out slowly, away from inhaler.	x
8. If another dose is prescribed, wait minimum 30 seconds and repeat from step 2	x
9. Rinse mouth with water	
10. Close cap	
Spiromax	
1. Hold inhaler upright with mouthpiece at bottom	x
2. Open the protective cap by folding it down until you hear a click	x
3. Breathe out fully, away from inhaler	x
4. Close your lips around the mouthpiece	x
5. Breathe in forcefully and deeply through the mouth	x
6. Remove inhaler form mouth	
7. Hold breath for 8-10 seconds and breathe out gently, away from inhaler	x
8. Close the cap	
Turbuhaler	
1. Unscrew and remove cover	x
2. Keep inhaler upright	x
3. Twist around and then back until click is heard	x
4. Breathe out gently, away from the inhaler.	x
5. Place mouthpiece in mouth and close lips to form a good seal.	x
6. Breathe in strongly and deeply	x
7. Remove inhaler from mouth, hold breath for about 8-10 seconds and breathe out slowly, away from inhaler	x
8. If another dose is needed, wait at least 30 seconds and repeat from step 2	x

9. Rinse mouth with water	
10. Replace cover	
Twisthaler	
1. Before removing the white cap, be sure the counter and the pointer on the cap are lined up.	x
2. Remove cap.	x
3. Breathe out slowly, away from inhaler	x
4. Place mouthpiece in mouth and close lips to form a good seal	x
5. Breathe in steadily and deeply	x
6. Remove mouthpiece from mouth	
7. Hold breath for 8-10 seconds and breathe out gently, away from inhaler	x
8. Replace inhaler cap, pressing down until a click sound is heard	
8. Rinse mouth with water	
Mist inhaler (multi-dose solution for inhalation)	**CRITICAL STEP**
Respimat	
1. Hold inhaler upright with cap closed.	
2. Turn base in direction of arrows until it clicks.	x
3. Open the cap until it snaps fully open.	x
4. Breathe out gently, away from the inhaler.	
5. Place mouthpiece in mouth and close lips to form a good seal.	x
6. Breathe in slowly and deeply through mouth and, at the same time, press down on the dose button.	x
7. Remove inhaler from mouth	
8. Hold breath for about 8-10 seconds with the inhaler away.	x
9. Click cap shut	
Pressurised Metered-dose inhalers (MDIs)	**CRITICAL STEP**
Conventional pMDI	
1. Shake inhaler and remove cap	x
2. Hold inhaler upright ('L' shape)	x
3. Breathe out gently, away from the inhaler.	
4. Place mouthpiece in mouth and close lips to form a good seal. Breathe in slowly through mouth and, at the same time, press down firmly on canister.	x
5. Remove inhaler from mouth	
6. Hold breath for about 8-10 seconds with the inhaler away	x
7. If an extra dose is prescribed, wait minimum 30 seconds and repeat from step 1	x
8. Rinse mouth with water	
9. Replace cap	
Flutiform	
1. Shake inhaler and remove cap	x
2. Hold inhaler upright ('L' shape)	x
3. Breathe out gently, away from the inhaler.	
4. Place mouthpiece in mouth and close lips to form a good seal. Breathe in slowly through mouth and, at the same time, press down firmly on canister.	x
5. Remove inhaler from mouth	
6. Hold breath for about 8-10 seconds with the inhaler away	x

7. If an extra dose is prescribed, wait minimum 30 seconds and repeat from step 1	x
8. Rinse mouth with water	
9. Replace cap	
Modulite	
1. Remove cap	x
2. Hold inhaler upright ('L' shape)	x
3. Breathe out gently, away from the inhaler.	
4. Place mouthpiece in mouth and close lips to form a good seal. Breathe in slowly through mouth and, at the same time, press down firmly on canister.	x
5. Remove inhaler from mouth	
6. Hold breath for about 8-10 seconds with the inhaler away	x
7. If an extra dose is prescribed, wait minimum 30 seconds and repeat from step 1	x
8. Rinse mouth with water	
9. Replace cap	
pMDI + spacer + mask	
1. Assemble spacer	x
2. If using facemask, adjust well to cover nose and mouth	x
3. Hold inhaler upright and shake well	x
4. Place mouthpiece in mouth and close lips to form a good seal.	x
5. Hold spacer level and press down firmly on inhaler canister once. Breathe in slowly and deeply	x
6. Hold breath for about 8-10 seconds with the inhaler away and breath out gently	x
7. If an extra dose is needed, wait at least 30 seconds and repeat from step 3	x
8. Remove inhaler from spacer	
9. Clean spacer with water and let it dry	
pMDI + spacer	
1. Assemble spacer	X
2. Hold inhaler upright and shake well	X
3. Place mouthpiece in mouth and close lips to form a good seal.	X
4. Hold spacer level and press down firmly on inhaler canister once. Breathe in slowly and deeply	X
5. Hold breath for about 8-10 seconds with the inhaler away and breath out gently	X
6. If an extra dose is needed, wait at least 30 seconds and repeat from step 3	X
7. Remove inhaler from spacer	
8. Clean spacer with water and let it dry	

2. Supplementary Material 2:

Table 1. Proportion of patients with correct inhaler technique per disease:

	Proportion of patients with total correct inhaler technique									
	1. Asthma					2. COPD				
Visit	CONTROL		INTERVENTION		p-value	CONTROL		INTERVENTION		p-value
	N	%	N	%		N	%	N	%	
1	59	35.60%	66	32.50%	0.573	57	28.70%	37	12.10%	0.002
3	82	64.60%	126	81.50%	<0.05	73	58.10%	88	68.90%	0.034
6	91	74.50%	141	92.20%	<0.05	65	65.10%	106	95.80%	<0.005

	Proportion of patients with optimal Critical correct inhaler technique									
	1. Asthma					2. COPD				
Visit	CONTROL		INTERVENTION		p-value	CONTROL		INTERVENTION		p-value
	N	%	N	%		N	%	N	%	
1	79	52.70%	91	49.60%	0.638	64	46.90%	55	34.60%	0.096
3	98	78.70%	122	90.10%	<0.05	82	70.40%	92	76.70%	0.127
6	101	81.90%	144	94.80%	<0.05	74	75.20%	108	94.80%	<0.005

Table 2. Comparison of treatment effect according to subgroups (age group, number of inhalers, clinical condition and inhaler type).

Subgroup	*Level*	*Odds Ratio (95% CI)*	*p-value*
Correct inhaler technique (all steps)			
Age group	>=65 yrs	1.94 (0.91 - 4.14)	0.40
	<65 yrs	1.50 (0.70 - 3.23)	
Number of inhalers	1 inhaler	1.92 (0.90 - 4.11)	0.45
	>=2 inhalers	1.54 (0.72 - 3.29)	
Clinical Condition	Asthma	1.66 (0.79 - 3.51)	0.88
	COPD	1.74 (0.81 - 3.74)	
Inhaler type	Aerosols	2.40 (0.95 - 6.06)	0.27
	DPI	1.57 (0.77 - 3.21)	
Correct inhaler technique (only critical steps)			
Age Group	>= 65 yrs	1.78 (0.85 - 3.72)	0.42
	<65 yrs	1.40 (0.66 - 2.95)	
Number of Inhalers	1 inhaler	1.57 (0.75 - 3.27)	0.95
	>=2 inhalers	1.54 (0.74 - 3.22)	
Clinical Condition	Asthma	1.51 (0.74 - 3.12)	0.89
	COPD	1.58 (0.76 - 3.29)	
Inhaler type	Aerosols	2.27 (0.89 - 5.78)	0.25
	DPI	1.46 (0.73 - 2.91)	

Chapter 6

1. Supplementary Material:

Table 1. Implementation strategies

Stage	Objective	Strategy
Exploration	Recruiting and confirmation of participant pharmacies. Preparation of the pharmacists.	- Exploration of pharmacies and pharmacy owners that could participate in the study. - Training of practice change facilitators in adherence management and implementation study design.
Preparation	Preparation of community pharmacies to integrate the service.	- Training of pharmacists, providers of the intervention. - Evaluation of barriers and facilitators for the implementation of the medication adherence management service.
Testing:	Adjustment and implementation of the service in routine practice through the provision of the service to a pilot number of patients.	- Monthly visits to the pharmacy by the practice change facilitators to support and validate the quality of the process. - Pharmacists and 'practice change facilitators' evaluation of the changes implemented in the service.
Implementation	Provide the intervention to the total of patients.	- Continuous support to pharmacists provided by practice change facilitators. - Periodic training to pharmacists. - Continuous monitoring and follow-up

End of Thesis