MONASH University

Optimising medication use and medication management in older people with cognitive impairment

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"The more that you read,

the more things you will know.

The more that you learn,

the more places you'll go."

Dr. Seuss, I Can Read With My Eyes Shut!

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ABSTRACT

Background

Ageing populations and increasing prevalence of cognitive impairment represent a growing burden for health systems globally. Older people (≥65 years) commonly have multiple chronic health problems which require the use of multiple medications. Older people, particularly those with cognitive impairment, are at increased risk of medication-related problems and adverse drug events.

Aim

To review, explore and evaluate patterns of medication use and interventions for improving medication use and medication management in older people, particularly those living with cognitive impairment.

Methods

The thesis comprised three main projects.

Project 1: A Cochrane systematic review was undertaken to review the effectiveness of interventions for improving medication-taking ability and medication adherence in older community-dwelling people prescribed multiple medications (or their carers).

Project 2: Cross-sectional and longitudinal analyses of data from a three year observational study were performed to explore the types and appropriateness of medications and dietary supplements used by 964 older people attending nine memory clinics across Australia. The association between potentially inappropriate medications for a person with cognitive impairment (PIMcogs), anticholinergic cognitive burden (ACB) and mortality over a three year follow-up were investigated using time-dependent Cox-proportional hazards regression.

Project 3: A before-and-after feasibility study was conducted at a memory clinic to evaluate a pharmacist-led, inter-disciplinary deprescribing intervention. Stakeholder acceptability was explored using patient/carer questionnaires, general practitioner (GP) surveys, a memory clinic staff focus group and pharmacist interview.

Key findings

Project 1: There were few controlled studies evaluating interventions for improving medication-taking ability, and large variations in quality, design and impact of studies

evaluating interventions for improving medication adherence. Mixed educational and behavioural interventions, particularly those led by pharmacists and delivered at transitions of care, showed potential to improve medication adherence, but heterogeneity and high risk of bias prevented firm conclusions.

Project 2: One in five memory clinic patients used a PIMcog, one in ten had clinically significant ACB and 57% used ≥1 dietary supplement. Both PIMcog use (adjusted hazard ratio: 1.42 95%CI: 1.12-1.80) and ACB scores (adjusted hazard ratio: 1.18 95%CI: 1.06-1.32) were associated with mortality.

Project 3: More than one-third of patients attending a memory clinic were eligible to participate in the deprescribing trial, 60% of eligible patients consented and 43% of medications recommended for deprescribing were ceased or dose-reduced at six months. Stakeholder feedback suggested patients, GPs and memory clinic staff were receptive to increased pharmacist involvement in the clinic.

Conclusions

There were three main findings: 1) there is a lack of high-quality research on interventions to improve medication-taking ability and medication adherence in older adults prescribed multiple medications; 2) potentially inappropriate medication use is prevalent among people attending memory clinics and is associated with increased mortality; and 3) it is feasible to recruit participants and deliver a pharmacist-led deprescribing intervention in a memory clinic. This thesis highlights the challenges of medication management in older people and the prevalence of inappropriate medication use in those with cognitive impairment. It provides clear direction and strong justification for further research to help optimise medication use and medication management in this population.

DECLARATION

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers published in peer reviewed journals and three submitted publications. The core theme of the thesis is optimising medication use and medication management in older people with cognitive impairment. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Science, under the supervision of Dr Johnson George and Dr Rohan Elliott.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters 2, 3 and 4 my contributions to the work were as described in the table below;

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution
2	Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications [protocol]	**Published**	60%. Concept and design of the study, drafted manuscript with co-authors, preparation of final manuscript.	1) Elliott RA. 20%. Concept and design of the study, critical revision of manuscript. 2) George J. 20%. Concept and design of the study, critical revision of manuscript.
2	Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications [review]	**Submitted**	70%. Data acquisition, data analysis and interpretation, drafted manuscript, preparation of final manuscript.	1) Elliott RA. 10%. Data acquisition, data interpretation, critical revision of manuscript. 2) Petrie K*. 5%. Data acquisition, critical revision of manuscript. 3) Kuruvilla L*. 5%. Data acquisition, critical revision of manuscript. 4) George J. 10%. Data acquisition, data interpretation, critical revision of manuscript.
3	Potentially inappropriate medications and anticholinergic burden in older people attending memory clinics in Australia	**Published**	60%. Concept and design of the study, data acquisition, data analysis and interpretation, drafted manuscript, preparation of final manuscript.	1) George J. 10%. Concept and design of the study, data interpretation, critical revision of manuscript. 2) Woodward MC. 5%. Data acquisition, critical revision of manuscript. 3) Ames D. 5%. Data acquisition, critical revision of manuscript. 4) Brodaty H. 5%. Data acquisition, critical revision of manuscript. 5) Ilomäki J. 5%. Data analysis, critical revision of manuscript. 6) Elliott RA. 10% Concept and design of the study, data acquisition, data interpretation, critical revision of manuscript.

		Status	Candidate's contribution	Co-authors' contribution
3	Dietary supplement use in older people attending memory clinics in Australia.	**Published**	65%. Concept and design of the study, data acquisition, data analysis and interpretation, drafted manuscript, preparation of final manuscript.	1) George J. 10%. Concept and design of the study, data interpretation, critical revision of manuscript. 2) Woodward MC. 5%. Data acquisition, critical revision of manuscript. 3) Ames D. 5%. Data acquisition, critical revision of manuscript. 4) Brodaty H. 5%. Data acquisition, critical revision of manuscript. 5) Elliott RA. 10% Concept and design of the study, data acquisition, data interpretation, critical revision of manuscript.
3	Potentially inappropriate medications, anticholinergic burden and mortality in people attending memory clinics.	**Published**	60%. Concept and design of the study, data acquisition, data analysis and interpretation, drafted manuscript, preparation of final manuscript.	1) George J. 10%. Concept and design of the study, data interpretation, critical revision of manuscript. 2) Woodward MC. 5%. Data acquisition, critical revision of manuscript. 3) Ames D. 2.5%. Data acquisition, critical revision of manuscript. 4) Brodaty H. 2.5%. Data acquisition, critical revision of manuscript. 5) Wolfe R. 5%. Data analysis and interpretation, critical revision of manuscript. 6) Connors MH. 5%. Data acquisition, critical revision of manuscript. 7) Elliott RA. 10%. Concept and design of the study, data acquisition, data interpretation, critical revision of manuscript.

4	Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM): a feasibility study	**Submitted**	70%. Concept and design of the study, data acquisition, data analysis and interpretation, drafted manuscript, preparation of final manuscript.	1) George J. 10%. Concept and design of the study, data interpretation, critical revision of manuscript. 2) Woodward MC. 5%. Concept and design of the study, critical revision of manuscript. 3) Le VJ*. 5%. Data analysis, critical revision of manuscript. 4) Elliott RA. 10%. Concept and design of the study, data interpretation, critical revision of manuscript.
4	Stakeholder perspectives on pharmacist involvement in a memory clinic to review patients' medication management and assist with deprescribing	**Submitted**	70%. Concept and design of the study, data acquisition, data analysis and interpretation, drafted manuscript, preparation of final manuscript.	1) Le VJ*. 5%. Data acquisition, data analysis and interpretation, critical revision of manuscript. 2) George J. 10%. Concept and design of the study, data interpretation, critical revision of manuscript. 3) Woodward MC. 5%. Concept and design of the study, data interpretation, critical revision of manuscript. 4) Elliott RA. 10%. Concept and design of the study, data interpretation, data interpretation, critical revision of manuscript.

* Co-author is a Monash student

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I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: **Date:** 30/05/2019

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: **Date:** 30/05/2019

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PUBLICATIONS AND PRESENTATIONS

Publications included in the thesis

Cross AJ, Elliott RA, George J. *Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications [protocol].* Cochrane Database of Systematic Reviews. 2016. Issue 10. Art. No.: CD012419.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Ilomäki J, Elliott RA. *Potentially inappropriate medications and anticholinergic burden in older people attending memory clinics in Australia*. Drugs Aging. 2016. 33: 37-44.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Elliott RA. *Dietary supplement use in older people attending memory clinics in Australia*. J Nutr Health Aging. 2017. 21: 46-50.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Wolfe R, Connors MH, Elliott RA. *Potentially inappropriate medications, anticholinergic burden and mortality in people attending memory clinics*. J Alzheimers Dis. 2017. 60: 349-358.

Manuscripts submitted for publication

Cross AJ, Elliott RA, Petrie K, Kuruvilla L, George J. *Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications [review].*

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM): a feasibility study*.

Cross AJ, Le VJ, George J, Woodward MC, Elliott RA. *Stakeholder perspectives on pharmacist involvement in a memory clinic to review patients' medication management and assist with deprescribing.*

Other publications during candidature which do not form part of the thesis

Wimmer BC, **Cross AJ**, Jokanovic N, Wiese MD, George J, Johnell K, Diug B, Bell JS. *Clinical Outcomes Associated with Medication Regimen Complexity in Older People: A Systematic Review*. J Am Geriatr Soc. 2017. 65: 747-753

Page A, **Cross AJ**, Elliott RA, Pond D, Dooley M, Beanland C, Etherton-Beer C. *Integrate health care to provide multidisciplinary consumer-centered medication management: Report from a working group formed from the National Stakeholders' Meeting for the Quality Use of Medicines to Optimise Ageing in Older Australians*. JPPR. 2018. 48: 459-66.

Petrie K, Abramson MJ, **Cross AJ**, George J. *Predicted life expectancy of older people using respiratory symptoms and smoking status: Data from the Australian Longitudinal Study of Ageing*. Respirology. 2019. doi: 10.1111/resp.13603. [In Press].

Presentations during candidature

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM): a role for pharmacists?* Australian Deprescribing Network Meeting, Adelaide, Australia (December 2018). Oral presentation.

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Deprescribing in a memory clinic setting – is it feasible?* Australian Association of Gerontology Conference, Melbourne. Australia (November 2018). Oral presentation.

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM): a role for pharmacists?* Austin Health Research Week, Melbourne, Australia (October 2018). Poster presentation.

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Exploring stakeholder acceptability of memory clinic pharmacists*. 13th Annual Monash University Post Graduate Symposium, Melbourne, Australia (September 2018). Oral presentation.

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Do we need memory clinic pharmacists?* Monash University Three Minute Thesis Final, Melbourne, Australia (August 2018). Oral presentation.

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Do we need memory clinic pharmacists?* Monash University Three Minute Thesis Faculty of Pharmacy and Pharmaceutical Sciences Round, Melbourne, Australia (July 2018). Oral presentation.

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM): Preliminary results of a feasibility study.* NHMRC National Institute for Dementia Research Australian Dementia Forum, Sydney, Australia (June 2018). Poster presentation.

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Deprescribing medicines in memory clinic patients.* Victorian Medicines Roundtable, Melbourne, Australia (May 2018). Oral presentation.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Wolfe R, Connors MH, Elliott RA. *Is inappropriate medication use associated with mortality in people attending Australian*

memory clinics, 12th Annual Monash University Post Graduate Symposium, Melbourne, Australia (October 2017). Oral presentation.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Wolfe R, Connors MH, Elliott RA. *Potentially inappropriate medication and mortality in people attending memory clinics,* 12th Annual Monash University Post Graduate Symposium, Melbourne, Australia (October 2017). Poster presentation.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Wolfe R, Connors MH, Elliott RA. *Potentially inappropriate medication and mortality in people attending memory clinics,* NHMRC National Institute for Dementia Research (NNIDR) Australian Dementia Forum, Melbourne (October 2017). Poster presentation.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Wolfe R, Connors MH, Elliott RA. *Potentially inappropriate medication and mortality in older people attending memory clinics,* IAGG 2017 World Congress of Gerontology and Geriatrics, San Francisco, USA (July 2017). Oral presentation.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Elliott RA. *Dietary supplement use in older people attending Australian memory clinics,* 14th National Conference of Emerging Researchers in Ageing, Melbourne, Australia (December 2015). Oral presentation.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Ilomäki J, Elliott RA. *Potentially inappropriate medication use in older people with cognitive impairment*, 14th National Conference of Emerging Researchers in Ageing, Melbourne, Australia (December 2015). Rapid Fire Presentation.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Ilomäki J, Elliott RA. *Potentially inappropriate medications and anticholinergic burden in older people attending memory clinics in Australia*, 10th Annual Monash University Post Graduate Symposium, Melbourne, Australia (October 2015). Oral presentation.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Ilomäki J, Elliott RA. *Potentially inappropriate medication use in patients attending Australian memory clinics*, Pharmaceutical Society of Australia (PSA) National Conference, Sydney, Australia (July 2015). Oral presentation.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Elliott RA. *Dietary supplement use in patients attending Australian memory clinics*, Pharmaceutical Society of Australia (PSA) National Conference, Sydney, Australia (July 2015). Poster presentation.

Grants received during candidature

Elliott RA, George J, Woodward M, **Cross AJ**. *Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) pilot study* ($10,000). Victorian Therapeutics Advisory Group (VicTAG) grant (2017)

Awards received during candidature

Most Outstanding Oral Presentation, 13th Annual Monash University Post Graduate Symposium. Melbourne, Australia (2018).

Faculty Winner of the Monash University Three Minute Thesis Faculty of Pharmacy and Pharmaceutical Sciences Round. Melbourne, Australia (2018).

International Association of Gerontology and Geriatrics (IAGG) 2017 World Congress Travel Stipend to attend the IAGG 2017 World Congress of Gerontology and Geriatrics conference. San Francisco, USA (2017).

Most Outstanding Oral Presentation, 12th Annual Monash University Post Graduate Symposium. Melbourne, Australia (2017).

Best Presentation by an Australian Association of Gerontology member, 14th National Conference of Emerging Researchers in Ageing. Melbourne, Australia (2015).

Third Prize Oral Presentation, 10th Annual Monash University Post Graduate Symposium. Melbourne, Australia (2015).

LIST OF ABBREVIATIONS

ACB	Anticholinergic Cognitive Burden
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive
ADE	Adverse Drug Event
ADL	Activities of Daily Living
ADS	Anticholinergic Drug Scale
aMCI	Amnestic Mild Cognitive Impairment
ARS	Anticholinergic Risk Scale
BPSD	Behavioural and Psychological Symptoms of Dementia
CDAMS	Cognitive, Dementia And Memory Services
CDR	Clinical Dementia Rating
ChEI	Cholinesterase Inhibitor
DBI	Drug Burden Index
DePIMM	Deprescribing Potentially Inappropriate Medication in Memory clinic patients
DHA	Docosahexaenoic Acid
DLB	Dementia with Lewy Bodies
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – version 5
FTD	Frontotemporal Dementia
GP	General Practitioner
MATCH-D	Medication Appropriateness Tool for Co-morbid Health conditions in Dementia
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRCI	Medication Regimen Complexity Index
MRP	Medication-Related Problem
naMCI	Non-amnestic Mild Cognitive Impairment
NMDA	N-methyl-D-aspartate receptor
NPI	Neuropsychiatric Index
PATD	Patient Attitudes Towards Deprescribing questionnaire

PBS	Pharmaceutical Benefits Scheme
PET	Positron Emission Tomography Scan
PIM	Potentially Inappropriate Medication
PIMcog	Potentially Inappropriate Medication for a person with cognitive impairment
PRIME	Prospective Research In MEmory clinics
rPATD	Revised Patient Attitudes Towards Deprescribing questionnaire
rPATDcog	Revised Patient Attitudes Towards Deprescribing questionnaire for people with cognitive impairment
RUDAS	Rowland Universal Dementia Assessment Scale
START	Screening Tool to Alert doctors to the Right Treatment
STOPP	Screening Tool of Older People's Prescriptions
TGA	Therapeutic Goods Administration
VaD	Vascular Dementia
WHO	World Health Organization

GENERAL OVERVIEW

Problem statement

Older people, conventionally defined as those aged 65 years and above, often have multiple chronic health problems that require ongoing interventions [1, 2]. An expanding evidence base supporting multidrug regimens in the management of chronic diseases means that polypharmacy (the use of multiple medications) is often unavoidable [2, 3].

Medication management in older people

Managing multiple long-term medications can be a complex and challenging task for many older people who often have an increasing level of cognitive and/or functional impairment. There is evidence that non-adherence and medication errors are common among older people. Evidence from well-designed studies testing interventions to improve medication-taking ability and adherence in older adults could provide valuable information for practitioners, researchers, carers and consumers. To date, there has been no systematic reviews of medication-taking ability, and no recent reviews of medication adherence focussing on older people prescribed multiple medications.

Prescribing for older people

Prescribing for older people, especially those with multiple chronic health problems or cognitive impairment can be challenging, as these people are often excluded from or underrepresented in, clinical trials [4]. Most clinical guidelines do not discuss the applicability of their recommendations to complex multi-morbid patients [2, 5]. Older people, particularly those with cognitive impairment, are also at increased risk of adverse drug events (ADEs) due to altered pharmacokinetics and pharmacodynamics [6].

Dementia, an umbrella term for several diseases affecting cognitive abilities, is a worldwide public health priority [7]. In Australia there are over 436,000 people living with dementia [8], with this number increasing by an estimated 250 people every day [9]. Clinical practice guidelines recommend a review of medication as part of the dementia diagnostic process in order to identify and minimise use of medications that may adversely affect cognitive function [10]. Whilst memory clinics specialise in the assessment and diagnosis of people with suspected cognitive impairment [11], there has been limited research regarding medication use or interventions for improving medication use in this setting.

Aim and objectives

The overall <u>aim</u> of this thesis was to review, explore and evaluate patterns of medication use and interventions for improving medication use and medication management in older people, particularly those living with cognitive impairment.

The specific <u>objectives</u> were:

1. To systematically review the effectiveness of interventions for improving medication-taking ability and medication adherence in older people prescribed multiple medications;
2. To explore the types and appropriateness of medications used by older people with dementia or mild cognitive impairment (MCI) attending memory clinics; and
3. To evaluate the feasibility of a pharmacist-led, inter-disciplinary deprescribing intervention aimed at improving the appropriateness of medications used by people attending a memory clinic.

Thesis outline

This thesis by publication is composed of five chapters including seven manuscripts. At the time of submission of this thesis, four of the seven manuscripts have been published and three have been submitted for publication. A brief description of each chapter is provided below.

Chapter 1 provides a general background about medication use in older people, cognitive impairment and deprescribing.

Chapter 2 is a Cochrane systematic review of interventions for improving medication-taking ability and medication adherence in older community-dwelling people prescribed multiple medications. This review addresses the first thesis objective and has been conducted under the auspices of the Cochrane Consumers and Communication Group. This chapter includes two manuscripts: the first is the protocol for the systematic review (published) and the second presents the review findings (submitted).

Chapter 3 presents cross-sectional and longitudinal analyses of data from the Prospective Research In MEmory clinics (PRIME) study. It addresses the second thesis objective, by exploring medication use in people attending nine Australian memory clinics. This chapter includes three published manuscripts: the first describes the prevalence of potentially inappropriate medication use, the second describes the prevalence of dietary supplement use and its impact on polypharmacy and potential drug interactions, and the third describes the association between inappropriate medication use and mortality.

Chapter 4 presents the results of a feasibility study exploring pharmacist-led, interdisciplinary medication review and deprescribing for people attending a memory clinic. This study addresses the third thesis objective. It includes two submitted manuscripts: the first describes an evaluation of the feasibility of recruiting patients and deprescribing medications in a memory clinic setting, and the second describes a mixed-methods evaluation of stakeholder acceptability of pharmacist involvement in memory clinics.

Chapter 5 summarises the key findings of the research presented in the thesis, discusses how the research has contributed to knowledge in this field, and summarises the implications of the findings on practice and recommendations for future research.

1. CHAPTER ONE: Background

1.1 Preface

The purpose of this chapter is to provide general information about the significance of the research topic and the characteristics of the study population. It begins with a snapshot of Australia's ageing population (section 1.2), followed by a discussion regarding challenges associated with, and strategies for improving, medication use in older people (section 1.3). The subsequent sections discuss diagnosis, prevalence and management of cognitive impairment (section 1.4), and medication use considerations for people living with cognitive impairment (section 1.5). The chapter ends with a summary of the gaps in the literature (section 1.6) and rationale for the proposed projects as part of the PhD.

1.2 Australia's ageing population

Australia's older population (those aged 65 years and above) continues to grow. In 2017, older people represented 15% of the population, equivalent to 3.8 million people [12]. The proportion of older people in Australia has tripled since 1927 and is expected to continue to grow, reaching 22% by 2057 [12] (Figure 1).
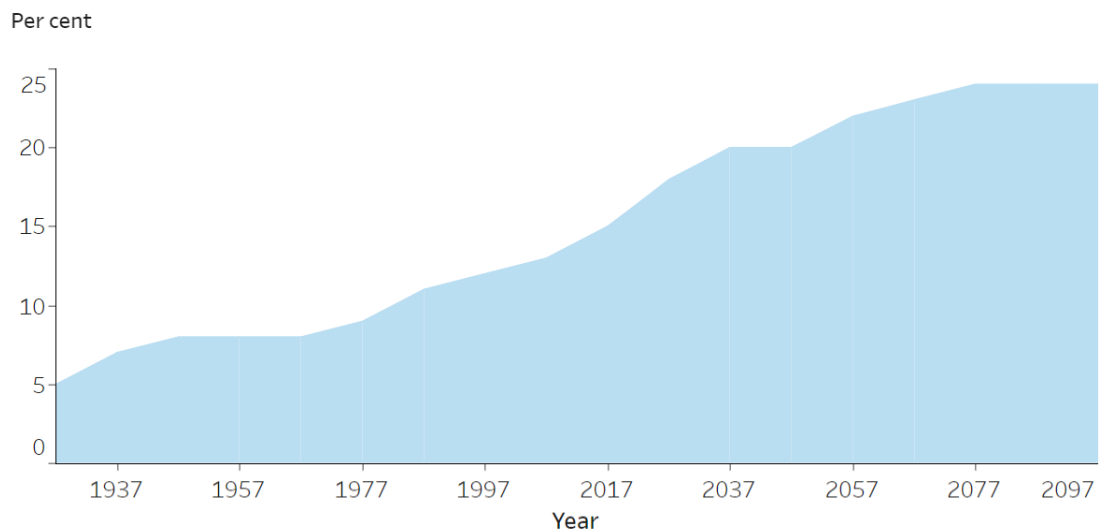

Figure 1. Proportion of the Australian population aged 65 years and over, over time and projections for the future.

Source: Australian Institute of Health and Welfare (AIHW). Older Australians at a glance [12].

Our ageing population has developed due to increasing life expectancy and decreasing birth rates. In Australia, a male born in 2011–2013 can expect to live to the age of 80.1 years and a female can expect to live to 84.3 years compared to 47.2 and 50.8 years, respectively, for people born in 1881–1890 [13]. Australian birth rates have halved over the past half century from 3.55 births per woman in 1961 to 1.71 births per woman in 2017 [14].

The ageing population presents many challenges to the healthcare system. One of these challenges is the increasing prevalence of chronic diseases (e.g. cardiovascular disease, diabetes, chronic obstructive pulmonary disease and dementia) and the higher rates of people living with multiple co-morbid diseases. In 2015, 29% of older Australians reported having three or more chronic diseases from a list of eight common chronic diseases, compared with just 2.4% in those under 45 years [15]. These chronic diseases often require ongoing interventions, such as medication, health appointments and monitoring, resulting in a large economic and personal burden [1].

1.3 Medication use in older people

1.3.1   Polypharmacy

Medication use, particularly multiple medication use, increases with age. There is an expanding evidence base supporting multidrug regimens in the management of individual chronic diseases, which means that the use of multiple medications is often unavoidable in older people with multiple chronic diseases [2, 3].

The use of multiple medications is commonly referred to as 'polypharmacy' [16]. While polypharmacy has a number of definitions, it is often used to describe a medication regimen that includes five or more regular medications [17]. More recently, the term 'hyper-polypharmacy' has been used to define regimens of ten or more regular medications [17].

The prevalence of polypharmacy continues to rise both nationally and internationally. The incidence of polypharmacy in older Americans increased from 24% in 1999-2000 to 39% in 2011-2012 [18]. In 2012, it was reported that more than 40% of older Australians were exposed to polypharmacy and almost 5% were exposed to hyper-polypharmacy [19, 20]. The proportion of Australians aged over 75 years who were exposed to hyper-polypharmacy was double that of people aged 50-64 years [19].

The prevalence of physical and cognitive impairment increase with age, and polypharmacy can further increase and accelerate this impairment. Polypharmacy has been associated with

reduced ability to perform activities of daily living, reduced functional capacity and an increased risk of falling [21-25]. Falls are particularly concerning in older people as they are associated with a high risk of morbidity and mortality [26]. In additional to physical impairment, polypharmacy has been associated with impaired cognition, delirium and dementia [22, 27].

Polypharmacy increases the risk of experiencing adverse drug events (ADEs) [28]. An ADE is defined as any "untoward medical occurrence that may present during treatment with a pharmaceutical product". ADEs include adverse drug reactions (ADRs), which are defined as "noxious and unintended" responses to medications, as well as other adverse events such as those that result from medication non-adherence, medication errors and under-treatment [29]. People exposed to polypharmacy are almost four times more likely to be hospitalised from an ADE than those taking fewer medications [30]. Polypharmacy is also associated with greater risk of drug interactions and makes it more difficult for health professionals to identify interactions and the consequences of those interactions [31].

A further consequence of polypharmacy, is increased health care costs for both the individual and society. These costs include the direct cost of medications [32] and indirect costs associated with the adverse consequences of polypharmacy as mentioned above (e.g. ADRs, non-adherence, hospitalisations, falls, functional and cognitive impairment). Medication-related hospitalisations alone are estimated to cost the Australian Government $1.2 billion annually [33]. The financial burden of medications can also contribute to non-adherence, where people stop taking their medication because they cannot afford them [34].

Despite the multiple risks associated with polypharmacy, there remains a limited body of evidence to guide health professionals in managing polypharmacy in older people. Most treatment guidelines are not designed for this population and do not discuss the applicability of their recommendations to older people with multiple comorbidities and multiple medications [2, 5]. The American Geriatrics Society and the National Institute for Health and Care Excellence have both recently released documents to guide health professionals in managing older people with multiple comorbidities [35, 36]. These documents support the need for a patient-centred comprehensive approach to care. They urge health professionals to elicit and incorporate patient preferences and goals, consider the patient's prognosis and make clinical management decisions that will optimise benefits and minimise potential harm.

1.3.2   Dietary supplements

Dietary supplement use is highly prevalent in older people and can contribute to polypharmacy, medication burden and regimen complexity. A dietary supplement, as defined by the Dietary Supplement Health and Education Act, is a product (other than tobacco) that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, a herb or other botanical, an amino acid or other dietary substance [37]. Many people use dietary supplements as complementary medication alongside or instead of their prescription medication. A national census snapshot of medication use in Australians aged 50 years or older in 2009-10 found that dietary supplements were used by 46.3% of participants [19].

In Australia, most dietary supplements are listed on the Australian Register of Therapeutic Goods, overseen by the Therapeutic Goods Administration (TGA) [38]. The TGA assesses supplements for quality and safety but, unlike prescription medications, supplements are not generally assessed for efficacy [38]. Patients' decisions to use, or not use, dietary supplements may be influenced by their personal beliefs, family or friends, advertising, health practitioner advice or comorbidities. More than half of those who use supplements believe that they are safe and natural and cause no adverse effects [39]. Research also suggests that most people do not disclose their use of supplements to a physician, either due to their belief that they are safe, or because they fear criticism [39, 40]. Consequently, health professionals often underestimate supplement use [41]. This lack of awareness is concerning as dietary supplements contribute to polypharmacy and medication regimen complexity, and may increase the risk of drug interactions, ADEs and healthcare costs [40, 42].

1.3.2   Potentially inappropriate medication (PIM)

Due to older people commonly having multiple comorbidities, multiple medications, and altered pharmacokinetics and pharmacodynamics, they have an increased likelihood of ADEs [6]. Some medications are considered 'potentially inappropriate' in older people because the risks of ADEs generally outweigh the potential clinical benefits in this population [6]. PIM use has been associated with increased risk of medication-related problems (MRPs) [43], defined as "an event or circumstance involving drug treatment that actually or potentially interferes with the patient experiencing an optimum outcome of medical care" [44]. MRPs may be caused by many factors including inappropriate drug selection, over or under dosing, inadequate monitoring of efficacy or adverse effects, or toxicity [44]. PIM use has also been associated with earlier transition from community into a nursing home, higher healthcare expenditure, morbidity and mortality [43, 45-47].

A 2014 systematic review found 46 tools that have been developed to help health professionals identify and avoid PIM use in older people [48]. These tools vary in their target population and setting, and each one has limitations, strengths and weaknesses [48]. The most well-known, widely used and validated criteria are the Beers criteria [49] and the Screening Tool of Older Peoples' Prescriptions (STOPP) [50].

The Beers criteria were developed in the US in 1991 with a focus on medication use in nursing home residents [51]. It was subsequently expanded to include all geriatric settings [49]. The latest version of the Beers criteria (at the time that this PhD was undertaken) was published in 2015 after an expert panel, in collaboration with the American Geriatrics Society, conducted a comprehensive, systematic review and grading of the evidence on MRPs and ADEs in older adults [52]. The Beers criteria is considered an important indicator of medication prescribing quality and an important educational tool for clinicians [49]. The criteria are divided into three categories: PIMs to be avoided in all older adults, PIMs to be avoided in older adults with certain medical conditions, and PIMs to be used with caution [49]. Using the Beers criteria, PIMs use has been found in approximately 40% of community dwelling older adults in the US [53].

The STOPP criteria were originally published in 2008 [54] and subsequently updated in 2015 [50]. They were developed by a panel of experts from 13 European countries. The STOPP criteria were developed along with the Screening Tool to Alert doctors to the Right Treatment (START) criteria (designed to identify potential under-prescribing), and the latest version includes 80 STOPP criteria and 34 START criteria. The STOPP criteria are more sensitive than the Beers criteria, with some studies using the STOPP criteria finding that almost 50% of community dwelling older adults use at least one PIM [55].

1.3.3   *Anticholinergic and sedative burden*

Two medication classes common to both the STOPP and Beers criteria are anticholinergics and sedatives. Sedatives, such as barbiturates, benzodiazepines and other hypnotics, should generally be avoided in older people as they are associated with increased risk of cognitive impairment, delirium, falls, fractures, motor vehicle crashes and hospitalisations [52, 56]. Anticholinergic medications include some antihistamines, tricyclic antidepressants, antimuscarinics and some antipsychotics. Older people are particularly sensitive to anticholinergic ADRs, which include confusion, dry mouth, constipation, dizziness, blurred vision, tachycardia and urinary retention [52, 57-59].

A number of tools can be used to assess the potential additive sedative and/or anticholinergic effects of multiple medications, often referred to as the sedative and/or anticholinergic burden of a medication regimen. Two widely used and validated tools are the Anticholinergic Cognitive Burden (ACB) scale [60, 61] and the Drug Burden Index (DBI) [62].

The ACB scale is based on a systematic literature review of medications with known anticholinergic activity [60]. A multi-disciplinary expert panel assessed individual drugs and assigned a score between 0 and 3 for each medication based on its anticholinergic potency: 0 for no known anticholinergic activity, 1 for possible anticholinergic properties (*in vitro* evidence of muscarinic receptor antagonism, e.g. furosemide, warfarin), 2 for definite clinical anticholinergic properties (e.g. carbamazepine, cyproheptadine) and 3 for definite anticholinergic properties that may cause delirium (e.g. amitriptyline, oxybutynin) [57, 60]. To generate an ACB score for a patient's regimen, the scores for each of their medications is tallied. A total medication regimen ACB score of three or more is considered to represent clinically significant anticholinergic burden [60]. Higher ACB scores have been associated with worse cognitive and functional performance [63].

The Drug Burden Index (DBI) [62] encompasses both sedative and anticholinergic burden. It estimates the impact of each sedative and/or anticholinergic medication using a formula that incorporates the daily dose used by the patient and the dose required to achieve 50% of maximal contributory effect [64]. The total DBI is the sum of individual medication scores in a person's medication regimen (Figure 2) [64].

$$\text{DBI} = \sum \frac{D}{D + DR_{50}}$$

Figure 2: Formula for calculating Drug Burden Index.

D is the daily dose, DR50 is the daily dose required to achieve 50% of maximal contributory effect.

Adapted from Kouladjian et al. Drug Burden Index in older adults: theoretical and practical issues [64]

The DBI score provides a tool for assessing the potential impact of a person's medication regimen on functional and cognitive outcomes [62]. Higher DBI scores have been associated with fall-related hospitalisations, lower physical function, higher frequency of general practitioner visits, and increased risk of mortality [65, 66]. Association between DBI scores and cognitive impairment is unclear with one study showing no significant association in

older men [67], and two others showing slight deterioration of cognitive function but no accelerated decline in cognition over time [68, 69].

1.3.4 *Medication management (adherence and medication-taking ability)*

Medication management is complex and challenging for many older people [70]. Medication management requires a person to have the ability to procure medication, confidence and knowledge regarding the use of their medication, and the physical and cognitive capacity to manage medication [70]. Managing one's own medications is a skill that is necessary for successful independent living [71]. Poor management of medications at home is a common reason for negative health outcomes such as suboptimal response to therapy, non-adherence, ADRs, unplanned medication-related doctor, hospital or emergency department visits, as well as nursing home admissions [72-76]. In Australia, it is estimated that up to 30% of all hospital admissions in older people are medication-related, and some of these admissions are due to factors such as non-adherence and errors in taking medications [77].

Increased medication burden and regimen complexity have been associated with non-adherence, unplanned hospitalisations and mortality [78-83]. Medication regimen complexity, commonly measured using the medication regimen complexity index (MRCI) [84], increases with each additional medication in a patient's regimen. Regimen complexity is also impacted by dosage frequency (e.g. twice daily, weekly or alternate days scored more complex than once daily dosing), administration instructions (e.g. with food, at night, or multiple doses) and dosage form (e.g. metered dose inhaler or patch scored more complex than tablets) [84].

Medication compliance is defined as "the extent to which a patient follows the health professionals' advice and takes the treatment" and refers to a passive decision process [85]. Medication adherence is defined as "the extent to which a person's behaviour (taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed recommendations from a health care provider" [85, 86]. The term 'adherence' is often preferred over 'compliance' because it refers to a more complex, yet active involvement from patients [85]. 'Non-adherence' refers to deviations from agreed treatment, and includes under-utilisation, over-utilisation and incorrect use of medication. There are two broad types of non-adherence: 'unintentional' – which may be due to factors such as forgetfulness or the complexity of the regimen; and 'intentional' – which occurs when a person decides not to take their medication or varies the way they take it [87]. A person is generally considered

'adherent' if they take between 80% and 120% of their medication over a given time period [88]. Unfortunately, the WHO suggests that adherence rates in developed countries average about 50% [86].

Medication-taking ability refers to a person's ability to accurately follow a prescribed regimen. It includes knowing what medications to take and when to take them, and being able to correctly administer the medication [89]. Up to one-third of older community-dwelling Australians self-report difficulty in removing medicines from packaging, reading medicine labels or using complex dose forms such as puffers and patches [90] and many older adults require assistance from informal carers (i.e. friends and family) with taking medications [91].

There are many factors that can affect medication adherence and medication-taking ability in older people, including (Figure 3) [86, 92]:

- *Social and economic factors*: low socioeconomic status, poverty, illiteracy, low level of education, lack of effective social support networks, unstable living conditions, cost of transport, cost of medication, family dysfunction;
- *Therapy-related factors*: route of administration, complexity of medication regimen, duration of treatment, immediacy of beneficial effects, medication side effects, degree of behavioural change required, availability of medical support;
- *Patient-related factors*: demographic factors, psychosocial factors, patient-prescriber relationship, health literacy, patient knowledge, physical difficulties, social history, forgetfulness, history of good compliance, hopelessness and negative feelings;
- *Condition-related factors*: severity of symptoms, level of disability, rate of progression, availability of effective treatments, comorbidities (e.g. depression); and
- *Health system/health care team factors*: lack of accessibility, long waiting time, overworked health care providers, short consultations, difficulty or delay in getting prescriptions filled, inadequate or non-existent reimbursement, weak capacity of the system to educate and follow-up patients.
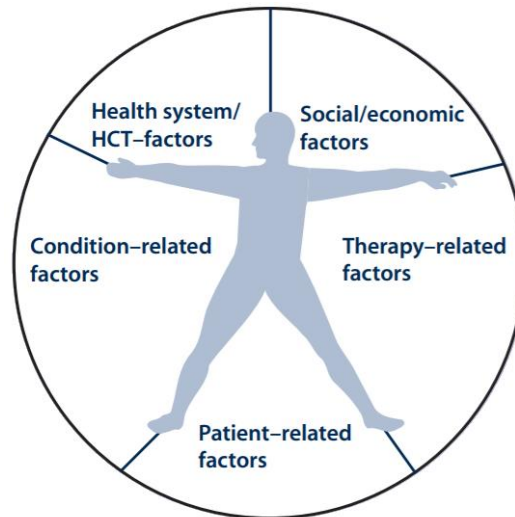
Figure 3: The five dimensions of adherence

Source: World Health Organization. Adherence to long term therapies – evidence for action [86].

Research suggests that interventions aimed at improving adherence and medication-taking ability need to address the specific contributing factors [93]. There are a range of behavioural, educational and provider-focused strategies that have been tested for improving medication adherence in older people with polypharmacy. These interventions were summarised in a 2008 systematic review by George et al. [94] that found most studies involved multifaceted interventions, but few were effective. Studies that did demonstrate moderate improvements in adherence involved individualised patient education provided by a pharmacist and one or more behavioural strategies with or without medication review [94]. The behavioural strategies included regularly scheduled patient follow-up [95], dose administration aids [95], group and individual education [96], individualised medication cards [96] and/or medication regimen simplification [97, 98]. George et al. concluded that further evidence from well-designed studies was needed to confirm if the above strategies are effective and recommended identification of novel ideas for improving medication management in older people taking multiple medications [94].

1.3.5 *Measuring medication adherence and medication-taking*

A major challenge for interventions aimed at improving medication adherence and medication-taking ability is agreement on an appropriate measure that is indicative of true adherence and/or ability [86, 88, 93]. Each measure is associated with its own strengths and weaknesses [99], and not all measures are appropriate in all clinical settings.

Three general types of measures exist, including:

- Subjective measures – patient/carer self-report or clinician assessments. These measures are typically low-cost and easy to administer. Unfortunately, they are also the least reliable, have relatively poor sensitivity and specificity and they can be subject to bias as patients may overestimate their adherence or ability or they may be unable to recall the number of medications taken.

- Objective measures – direct observation, electronic medication packaging devices, prescription refill data or pill counts. These measures are generally more accurate than subjective measures, are able to provide an assessment for multiple medications and may be able to identify patterns of medication taking. On the other hand, some measures can be expensive (e.g. electronic devices) or involve assumptions (e.g. refill data assume that a person actually took the medication, but this may not be the case). Observed adherence and/or medication-taking ability also may not be indicative of long-term patterns due to patients modifying their behaviour when they know they are being observed (Hawthorne effect).

- Direct measures - blood or urine analysis of serum drug levels. Direct measures can be used to monitor adherence for certain types of medications and provide the most accurate, physical evidence of adherence. Unfortunately these measures are expensive, invasive and time-consuming, and may also be influenced by pharmacokinetic and pharmacodynamic factors. Direct measures can also be subject to bias if the patients know the schedule of the tests.

1.3.6 Medication review and deprescribing

Increasing polypharmacy and PIM use in older people has created a growing emphasis on the need to review and rationalise medication use in older people. Deprescribing is the proactive, systematic, evidence-based process of discontinuing potentially inappropriate or unnecessary medication [100]. As well as withdrawal of inappropriate and unnecessary medications, the process of deprescribing may also include dose reduction or switching to a safer medication [101].

The term 'deprescribing' was originally described in 2003 [102], and is a rapidly growing area of research [103]. Deprescribing is a natural extension of the good prescribing

continuum, which spans medication initiation, dose titration, monitoring and dose adjustment and cessation. Deprescribing is also a core component of a medication review.

Deprescribing typically follows a five- step patient-centred process (Figure 4) [103].
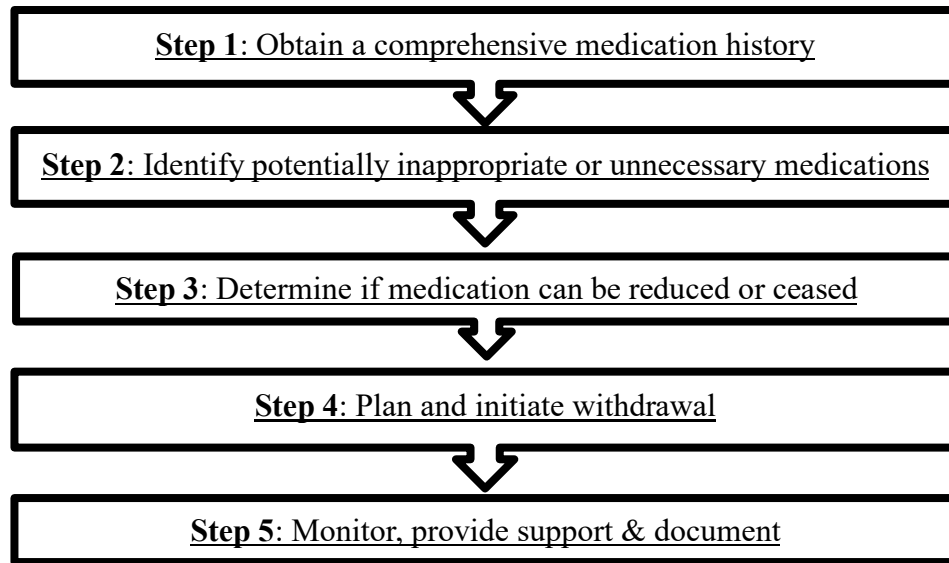
Figure 4: The five-step comprehensive patient-centred deprescribing process.

Adapted from Reeve et al. Review of deprescribing processes and development of an evidence-base, patient-centred deprescribing process [103].

The critical first step of deprescribing is obtaining a complete and accurate medication history. Acquisition of a comprehensive medication history involves gaining a complete list of all the medication that the patient takes regularly, 'as required' and intermittently, including all prescription and non-prescription medications (e.g. dietary supplements). The history should include the dose, frequency, formulation, route of administration, duration of use and indication for each medication [103]. The medication history should be derived from at least two sources of information such as the patient, carer/family, medical records and/or pharmacy dispensing history [104].

The second step is identifying potentially inappropriate or unnecessary medications. Explicit prescribing tools such as the Beers [49] and STOPP [50] criteria can assist with this process, but it is important to consider all medications, including those not on the Beers and STOPP lists. It is important to consider the potential risks and benefits of each medication, and their

dose regimens, in the context of the individual patient. Some factors that should be considered include ongoing need, benefit, contribution to or cause of ADE, future risk of ADEs, potential medication interactions, patient preferences, care goals and life expectancy [103]. Appropriateness of medication can change over time (i.e. due to ageing or new/developing medical conditions), thus this review of appropriateness should occur regularly.

The third step is to determine whether a medication can be ceased. Some medications may be identified as inappropriate, but may not be suitable to withdraw at that time, if at all. Deprescribing should usually only be attempted when patients are medically stable so that any withdrawal reactions can be attributed to the deprescribing, and if the condition was to return, it would not significantly impact the patient [103]. If more than one inappropriate or unnecessary medication is identified, it is best that they are withdrawn sequentially if possible, especially if they have overlapping indications or adverse withdrawal effects. The patient's willingness to cease the medication also needs to be considered. Patient barriers to deprescribing include feeling that the medication is essential, concerns relating to the process of deprescribing, fear of cessation and unwilling to 'change things' [105]. The Patient Attitudes Towards Deprescribing (PATD) questionnaire is a tool which can be used to determine patient willingness to cease medication and also helps identify patient-specific factors which may influence deprescribing [106]. The original PATD questionnaire was published in 2013 [106] and it was revised in 2016 (rPATD) [107]. In 2018, the rPATD for people with mild cognitive impairment (MCI) and mild-moderate dementia (rPATDcog) was published [108].

The fourth step is to plan and initiate withdrawal. Cessation of a medication is a common recommendation from a medication review, but general practitioners (GPs) face many challenges when deprescribing in routine practice [103, 109]. These challenges include the lack of easy-to-use and accessible evidence-based guidelines or decision support for deprescribing, social influences, timing/funding constraints, fear of consequences and poor communication between prescribers (e.g. GP and specialist) [109, 110]. Deprescribing needs to be planned carefully as some medications need to be tapered to prevent adverse withdrawal effects such as physiological responses, pharmacokinetic/pharmacodynamics changes and recurrence of the underlying condition [102, 111]. Tapering medications slowly may help to make the patient feel more comfortable with the idea of cessation [112].

The fifth step is to monitor for adverse withdrawal effects or recurrence of the underlying condition, provide support to the patient/care-giver and document outcomes. Support may come in the form of additional visits with healthcare professionals, education on lifestyle measures, advice on coping strategies or referral to allied health services (e.g. dietician or counselling service) [103]. The process and outcomes of deprescribing should be clearly documented in medical notes and all stakeholders (e.g. patient, family/carers, GP, community pharmacy) should update their medication lists to help prevent medication errors or accidental re-initiation of the medication [113, 114].

There is a growing body of evidence to support both the methods for, and outcomes of, deprescribing. A recent systematic review of randomised controlled trials concluded that successful deprescribing requires multi-disciplinary collaboration, patient and provider education and patient-specific drug recommendations [115]. The review also reiterated that successful deprescribing requires close, ongoing clinical follow-up [115]. While many health professionals recognise the potential benefits of deprescribing, the evidence for clinical benefits of deprescribing remains sparse. A number of recent reviews of deprescribing intervention studies have shown limited or unclear impact on clinical outcomes such as fall rates, cognition and quality of life [115-117]. While non-randomised data suggest deprescribing may reduce mortality, randomised studies have not shown any significant impact [118]. On the other hand, if medications are reduced with no ill-effects for the patient, then this may be a benefit in itself [119].

1.4 <u>Cognitive impairment</u>

Another key challenge presented by Australia's ageing population is the increasing prevalence of cognitive impairment. Cognitive impairment can occur at any age, but more commonly presents in older people [120]. There are many causes of and contributors to cognitive impairment including genetic syndromes, malnutrition, medication side effects, hypothyroidism, trauma, alcohol or substance misuse, stroke and dementia [121]. Some forms of cognitive impairment can be temporary and reversible, while others are progressive and irreversible [121].

Normal ageing commonly results in some progressive cognitive impairment that is often referred to as age-associated or normal cognitive decline [122]. This non-pathological decline varies greatly between individuals and can be influenced by different factors including lifestyle, genetics and comorbid conditions [123]. On the other hand, some older people

experience pathological cognitive impairment. MCI and dementia are diagnosed when cognitive impairment exceeds the cognitive decline associated with normal ageing [124].

In 2012 the WHO identified dementia as a 'public health priority' [125], and the Australian Government recognised dementia as a 'national health priority' [126]. In 2018 there were an estimated 436,000 Australians living with dementia, and this number is expected to increase to more than 1,076,000 by 2058 [8]. Dementia is the second leading cause of disease burden (a combined impact measure of morbidity and mortality) for older Australians [127], and the second leading cause of death for all Australians [128]. The number of deaths from dementia has increased by 68% over the past decade [128].

The progressive nature of dementia means people living with dementia have an increasing reliance on health and aged care services including doctor visits, allied health visits, hospital admissions and residential aged care. In Australia, an estimated 552,000 visits with GPs in 2010-11 involved the management of dementia [129], and the average hospital stay is six times longer for a person living with dementia compared to those without dementia (18 days versus 3 days) [130]. In 2018, the estimated cost of dementia in Australia was more than $15 billion [9]. Dementia is expected to become the third greatest source of health and residential aged care spending within two decades, and is set to outstrip any other condition by 2060 [131].

1.4.1   Mild Cognitive Impairment (MCI)

A person can experience a decline in cognition that is greater than would be associated with normal ageing long before meeting the diagnostic criteria for dementia. MCI is considered a transitional or intermediate stage between the cognitive decline associated with normal ageing and dementia [132]. The concept of MCI was first described by Reisberg et al. [133] in 1988, but it did not become a widespread term until Petersen et al. [134] developed criteria for diagnosing MCI in the 1990s. These criteria included: 1) complaint of defective memory; 2) normal activities of daily living (ADLs); 3) normal general cognitive function; 4) abnormal memory function for age; and 5) absence of dementia [134].

The definition of the 'MCI syndrome' has been revised and amended several times since then. While early definitions focussed on presentations with memory impairment (i.e. pre-Alzheimer's disease) [135], it is now recognised that there can be both amnestic and non-amnestic MCI [132]. In amnestic MCI (aMCI) people experience an objective decline in memory functioning but ADLs are largely preserved. In non-amnestic MCI (naMCI) people

present with other, non-memory presentations such as executive dysfunction, language difficulties and/or visuospatial deficits with ADLs largely preserved [132].

MCI does not always progress to dementia, but approximately 10-15% of cases per year do progress [135], which results in people with MCI being three to five times more likely to develop dementia than those without MCI [136]. There are no specific treatments for MCI, but some lifestyle and medical changes may help to slow progression [135] such as:

- Mental stimulation e.g. social engagements, reading, games to stimulate the mind.
- Maintaining general health e.g. aerobic exercise, healthy diet, cessation of smoking.
- Managing potential medical risk factors e.g. cardiovascular disease, diabetes mellitus.
- Avoiding medications with potential cognitive adverse effects (see section 1.5.2)

1.4.2 Dementia

Dementia, also referred to as major neurocognitive disorder, is a progressive disorder of memory loss and impaired cognitive ability, greater than that associated with normal ageing or MCI, with impairment of ADLs [124]. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-V defines dementia as a decline in memory with impairment of at least one other cognitive function, such as skilled movements (limb ataxia), language (aphasia), or executive function (e.g. planning, attention and abstract reasoning) [124]. As dementia progresses, patients become severely disabled, both physically and mentally, and require an increasing level of care. The prevalence, severity and progression of these signs and symptoms can vary greatly between different forms of dementia, and even between individuals with the same form of dementia [124].

Dementia is an umbrella term for several diseases affecting memory and cognitive function, including Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB) and frontotemporal lobar degeneration (FTD) [124]. Some people may experience 'mixed' dementia where they have signs and symptoms of two or more forms of dementia [124]. Diagnosing dementia requires comprehensive assessments including medical history, physical examination, neurological testing, psychiatric evaluation, laboratory tests and specialised imaging scans (e.g. positron emission tomography [PET] scan) [137, 138]. The DSM-V provides specific criteria for diagnosis of each type of dementia [124]. Accurate diagnosis of dementia is important for determining prognosis and to help guide therapy (Figure 5) [138, 139].
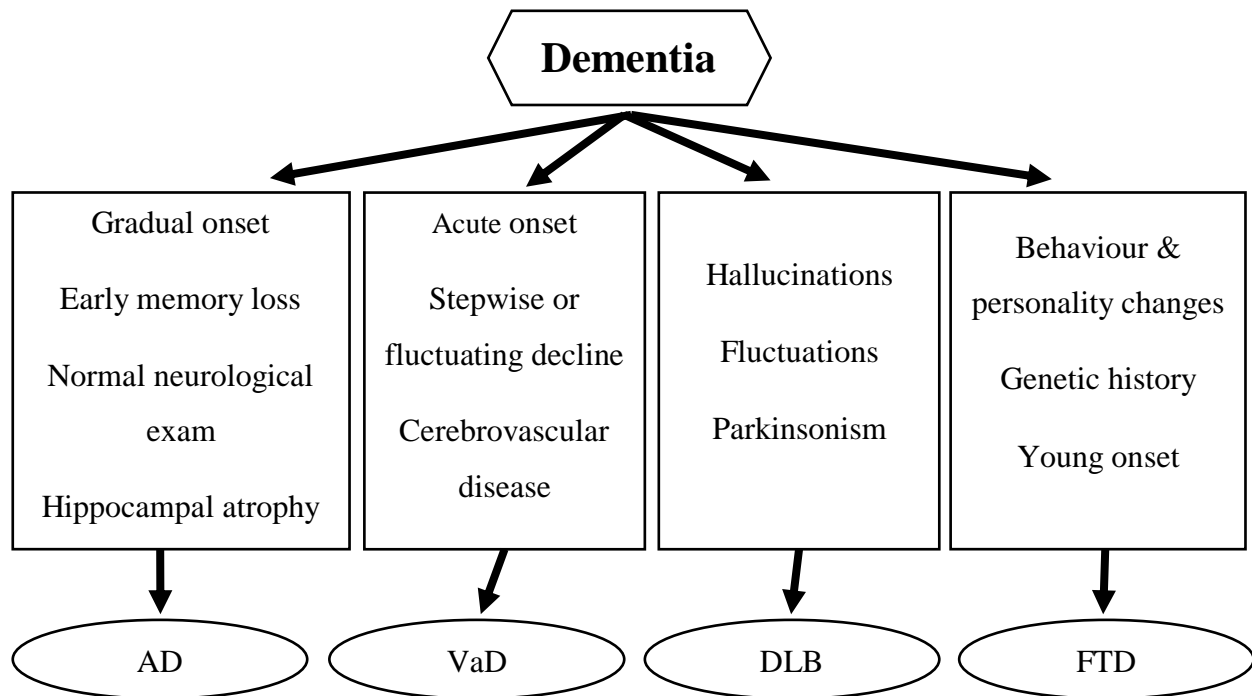
Figure 5: Differential diagnostic considerations and disease characteristics for the four main dementia subtypes; Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy Bodies (DLB), frontotemporal dementia (FTD)

Source: Adapted from information in *Diagnostic and Statistical Manual of Mental Disorders (DSM)-V, 2013* [124] and *Clinical diagnosis and management of Alzheimer's disease,* 2007 [139]

The most common form of dementia is AD, which constitutes approximately 50 to 70% of all dementia cases [132, 140]. AD is marked by insidious onset, gradual decline, and typically an early prominent memory decline [141]. People may present with difficulty remembering recent events or people, while motor signs, sensory abnormalities, gait difficulties and behavioural changes generally occur in later stages of the disease [124]. Diagnostic markers of AD may include hippocampal atrophy, amyloid-predominant neuritic plaques and tau-predominant neurofibrillary tangles [132, 142]. The rate of progression of AD varies from person to person, but median life span is around 4-8 years from diagnosis [132]. AD may be further classified as early or late onset. Early onset AD affects people younger than 65 years, but only accounts for about 2 to 5% of all cases [143].

VaD is the second most common form of dementia, accounting for 10-20% of cases [138, 144]. The definition of VaD has recently been expanded and is now considered the broad term for any dementia in which the dominant, if not exclusive, pathology is related to

cerebrovascular disease, including clinically apparent ischemic or haemorrhagic lesions or infarct(s) [124, 132]. Diagnosis of VaD involves thorough history, physical examination and/or neuroimaging to determine the existence of cerebrovascular disease considered sufficient to account for neurocognitive deficits [141]. People with VaD typically present with an acute stepwise or fluctuating decline in cognition [124, 138]. The clinical presentation and progression of VaD does vary depending on the size and location of the vessels involved [124, 132], and on average a person with VaD will live for five years after symptoms begin [35].

DLB is the third most frequent cause of dementia in older adults, accounting for approximately 5% of cases [145]. Lewy bodies are microscopic brain deposits which can cause damage to, and eventual death of, nerve cells in the brain [35]. The core diagnostic features of DLB are: fluctuation in alertness and attention, recurrent visual hallucinations that are well formed and detailed, and spontaneous features of Parkinsonism with onset occurring at least one year after cognitive symptoms [124, 138]. It is different from idiopathic Parkinson's disease where cognitive symptoms may appear when motor symptoms have been present for less than one year [124, 138]. DLB may be relatively non-amnesic [137]. After DLB symptoms begin, people live for an average of 6-12 years [35].

The fourth main type of dementia is FTD which is an umbrella term for dementia arising from degeneration in the frontal and/or temporal lobes of the brain [132]. FTD is characterised by the progressive development of behavioural and personality changes (e.g. inappropriate social conduct) and/or language impairment [124, 138]. FTD subtypes include both behavioural and language variants [124, 132]. Diagnostic features of FTD include evidence of a causative frontotemporal neurocognitive disorder genetic mutation (family history or genetic testing) or evidence of disproportionate atrophy of the frontal and/or temporal lobe as seen via neuroimaging [124]. The onset of frontotemporal lobar dementia is often earlier than other types of dementia, commonly presenting in people in their sixties [124]. The decline is faster than in AD, with median survival of 3-4 years after diagnosis [124].

1.4.3   *Measuring cognitive function*

There are a number of tools for assessing cognitive function and progression of dementia (Table 1). The most common screening tool for cognitive function is the mini-mental state examination (MMSE) [146]. The MMSE, developed in 1975 by Folstein et al., gives a total

score out of 30, with higher scores indicating better cognitive function. Despite some potential confounders (e.g. age, education and cultural background), the MMSE score is generally considered reliable, and is widely used across a variety of clinical, epidemiological and community settings [147].

Table 1: Tools for assessing cognitive function and progression to dementia.

Name of tool	Description of assessment
MMSE [146]	Quick, easily-administered test used to estimate dementia severity and assess change in cognitive function over time. Score /30, higher score = better function. Can indicate severity of impairment: mild (27-21), moderate (20-11) and severe (≤10).
Clock-drawing test [148]	Measures visuospatial ability by asking patients to draw an analogue clock face that reads a specific time (i.e. 2:45). Score /10, higher scores = better cognitive function.
Addenbrooke's cognitive examination [149]	Brief cognitive screening tool (15 mins) that assesses five cognitive domains (attention and orientation, memory, verbal fluency, language and visuospatial skills). Score /100, higher scores = better cognitive function.
Montreal cognitive assessment (MoCA) [150]	Ten minute cognitive screening tool with high sensitivity and specificity for detecting MCI. Score /30, higher scores = better cognitive function.
Rowland universal dementia assessment scale (RUDAS) [151]	Six-items that tests multiple cognitive domains (memory, praxis, language, judgement, drawing and body orientation). Easily interpreted into other languages and is recommended for use in people from culturally and linguistically diverse backgrounds. Score /30, higher scores = better cognitive function.
Alzheimer's disease assessment scale – cognitive (ADAS-Cog) [152]	Evaluates the severity of cognitive dysfunctions of persons with AD. It is usually administered by staff with specialist qualifications and is used for detailed assessments (30-45 mins). Score /70 indicates errors, lower scores = better cognitive function.
Neuropsychiatric index (NPI) [153]	Evaluates neuropsychiatric disturbances in persons with dementia (delusions; hallucinations; agitation; dysphoria; anxiety; apathy; irritability; euphoria; disinhibition; aberrant motor behaviour; night-time behaviour disturbances and appetite/eating abnormalities). Domain score: frequency (/4) x severity (/3), lower scores better.
Clinical dementia rating (CDR) [154]	Semi-structured interview that rates cognitive status in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care). Used to stage dementia severity: 0.5 = very mild, 1=mild, 2=moderate or 3=severe.

1.4.4   Dementia prevention, diagnosis and care

There is currently no disease-modifying treatment for dementia, but appropriate prevention, intervention and care is essential to help minimise the current and future emotional, physical

and financial burden of dementia on the person, their family/carers, and the wider community.

Early detection of MCI and dementia is important to ensure individuals can make changes in their lifestyle and access appropriate treatment that may delay or prevent cognitive decline, and plan ahead for issues relating to finances, lifestyle or health care. A timely diagnosis is a prerequisite for good dementia care, but many people receive a diagnosis when it is too late for them to make decisions about their own care or to benefit from interventions [155].

According to the *Clinical Practice Guidelines for Dementia in Australia* [10], a diagnosis of dementia should only be made after a comprehensive assessment, which should include:

- history taking from the person;
- history taking from a person who knows the person well (if possible);
- cognitive and mental state examination with a validated instrument;
- physical examination;
- a review of medication in order to identify and minimise use of medications, including over-the-counter products that may adversely affect cognitive function and to simplify medication dosing; and
- consideration of other causes (including delirium or depression).

Memory clinics, also known as cognitive, dementia and memory services (CDAMS) in Victoria, Australia, have been developed to assist people experiencing changes in their memory and thinking. Memory clinics are ambulatory, interdisciplinary centres dedicated to the initial assessment of cognitive impairment, diagnosis of a memory disorder, if applicable, creation of a management plan and referral to other services as appropriate [11]. Management plans for people diagnosed with cognitive impairment should be individualised, and span medical, social and cultural needs, preferences and proprieties and should incorporate support for family and carers [155].

Australian memory clinics are not designed for ongoing treatment or case management and patients are generally referred back to their primary health practitioner (e.g. GP). On average, a memory clinic patient will attend the clinic three times and spend nearly five hours being assessed [11]. The interdisciplinary memory clinic team typically includes geriatricians, psychiatrists, neurologists, neuropsychologists, occupational therapists, social workers and community nurses [11]. Pharmacists are not typically involved in memory clinics in

Australia, but some international studies have highlighted a potential role for pharmacist involvement [156, 157].

1.5 Medication use in cognitive impairment

Whilst there is no cure for dementia, safe and appropriate use of medications (where possible) is important to help reduce or delay further cognitive decline (where possible). Medications should also be reviewed to minimise the use of potentially inappropriate or unnecessary medications which may worsen cognitive impairment or increase risk of adverse effects, morbidity and mortality.

1.5.1   Medications to support cognitive function

There is currently no curative treatment for MCI or dementia, but some medications have been found to provide variable temporary improvement of cognitive impairment symptoms. There are currently two approved prescription treatments, cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists.

ChEIs act by inhibiting the enzyme acetylcholinesterase, thus reducing the breakdown of acetylcholine in the brain [158]. Acetylcholine is an important neurotransmitter involved in the communication of signals between brain cells [159], and reduced concentration and function of acetylcholine in the brain is thought to contribute to cognitive impairment, particularly in AD [160]. ChEIs can help to temporarily improve alertness and brain function, but they do not treat the underlying pathology of AD [158].

Currently, there are three ChEIs available in Australia: donepezil, galantamine and rivastigmine [161]. ChEIs are available on the Pharmaceutical Benefits Scheme (PBS) for people who have been diagnosed with mild to moderate AD (MMSE $\geq$ 10) by, or in conjunction with, a specialist/consultant [161]. ChEIs may offer modest benefits for people with mild to moderate AD [158]. To be eligible for ongoing treatment (after 6 months) the patient needs to demonstrate a clinically meaningful response to therapy (e.g. cognitive improvement of $\geq$ 2 on MMSE) [161].

Some research has suggested that donepezil may improve cognitive and neuropsychiatric symptoms associated with DLB [155, 162, 163] and reduce carer burden [162], but ChEIs are not approved for DLB in Australia.

NMDA antagonists, such as memantine, are a newer class of dementia medications that work by preventing excitatory amino acid neurotoxicity and restoring homeostasis in the

glutamatergic system in the brain [164, 165]. Memantine has some effect on cognition in moderate to severe AD and is PBS approved in Australia for use in this population [166].

In addition to prescription medications, there is also a medical food product (Souvenaid®) and a number of dietary supplements that claim to have beneficial effects on cognitive function, but the scientific evidence regarding their efficacy is generally limited (Table 2).

Using dietary supplements to support cognitive function is not a new phenomenon. In 1995, a Canadian study found that 39% of patients used one or more supplements, and 10% used them specifically to help with memory [167]. More recent studies have found that 47% of people with cognitive impairment used a dietary supplement or another form of alternative medicine (e.g. acupuncture) to support their cognitive health [167, 168].

Table 2: Common dietary supplements used to support cognitive function.

Supplement	Proposed mechanism of action	Evidence for efficacy and safety	References
Souvenaid®	Medical nutritional drink containing precursors and cofactors for formation of neuronal membranes	- May improve memory performance in mild AD - Few RCTs exist, all conducted by manufacturer - Generally well tolerated	[169-172]
Ginkgo biloba	Antioxidant effect, increases cerebral blood flow, modulate neurotransmitters	- Some evidence of mild benefit - Limited well-designed studies showing predictable, clinical benefit - Generally safe, may increase risk of bleeding	[173-180]
Fish oil (omega 3)	Cognitive protective effects, reduces pro-inflammatory cytokines, low docosahexaenoic acid (DHA) levels found in brains of those with AD	- Some evidence of protective effect and reduced chance of developing dementia - No consistent evidence from large, well-designed studies - Generally well tolerated, may increase risk of bleeding	[176, 177, 181-186]
Vitamin B9 (folic acid)	Deficiency can affect memory and increase risk of dementia	- No reported benefit on cognitive function in healthy or cognitively impaired older people - Well tolerated, minimal interactions	[176, 177, 187-189]
Vitamin B12 (cyano-cobalamin)	Deficiency can affect memory and increase risk of dementia	- No reported benefit on cognitive decline or development of dementia - Well tolerated, minimal interactions	[138, 176, 177, 187, 190, 191]
Vitamin E (tocopherol)	Antioxidant, may delay clinical worsening, deficiency can result in neurological signs and symptoms	- No consistent evidence of benefit in preventing MCI progressing to dementia, or improving cognitive function in people with MCI or AD - Some studies suggests high doses may reduce likelihood of dementia and delay cognitive decline, but high doses are linked to increased ADEs	[138, 176, 192-196]

1.5.2   Medications with adverse cognitive effects

Use of PIMs in people with MCI and dementia is a growing area of research. In addition to age-related pharmacokinetic and pharmacodynamics changes that occur in older people, an altered blood-brain permeability in people living with dementia means those with cognitive impairment often have increased susceptibility to cognitive ADRs, such as sedation, confusion and delirium [197-199].

While there are numerous criteria for identifying PIM use in the general older population, few tools are available for identifying medications that are associated with cognitive impairment and thus may be potentially inappropriate for people with MCI or dementia. Some studies have used subsets of the Beers criteria [59], STOPP criteria [200] or evidence of drug-disease interactions (i.e. medications which may worsen cognitive function) [201] to define PIM use. Common medication classes identified include anticholinergics, sedatives and other medications which may cause or worsen delirium (e.g. histamine-2 receptor antagonists). Recent studies (post-2017) have reported that the prevalence of PIM use varies from 14 to 74% depending on the criteria used, setting (community versus residential care) and dementia severity [202, 203].

1.5.3   Medications considered potentially inappropriate in dementia

In clinical practice, identifying PIM use in people with dementia involves review of life expectancy and patient treatment goals as these can impact the risk-benefit profile of a medication [202]. Medications for primary or secondary prevention that require years of treatment to achieve benefit may be considered inappropriate or unnecessary if the person is not expected to survive to realize the benefit [202].

Two criteria exist for identifying PIM use in people with advanced dementia, when patients are severely disabled and the focus is on end-of-life care [204, 205]. Another tool, the Medication Appropriateness Tool for Co-morbid Health conditions in Dementia (MATCH-D), provides guidance on the appropriateness of preventative medications in early-, mid- and late-stage cognitive impairment [206].

Inappropriate or unnecessary polypharmacy can also be of concern in people living with dementia. The use of polypharmacy in people with cognitive impairment can make managing and self-administering medications more difficult, and those with dementia also often have a reduced ability to self-identify and report issues with poor medication management or ADEs [207, 208]. It is important that all medications be regularly reviewed for actual benefits, and

withdrawn if they have no benefit, even if they pose no immediate risk [206]. There has been limited research into polypharmacy in community dwelling Australians with dementia, however, international studies suggest that polypharmacy is present in 45% of community dwelling people with dementia [209].

1.5.3 Deprescribing in cognitive impairment

Ensuring optimal medication use in people living with cognitive impairment includes prescribing appropriate medication and deprescribing inappropriate or unnecessary medications. Unfortunately, there can be additional barriers to deprescribing in a person with cognitive impairment compared to a general older person [210]. People with cognitive impairment often have diminished decision making capacity and it can be more difficult to establish the patient's goals of care. As dementia progresses, there is increased involvement of carers and other family members in medical decisions, and these people may have difficulties being surrogate decision makers (e.g. they may feel like deprescribing is 'giving up'). People with cognitive impairment also may not be able to adapt as easily to changes in their medication regimen, which could result in medication errors, non-adherence and ADE [211].

Inadequate guidelines and lack of training on how to perform deprescribing result in system-related barriers to deprescribing in older adults with and without cognitive impairment. Evidence-based guidelines exist to guide the cessation of certain classes of medications in people with dementia, including antipsychotics for behavioural and psychological symptoms of dementia (BPSD) [212], sedative/hypnotic medications [213], and cholinesterase inhibitors and memantine [214]. There is an ongoing trial investigating the withdrawal of antihypertensive therapy in people with dementia [215]. Further research investigating the ideal setting, timing and process for deprescribing in people with cognitive impairment is required, as well as evidence showing the potential short- and long-term clinical benefits.

1.6 Gaps in the literature

At the time of commencement of this PhD, after a thorough review of the literature, several gaps were identified in relation to medication adherence, medication-taking ability and medication use in older people with cognitive impairment.

Older people taking multiple medications represent a large and growing proportion of the population. Although a number of systematic reviews of interventions to improve medication adherence have been published, few have focused on older people taking multiple

medications and no reviews have evaluated medication-taking ability. Managing multiple medications can be challenging for some older people, and interventions that are effective in younger populations or in people prescribed fewer medications may not be generalisable to this population. Evidence from well-designed randomised controlled studies focussed on older people prescribed multiple medications could provide valuable information for patients/carers, health professionals, researchers and policy makers.

Prescribing for older people, especially those with multiple chronic health problems or cognitive impairment, can also be challenging. Older people are at increased risk of ADEs, and inappropriate or unnecessary medication use can further increase the risk. Studies investigating prevalence of inappropriate medication use in people with cognitive impairment suggest that the prevalence varies depending on the criteria used, the setting (community versus residential care) and dementia severity.

In Australia, memory clinics assess and diagnose people with suspected cognitive impairment. Clinical practice guidelines for dementia recommend a review of medication as part of the diagnostic process in order to identify and minimise use of medications, including over-the-counter products, that may adversely affect cognitive function and to simplify medication dosing. Prior to this PhD, there had been little research investigating the prevalence of inappropriate medication use and the potential role of pharmacist-initiated medication reviews and deprescribing in a memory clinic setting.

2. CHAPTER TWO: Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications

2.1 <u>Preface</u>

Chapter one provided an overview of the challenges associated with medication use in older people and highlighted the lack of systematic reviews evaluating interventions for improving medication-taking ability and medication adherence in older people prescribed multiple medications. Rigorous systematic reviews of well-conducted randomised controlled trials provide the highest level of research evidence. Thus, this chapter presents a comprehensive, systematic review of randomised controlled studies that investigated interventions for improving medication-taking ability and/or medication adherence in older adults prescribed multiple medications. This review focussed on the general older adult population as a scoping review suggested a lack of interventions focussing specifically on older adults with cognitive impairment. Given older adults with cognitive impairment are a subgroup of the general older adult population, the findings from a broader review may still be relevant until further evidence is generated in this subpopulation.

2.2 <u>Chapter objective</u>

To systematically review the effectiveness of interventions for improving medication-taking ability and medication adherence in older people prescribed multiple medications.

2.3 <u>Publications</u>

Cross AJ, Elliott RA, George J. *Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications [protocol].* Cochrane Database of Systematic Reviews. 2016. Issue 10. Art. No.: CD012419.

Cross AJ, Elliott RA, Petrie K, Kuruvilla L, George J. *Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications [review]. [submitted]**

*Note: This is a draft and pre-peer review version of the Cochrane Review. Upon completion and approval, the final version is expected to be published in the Cochrane Database of Systematic Reviews. This draft has been exported from Review Manager v5.3 into Word.

2.4 <u>Appendices</u>

Appendix 1: Search strategies (Medline, CENTRAL, CINAHL, EMBASE, IPA and PsycINFO).

[Intervention Protocol]

Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications

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A B S T R A C T

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effectiveness of interventions designed to improve medication-taking ability and/or adherence in older community-dwelling people (or their carers). We will focus on interventions that target medication-taking behaviour by consumers who are being treated with multiple long-term, prescribed medications, and will include measures of both medication-taking ability and adherence to the prescribed medication regimen.

B A C K G R O U N D

Description of the condition

Older people, conventionally defined as those aged 65 years and above, often have multiple chronic health problems that require ongoing healthcare interventions (Hilmer 2007; WHO 2000). An expanding evidence base supporting multidrug regimens in the management of many chronic diseases means that polypharmacy (use of multiple medications) is often unavoidable in older people. Polypharmacy has a range of definitions, but is commonly defined as the use of four or more medications (Department of Health (UK) 2001; Patterson 2014). About two-thirds of people aged over 60 years who live in community settings use four or more medicines daily (Elliott 2014). There is also a substantial subgroup who are prescribed an average of 10 or more different medications, which is sometimes referred to as hyperpolypharmacy (Elliott 2014).

Medication-taking ability refers to a person's ability to accurately follow a prescribed medication regimen. It includes knowing what medications to take and when to take them, and being able to correctly administer the medication (Maddigan 2003). Managing multiple long-term medications can be a complex and challenging task, especially for older adults who may experience a decline in the cognitive and physical abilities required for taking medication (Barbas 2001; Beckman 2005). More than a quarter of older adults experience difficulties in opening medication packages, including opening bottles and removing medication from blister packs (Philbert 2014). Older people with visual impairment are more than twice as likely to require help in managing their med-

ication than those without visual impairment (McCann 2012). Many older adults receive assistance from informal or non-professional carers with taking medication (ACSQHC 2012). Thus, interventions that aim to improve medication-taking ability in older adults may need to target carers as well as consumers.

Medication adherence refers to the extent to which a person's medication-taking behaviour corresponds with agreed treatment recommendations from a healthcare provider (WHO 2003). Non-adherence refers to deviations from that agreed treatment, and includes under-utilisation, over-utilisation and incorrect use of medication. There are two broad types of non-adherence: unintentional non-adherence - which may be due to factors such as forgetfulness, lack of understanding, physical problems or the complexity of the regimen; and intentional non-adherence - which occurs when a person decides not to take their treatment as instructed (Wroe 2002). A person is generally considered adherent if they take between 80% and 120% of their prescribed medication over a given time period (WHO 2003). Non-adherence to medications has been reported in up to 50% of older people in different countries and settings (George 2006; Gilbert 1993; Gray 2001; Hemminki 1975; Lau 1996; Lee 2010; Mansur 2008; McElnay 1997; Okuno 1999; Sewitch 2008; Spagnoli 1989; Stoehr 2008; Thorpe 2009; Vik 2006). The World Health Organization (WHO) has recognised the importance of enhancing adherence as a strategy to tackle chronic health conditions effectively (WHO 2003).

Consequences of poor medication-taking ability and non-adherence may include suboptimal response to treatment, recurrence of illness, adverse drug events, increased healthcare service utilisation, unplanned hospitalisations, increased morbidity and mortality, and increased healthcare costs (Balkrishnan 2003; Col 1990; DiMatteo 2002; Howard 2003; Leendertse 2008; Tafreshi 1999). Among older adults, adverse drug events are a significant and increasing problem (Burgess 2005; Elliott 2014). Almost a quarter of preventable adverse drug events in older people are attributable to consumer errors (Field 2007; Gurwitz 2003). Between USD 100 and USD 300 billion of avoidable healthcare costs have been attributed to non-adherence in the US annually (IMS 2013).

Medication-taking ability and adherence are influenced by a range of factors related to healthcare consumers, their therapies, medical conditions, and social-, healthcare provider-, and health system-related factors (Balkrishnan 1998; Jin 2008; WHO 2003). Age itself is generally not an independent predictor of poor medication-taking ability or non-adherence (DiMatteo 2004; Vik 2004). Nevertheless, the prevalence of risk factors for medication use problems increases with age (Col 1990). These include polypharmacy (Gray 2001; Vik 2006), medication regimen complexity (Corsonello 2009; Jansa 2010; Vik 2006), cognitive and functional decline (Gray 2001; Hutchison 2006; Spiers 1995; Vik 2006), inadequate contact with health professionals (George 2006), depressive symptoms (Vik 2006), poor social support (DiMatteo 2000; Spiers 1995), and absence of assistance with administration of medica-

tions (Vik 2006). The risk factors for suboptimal use of medications by older people have been studied extensively in cross-sectional studies (George 2006; Gilbert 1993; Gray 2001; Hemminki 1975; Jerant 2011; Lau 1996; McElnay 1997; Okuno 1999; Sears 2012; Spagnoli 1989; Tavares 2013; Vik 2006). Many adverse health outcomes may be preventable if appropriate measures are taken to address these risk factors and optimise medication-taking ability and adherence (George 2008; Jokanovic 2016; Sorensen 2004).

Description of the intervention

A range of simple to complex behavioural and educational interventions, alone or in combination, have been tested for improving the medication-taking ability and adherence of consumers (George 2008). Behavioural strategies include:

- alarm/beeper,
- calendar/diary,
- reminder chart/medication list,
- large print labels,
- packaging change,
- pillbox/calendar pack (also known as dose administration aid),
- contracting (verbal or written agreement),
- adherence monitoring with or without feedback,
- reminders (mail, telephone, email),
- inpatient programs of self-administration of medications,
- simplification of medication regimens,
- skill building (supervised, group),
- tailoring (routinisation), and
- follow-up (home visit, scheduled clinic visit, video/ teleconferencing).

Educational strategies comprise group (in-patient, family, and group) and/or individual (oral, audiovisual, visual, written, telephone, mail) education provided by physicians, pharmacists, nurses, and others. We plan to evaluate which types of interventions targeted for consumers improve medication-taking ability and adherence in older adults prescribed multiple medications.

How the intervention might work

Behavioural and educational interventions, used alone or in combination, are intended to improve older peoples' (and/or their carers') ability to manage medications and adhere to medication regimens.

These interventions may also lead to: improvements in knowledge about medications and confidence regarding medication management; greater satisfaction with treatment; better health-related quality of life; reductions in the incidence of adverse drug events; and reductions in health service utilisation.

Why it is important to do this review

Evidence from well-designed studies testing interventions to improve medication-taking ability and adherence in older people prescribed multiple long-term medications could provide valuable information for practitioners, researchers, and consumers to help optimise medication use among older people living in the community. Older people taking multiple medications represent a large and growing proportion of consumers seen by health professionals in clinical practice. They are also the group most likely to experience adverse drug events.

Interventions to improve medication adherence have been widely investigated (Bosch-Capblanch 2007; Campbell 2012; Chong 2011; Conn 2009; Conn 2015; Haynes 2008; Kripalani 2007; Krueger 2003; Linn 2011; McDonald 2002; Nieuwlaat 2014; Peterson 2003; Roter 1998; Ruppar 2008; Russell 2006; Sapkota 2015; Schedlbauer 2010; Schlenk 2004; Van Eijken 2003; Van Wijk 2005; Viswanathan 2012; Williams 2008). Most studies, and therefore most reviews, have focussed on one health condition and/or the use of one medication or one medication class. However, older people form a heterogeneous population in terms of their medication consumption and disease patterns; therefore studies recruiting relatively homogenous samples of people experiencing one specific disease or consuming one type of medication have limited generalisability. We found only one systematic review focusing on older people taking multiple medications (George 2008). That review analysed adherence only, and is now almost 10 years old.

To date, no systematic review has included measures of medication taking other than adherence, such as medication errors or ability to manage medications. Standardised methods for measuring the ability of people to manage medications have been developed (Elliott 2009; Elliott 2015), some of which have recently been used in studies of medication use in older people (Lam 2011). Two of the most well-studied medication assessment tools are the Drug Regimen Unassisted Grading Scale (DRUGS) (Edelberg 1999), which utilises a person's own medications, and the Medication Management Ability Assessment (MMAA) (Patterson 2002), which uses a simulated medication regimen.

We will focus on interventions to improve medication-taking ability or adherence, or both, in older adults who are prescribed multiple medications, or their non-professional carers.

This review will complement previous Cochrane reviews looking at interventions for improving medication adherence in the general population (Nieuwlaat 2014), including the impact of dose reminder packaging (Mahtani 2011), and interventions for improving clinical outcomes in people with multi-morbidities (Smith 2016). The appropriateness of people's medication regimens will not be considered as part of this review, but only their ability to take the medications and their adherence to the agreed regimen. There has been a previous Cochrane review of interventions, targeted at health professionals, designed to improve the appropriateness of prescribing and polypharmacy (Patterson 2014).

O B J E C T I V E S

To evaluate the effectiveness of interventions designed to improve medication-taking ability and/or adherence in older community-dwelling people (or their carers). We will focus on interventions that target medication-taking behaviour by consumers who are being treated with multiple long-term, prescribed medications, and will include measures of both medication-taking ability and adherence to the prescribed medication regimen.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), cluster RCTs and quasi-RCTs as specified by the Cochrane Consumers and Communication Review Group (CCCRG 2014).

Types of participants

We will include studies in which:
- most participants (80% or more) were aged 65 years and over, or the mean age was over 65 years. If studies are identified that do not meet these criteria, but have relevant data regarding older people that can be extracted separately, these will also be included.
- participants were living in the community or were discharged from a hospital or other healthcare facility to the community (living in the community includes in a person's own home or retirement village/independent living unit, with or without additional support; it does not include situations in which professional carers or nurses administer the person's medications, such as in nursing homes, residential care facilities or full nursing care in the home).
- participants used at least four long-term regular prescription medications, or the group mean/median was more than four (irrespective of the participants' number of medical conditions).

Studies that involve carers of consumers who meet these criteria will also be included. Carers are defined as "people who provide unpaid care and support to family members and friends who have disability, mental illness, chronic condition, terminal illness or general frailty" (ACSQHC 2012).

Types of interventions

We will include studies that tested single interventions or combinations of interventions directed at the consumer or their carer

that sought to improve medication-taking ability and/or adherence by the consumer.

Examples include the following behavioural and educational interventions:

- support for behaviour change;
- provision of medication aids (e.g. dose administration aids, medication lists);
- medication regimen simplification;
- remote monitoring of medication use with or without feedback;
- facilitation of communication and decision making about medications;
- provision of information or education; and
- acquisition of skills and competencies.

This list of interventions is not exhaustive, since the types of interventions that might be used to improve the medication-taking ability and adherence of consumers is potentially unlimited. Acknowledging that this is the case, the search strategy (see Appendix 1) to be used will focus on terms that describe the outcomes of interest to avoid missing potentially-relevant studies that tested novel interventions.

We will include the following comparisons:

- interventions to improve medication-taking ability and/or adherence versus no intervention;
- interventions to improve medication-taking ability and/or adherence versus standard or usual care; and
- one form of intervention to improve medication-taking ability and/or adherence versus another - including simple versus complex interventions.

Types of outcome measures

Primary outcomes

This review will focus on two outcomes directly related to the medication-taking behaviour of older adults (or their carers): ability to manage medications and adherence to medication regimens. To be eligible for inclusion in this review, studies must have assessed at least one of these outcome measures for at least four medications (which could be either the person's own medications or, for assessment of ability to manage medication, a validated, simulated medication regimen instrument) (Elliott 2009). These two outcomes will be evaluated separately.

Ability to manage medications

This outcome may include objective and subjective measures of participant or carer ability to manage medications.

1. Objective measures: direct observation using standardised assessment instruments/methods (e.g. Drug Regimen Unassisted Grading Scale (DRUGS) tool, Medication Management Ability

Assessment (MMAA), inhaler technique checklists) (Elliott 2006; Elliott 2009; Patterson 2002).

2. Subjective measures: self-reported ability or self-efficacy (e.g. Self-efficacy for Appropriate Medication Use Scale (SEAMS)) (Risser 2007).

Adherence to medication regimens

This outcome will be assessed in terms of consumer adherence to their prescribed medication regimens, using objective and/or subjective measures as listed below:

1. Objective measures: refill data, pharmaceutical claims data, electronic monitoring, biological assay, measure of used/unused medications (e.g. pill count).

2. Subjective measures: self-report of missed/used doses, validated questionnaires (e.g. Morisky scale; Morisky 1986).

If an included study measures adherence and/or ability using more than one type of outcome measure, then the most reliable measure will be extracted (i.e. objective measures will be preferentially reported over subjective measures).

Secondary outcomes

The following secondary outcomes will be analysed from studies that also measured at least one of the primary outcomes listed above:

- consumer (or carer) knowledge about their medications;
- consumer (or carer) satisfaction with the intervention;
- health-related quality of life;
- adverse clinical health outcomes (e.g. unplanned hospital presentations, general practitioner visits, adverse drug events);
- condition-specific outcomes (e.g. cardiovascular events, blood pressure, blood glucose levels or lung function); and
- cost effectiveness of the intervention.

Timing of outcome assessment

For adherence outcomes the minimum duration of follow-up must be four weeks. For ability outcomes a follow-up period of at least 48 hours after the intervention is required.

If an included study measures adherence and/or ability more than once, then the outcome measure with the longest follow-up will be extracted.

If sufficient trials exist, studies with different lengths of follow up will be compared. For adherence this will involve short-term (4 weeks), medium-term (3 months) and long-term (6 months) follow up. For ability outcomes this will involve short-term (48 hours), medium-term (1 week) and long-term (1 month) follow up.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases using search strategies tailored to each database:

• Cochrane Central Register of Controlled Trials (CENTRAL,*Cochrane Library*, latest issue);
• MEDLINE (OvidSP) (1966 to present);
• Embase (OvidSP) (1973 to present);
• PsycINFO (OvidSP) (1967 to present);
• CINAHL Plus (1981 to present); and
• International Pharmaceutical Abstracts (IPA) (1971 to present).

The strategy for MEDLINE (OvidSP) is presented in Appendix 1. We will tailor strategies to other databases and report them in the review.
There will be no language restrictions (provided the title and abstract are in English).

Searching other resources

For grey literature, we will search:
• the Joanna Briggs Institute Evidence Based Practice (EBP) Database; and
• conference proceedings (e.g. Scopus).

We will check the reference lists of included studies and previously published relevant systematic reviews to locate potential studies that have not been identified via electronic searches.
We will contact experts in the field and authors of included studies for advice as to other relevant studies.
We will also search the following online trial registries for ongoing and recently-completed studies:
• World Health Organization International Clinical Trials Registry Platform (ICTRP);
• ClinicalTrials.gov;
• ClinicalTrials.com;
• TrialsCentral;
• Australian New Zealand Clinical Trials Registry (ANZCTR);
• United Kingdom Clinical Research Network (UKCRN);
• Networked Digital Library of Theses and Dissertations (NDLTD); and
• ISRCTN registry.

Non-English language studies will be translated and included if they meet the eligibility criteria.

Data collection and analysis

Selection of studies

Abstracts will be screened independently by two review authors and full text of any papers identified as potentially relevant by at least one author will be retrieved. Two authors will independently screen full-text articles for inclusion or exclusion, with discrepancies resolved by discussion and by consulting a third author if necessary to reach consensus. Review authors will not be responsible for the screening of studies in which they were involved or associated. All potentially-relevant papers excluded from the review at this stage will be listed as excluded studies, with reasons provided in the 'Characteristics of excluded studies' table. We will also provide citation details and any available information about ongoing studies, and collate and report details of duplicate publications, so that each study (rather than each report) is the unit of interest in the review. We will report the screening and selection process in an adapted PRISMA flow cart (Liberati 2009).

Data extraction and management

Two review authors will extract data independently from included studies. Any discrepancies will be resolved by discussion until consensus is reached, or through consultation with a third author where necessary. We will develop and pilot a data extraction form using the Cochrane Consumers and Communication Review Group Data Extraction Template (cccrg.cochrane.org/author-resources). Data to be extracted will include the following study details: aim of the intervention, study design, study population, intervention details, risk factor(s) for poor medication adherence and/or medication-taking ability targeted by the intervention(s), control/comparison group(s), outcome(s), and follow-up period(s). All extracted data will be entered into Review Manager (RevMan 2014, v. 5.3) by one review author, and will be checked for accuracy against the data extraction sheets by a second review author working independently.

Assessment of risk of bias in included studies

We will assess and report on the methodological risk of bias of included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and Cochrane Consumers and Communication guidelines (CCCRG 2014), which recommend the explicit reporting of the following individual elements for RCTs: random sequence generation; allocation sequence concealment; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data, selective outcome reporting; and other sources of bias. We will consider blinding separately for different outcomes where appropriate (for example, blinding may have the potential to differently affect subjective versus objective outcome measures). We will judge each

item as being at high, low or unclear risk of bias as set out in the criteria provided by Higgins 2011, and provide a quote from the study report and a justification for our judgement for each item in the 'Risk of bias' table.

Studies will be deemed to be at the highest risk of bias if they are scored at high or unclear risk of bias for either the sequence generation or allocation concealment domains, based on growing empirical evidence that these factors are particularly important potential sources of bias (Higgins 2011).

We will assess and report quasi-RCTs as being at high risk of bias on the random sequence generation item of the 'Risk of bias' tool. For cluster-RCTs we will also assess and report risk of bias associated with an additional domain: selective recruitment of cluster participants.

In all cases, two authors will independently assess the risk of bias of included studies, with any disagreements resolved by discussion to reach consensus. We will contact study authors for additional information about the included studies, or for clarification of the study methods as required. We will incorporate the results of the 'Risk of bias' assessment into the review through standard tables, and systematic narrative description and commentary about each of the elements, leading to an overall assessment of the risk of bias of included studies and a judgement about the internal validity of the review's results.

Measures of treatment effect

The primary outcomes will be considered as dichotomous variables where possible. That is, the person (or carer) would be assessed as able to manage medications or not, and similarly have satisfactory (80% to 120%) or not satisfactory adherence. If sufficient studies that use the same outcome measure for a primary outcome exist, or if a study does not report its outcome as dichotomous, then additional analyses using continuous variables may be performed. For dichotomous outcomes, we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the risk ratio (RR) and 95% confidence interval (CI). For continuous measures, we will analyse data based on the mean, standard deviation (SD) and number of people assessed for both the intervention and comparison groups to calculate mean difference (MD) and 95% CI. If the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method in Review Manager 5.

Unit of analysis issues

If cluster-RCTs are included we will check for unit of analysis errors. If errors are found, and sufficient information is available, we will re-analyse data using the appropriate unit of analysis, by taking account of the intracluster correlation (ICC). We will obtain estimates of the ICC by contacting authors of included studies, or impute the ICC using estimates from external sources. If it is not possible to obtain sufficient information to re-analyse data we will report effect estimates and annotate "unit of analysis error".

Dealing with missing data

We will attempt to contact study authors to obtain missing data (participant, outcome, or summary data). Where possible we will conduct analysis of participant data on an intention-to-treat basis; otherwise data will be analysed as reported. We will report on levels of loss to follow-up and assess this as a potential source of bias.

For missing outcome or summary data we will impute missing data where possible and report any assumptions in the review. We will investigate, through sensitivity analyses, the effects of any imputed data on pooled effect estimates.

We will also conduct a sensitivity analysis that excludes studies presenting data with loss to follow-up greater than 20%, including total reported lost to follow-up and differential loss to follow-up between groups. This is due to potential serious threats to validity associated with high loss to follow-up (Sackett 2000).

Assessment of heterogeneity

We anticipate substantial variations in types of interventions, populations studied, study designs and settings. Where studies are considered similar enough to enable data pooling using meta-analysis, we will assess the degree of heterogeneity by visual inspection of forest plots and examining the Chi² test for heterogeneity. Heterogeneity will be quantified using the I² statistic. An I² value of 50% or more will be considered to represent substantial levels of heterogeneity, but this value will be interpreted in light of the size and direction of effects and the strength of the evidence for heterogeneity, based on the P value from the Chi² test (Higgins 2011). Where heterogeneity is present in pooled effect estimates we will explore possible reasons for variability by conducting subgroup analysis.

Where we detect substantial clinical, methodological or statistical heterogeneity across included studies we will not report pooled results from meta-analysis but will instead use a narrative approach to data synthesis.

Assessment of reporting biases

We will assess reporting bias qualitatively based on the characteristics of the included studies (e.g. if only small studies that indicate positive findings are identified for inclusion), and if information that we obtain from contacting experts and authors of studies suggests that there are relevant unpublished studies.

If we identify sufficient studies (at least 10) for inclusion in the review we will construct a funnel plot to investigate small study effects, which may indicate the presence of publication bias. We will formally test for funnel plot asymmetry, with the choice of

test made based on advice in Higgins 2011, and bearing in mind that there may be several reasons for funnel plot asymmetry when interpreting the results.

Data synthesis

We will decide whether to meta-analyse data based on whether the interventions in included trials are similar enough in terms of participants, settings, intervention, comparison and outcome measures to ensure meaningful conclusions from a statistically pooled result. Due to the anticipated variability in the interventions of included studies, we will use a random-effects model for meta-analysis.

If we are unable to pool data for meta-analysis we will conduct a narrative synthesis of results. We will group data based on the category that best explores the heterogeneity of studies and makes most sense to the reader (such as by interventions, populations or outcomes). We will present data in tables and narratively summarise the results for each category.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses are proposed if adequate studies exist for each variable. These include:

* duration of intervention (short versus long);
* duration of follow-up (short, medium and long term) as described in 'Timing of outcome assessment';
* type of outcome measure (objective versus subjective);
* person managing the medication (consumer versus carer);
* number of medications (up to 10 versus 11 or more medications);
* frailty and/or functional ability (e.g. level of home-assistance required); and
* health professional group delivering the intervention (e.g. pharmacist versus nurse versus medical professional versus automated).

Sensitivity analysis

Should meta-analysis be possible for the outcomes of interest, two sensitivity analyses will be performed that exclude studies assessed to have losses to follow-up of greater than 20% and high risk of bias (determined by conducting 'Risk of bias' assessment).

'Summary of findings' table

We will prepare a 'Summary of findings' table to present the results of the meta-analysis, based on the methods described in chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We will present the results of meta-analysis for the major comparisons of the review and for each of the primary outcomes, as outlined in Types of outcome measures. We will provide a source and rationale for each assumed risk cited in the table(s) and will use the GRADE criteria to rank the quality of the evidence using the GRADEprofile (GRADEpro) software (Schünemann 2011). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table format, such as that used by Chan 2011.

Ensuring relevance to decisions in health care

The review will receive feedback from at least one consumer referee in addition to a health professional as part of Cochrane Consumers and Communication's standard editorial process.

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* *Indicates the major publication for the study*

A P P E N D I C E S

Appendix 1. MEDLINE (Ovid SP) search strategy

1. exp aged/

2. ((old or older or aged or senior) adj2 (person? or people or adult? or patient* or consumer* or carer* or caregiver* or care giver*)).ti,ab,kw.

3. (late life or ag?ing or old age or seniors).ti,ab,kw.

4. (elder* or geriatric* or veteran*).mp.

5. or/1-4

6. exp Pharmaceutical Preparations/

7. (medication* or medicine? or medicament* or pharmaceutical* or pharmacotherap* or drug?).ti,ab,kw.

8. exp drug therapy/

9. exp pharmaceutical services/

10. exp therapeutic uses/

11. or/6-10

12. 5 and 11

13. primary health care/

14. (primary adj2 care).ti,ab,kw.

15. ambulatory care/

16. ambulatory.ti,ab,kw.

17. exp general practice/

18. general practitioners/

19. physicians primary care/

20. physicians family/

21. ((general or family) adj practi*).ti,ab,kw.

22. exp ambulatory care facilities/

23. home care services/

24. exp community health services/

25. patient discharge/

26. (hospital adj3 discharge).ti,ab,kw.

27. continuity of patient care/

28. (community or home or domicil* or outreach or post-discharge or post-acute or discharge plan*).ti,ab,kw.

29. or/13-28

30. 12 and 29

31. patient education as topic/

32. ((educat* or instruct* or advis* or advice* or counsel* or teach* or train* or coach* or learn*) and (patient* or client* or consumer* or user* or carer* or caregiver* or care giver*)).mp.

33. exp counseling/
34. information services/
35. drug information services/
36. (inform* adj5 (patient* or client* or consumer* or user* or carer* or caregiver* or care giver*)).ti,ab,kw.
37. reminder systems/
38. drug packaging/
39. drug prescriptions/
40. medication therapy management/
41. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) and (manag* adj5 (medication* or medicines)).ti,ab,kw
42. pharmac* care.ti,ab,kw.
43. or/31-42
44. medication adherence/ or patient compliance/
45. self efficacy/
46. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) and (competen* or confident or confidence or abilit* or capacit* or skill* or self-efficacy or cope? or coping or complian* or noncomplian* or adher* or nonadher* or underadheren* or concordan* or nonconcordan* or persisten* or nonpersist*)).ti,ab,kw.
47. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) adj5 (error* or mistak* or misus* or mismanag*)).ti,ab,kw.
48. (patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*).ti,ab,kw. and medication errors/
49. self-administration/
50. or/44-49
51. 30 and (43 or 50)
52. randomized controlled trial.pt.
53. controlled clinical trial.pt.
54. random*.tw.
55. placebo.ab.
56. clinical trials as topic.sh.
57. randomly.ab.
58. trial.ti.
59. or/52-58
60. 51 and 59

CONTRIBUTIONS OF AUTHORS

The review guarantor is JG.

- Writing of protocol and review: AC, RE, JG

- Screening of titles and abstracts: AC, RE, JG

- Assessment of studies for inclusion: AC, RE, JG

- Quality assessment: AC, RE, JG

- Data extraction: AC, RE, JG

- Data entry into RevMan: AC

- Data analysis: AC in consultation with RE and JG

- Disagreement resolution: AC, RE, JG

- Conduct the review update: AC, RE, JG

DECLARATIONS OF INTEREST

Amanda J Cross: Mrs Cross is a member of the Australian Association of Consultant Pharmacy and provides home medicine reviews as a private consultant pharmacist.

Rohan A Elliott: None known.

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Review authors may also have been authors of studies suitable for inclusion in this review. To avoid bias, selection, data extraction and management of such studies will be performed by other independent members of the review team. We will also discuss the potential bias with the contact editor or the review and include this in the Discussion, if appropriate.

NOTES

This protocol is based on standard text and guidance provided by Cochrane Consumers and Communication (CCCRG 2014).

Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications

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Abstract

Background

Older people taking multiple medications represent a large and growing proportion of the population. Managing multiple medications can be challenging, and this is especially the case for older people who have higher rates of physical and cognitive impairment than younger adults. Good medication-taking ability and medication adherence are necessary to ensure safe and effective use of medications. There have been no reviews of interventions to improve medication-taking ability, and no recent comprehensive reviews of interventions to improve medication adherence in this population.

Objective

The objective of this review was to evaluate the effectiveness of interventions designed to improve medication-taking ability and/or medication adherence in older community-dwelling adults prescribed multiple long-term medications.

Search methods

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, CINAHL Plus and International Pharmaceutical Abstracts (IPA) from inception until February 2017. Grey literature, online trial registries and reference lists of included studies were also searched.

Selection criteria

We included randomised controlled trials (RCTs), quasi-RCTs and cluster-RCTs. Eligible studies tested interventions aimed at improving medication-taking ability and/or medication adherence in people aged 65 years and older (or mean/median age >65 years), living in the community or being discharged from hospital back into the community and taking at least four regular prescription medications (or group mean/median >4 medications). Interventions that targeted carers of older people who met these criteria were also included.

Data collection and analysis

Two review authors independently reviewed abstracts and full texts of eligible studies, extracted data and assessed risk of bias of included studies. We conducted meta-analyses where possible, and used a random-effects model to yield summary estimates of effect, risk ratios (RR) for dichotomous outcomes or standardised mean differences for continuous outcomes, and 95% confidence intervals (CIs). Where meta-analysis was not possible, a narrative synthesis was performed. We assessed the overall certainty of evidence for each outcome using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

Main results

We identified 50 studies in total, comprising 40 RCTs, 6 cluster-RCTs and 4 quasi-RCTs. Five studies evaluated interventions for improving medication-taking ability, and 48 evaluated interventions for improving medication adherence (three studies evaluated both outcomes).

Interventions were grouped based on their educational and/or behavioural components: 14 involved educational components only, 7 involved behavioural strategies only and 29 were mixed educational and behavioural interventions. Overall, our confidence in results regarding the effectiveness of interventions was low to very low due to a high degree of heterogeneity of included studies and high or unclear risk of bias across multiple domains in most studies.

Low quality evidence from five studies, each using a different measure of medication-taking ability, meant we were unable to determine the impact of mixed educational and behavioural interventions on medication-taking ability. There were no studies involving educational or behavioural interventions alone for improving medication-taking ability.

Low quality evidence suggests that mixed educational and behavioural interventions may improve the proportion of people who are adherent, with meta-analysis of 12 studies using dichotomous measures of adherence resulting in a RR of 1.22 (95% CI 1.08 to 1.37). In contrast, low quality evidence from a meta-analysis of 7 studies of mixed educational and behavioural interventions that used continuous measures of medication adherence found no significant difference in adherence (SMD 0.48, 95% CI -0.08 to 1.04). Very low quality evidence meant we were uncertain whether educational or behavioural interventions alone improved medication adherence.

Authors' conclusions

Mixed educational and behavioural interventions may improve the proportion of people who satisfactorily adhere to their prescribed medications, but may have little or no impact on adherence when it is measured as a continuous variable. There is insufficient quality evidence to determine whether educational or behavioural interventions alone improve medication adherence. The impact of interventions on medication-taking ability was unable to be determined. The quality of evidence for these findings is low due to heterogeneity and poor quality of studies included in the review. There is a need for further well-designed RCTs to investigate the effects of interventions for improving medication-taking ability and medication adherence in older adults prescribed multiple medications.

Plain language summary

Background: Older people are often prescribed multiple medications. Managing multiple medications can be challenging. Medication-taking errors and non-adherence (intentional or unintentional under- or over-use of medication) can lead to negative health outcomes. Assisting older people to better use and adhere to their medications could improve health outcomes.

Question: What are the overall findings of studies that tested ways to assist older people who are using multiple medications with improving their medication-taking ability and medication adherence?

Search strategy: We retrieved studies published until February 2017. To find relevant studies we searched seven online databases, trial registries and reference lists in previous reviews.

Selection criteria: We selected studies reporting a randomised controlled trial (RCT) or similar study design comparing a group of people receiving an intervention to improve medication-taking ability or medication adherence with a group receiving usual care (no intervention) or receiving a different intervention. We included trials that included older adults (> 65 years) living at home (or being discharged from hospital back to their home), who were using four or more regular prescription medications.

Main results: We identified 50 studies in total. Five studies tested interventions to improve medication-taking ability and 48 studies tested interventions to improve medication adherence (3 studies tested both).

The studies identified were very different in terms of what intervention people received, where the intervention were conducted, and how and when the people's medication-taking ability or medication adherence was measured. Due to these differences and problems with how the trials were conducted, the quality of the evidence was considered low or very low.

Fourteen studies tested educational interventions (e.g. people received education regarding their medications, or a health professional reviewed their medications), 7 tested behavioural interventions (e.g. changing dosing times or packaging medications into pill boxes to make medication regimens easier to take, or text-message adherence reminders) and 29 tested mixed educational and behavioural interventions. Overall, mixed interventions were most common. There was some evidence that mixed interventions may improve the proportion of people who satisfactorily adhere to their prescribed medication, but the impact on medication-taking ability was unable to be determined.

Authors' conclusions: Characteristics of interventions varied greatly among studies and there were problems regarding how the trials were conducted that may have affected their results. Low quality evidence suggests mixed educational and behavioural interventions may improve the proportion of people who adhere to their prescribed medication. We were unable to determine the impact of interventions on medication-taking ability. High quality studies are necessary to confirm the most effective way to improve medication-taking ability and medication-adherence in older adults prescribed multiple medications.

Summary of findings tables

1 Summary of findings: mixed interventions

Mixed educational and behavioural interventions aimed at improving medication-taking ability and/or medication adherence compared with usual care for older community-dwelling patients taking multiple medications.

Patient or population: Older patients using at least four regular prescription medications (and/or their carers)
Settings: Community setting (including discharge from a hospital or other health care facility to the community)
Intervention: Interventions involving both educational and behavioural components
Comparison: Usual care

Outcomes	Impacts	No of Studies	Quality of the evidence (GRADE)
Medication-taking ability Follow-up: 2 weeks–12 months	The effect of mixed interventions on medication-taking ability was unable to be determined. Meta-analysis was not possible due to all five studies using different outcome measures. Of the five studies, two demonstrated significant improvement in medication-taking ability, two showed no significant impact and one did not report results.	5	LOW[1,2]
Medication adherence (dichotomous) Follow-up: 1–18 months	Mixed interventions may improve the proportion of people who are adherent (dichotomous adherence outcome). Twelve studies (3147 participants) were included in a meta-analysis. Risk ratio was 1.22 (95% CI 1.08 to 1.37), indicating interventions increased the absolute number of adherent participants by 12.8% (4.6% to 21.5%). Two studies were excluded from the meta-analysis due to alternate reporting of outcome data; one showed significant impact on adherence, one did not.	14	LOW[1,2]
Medication adherence (continuous) Follow-up: 1–12 months	Mixed interventions may have little or no impact on medication adherence measured using continuous adherence outcomes (e.g. proportion of pills dispensed or taken). Seven studies (1825 participants) were included in a meta-analysis. Standardised mean difference was 0.48 (95% CI -0.08 to 1.04), indicating that the mean adherence score in the intervention group was 0.48 standard deviations higher (0.08 lower to 1.04 higher) than the usual care group. Four studies were excluded from the meta-analysis due to alternate reporting of outcome data; one showed significant impact on adherence, three did not. Two additional studies were excluded due to unclear reporting of results.	13	LOW[1,2]

Outcome	Summary	No. of participants	Quality
Health-related quality of life Follow-up: 6-18 months	Mixed interventions may lead to little or no change in health-related quality of life. Six of seven studies showed no significant impact on this outcome. Meta-analysis was not possible due to differences in scales used and differences in the reporting of results.	7	LOW[1,2]
Emergency department (ED)/ Hospital admissions Follow-up: 1-24 months	Mixed interventions may reduce the number of emergency department (ED) and/or hospital admissions. Eleven studies (1827 participants) were included in meta-analysis. Risk ratio was 0.67 (95% CI 0.50 to 0.90), indicating mixed interventions reduce the absolute number of patients admitted to ED/hospital by 12.3% (18.6% to 3.7% fewer). Six studies were excluded from the meta-analysis due to alternate reporting of outcome data, none of these studies had a significant impact on ED/hospital admissions.	17	LOW[1,2]
Mortality Follow-up: 3-24 months	Mixed interventions may have little or no effect on mortality. Seven studies (1776 participants) were included in a meta-analysis. Risk ratio was 0.97 (95% CI 0.70 to 1.36), with an anticipated absolute effect of 0.4% fewer deaths (3.8% fewer to 4.5% more). One study was excluded from meta-analysis due to incomplete information.	8	LOW[1,2]

CI: Confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

1. One mark deducted due to high or unclear risk of bias across multiple domains

2. One mark deducted due to variations in intervention, provider, setting, duration and outcome measures.

2 Summary of findings: educational interventions alone

Educational interventions aimed at improving medication-taking ability and/or medication adherence compared with usual care for older community-dwelling patients taking multiple medications.

Patient or population: Older patients using at least four regular prescription medications (and/or their carers)
Settings: Community setting (including discharge from a hospital or other health care facility to the community)
Intervention: Interventions involving educational components only
Comparison: Usual care

Outcomes	Impacts	No of studies	Quality of the evidence (GRADE)
Medication-taking ability Follow-up: N/A	No studies were found that evaluated medication-taking ability.	-	-
Medication adherence (dichotomous) Follow-up: 1-6 months	We are uncertain whether educational interventions improve the proportion of people who are adherent. Two studies (182 participants) using dichotomous measures of adherence were included in a meta-analysis. Risk ratio was 1.66 (95%CI 1.33 to 2.06), indicating educational interventions increased the absolute number of adherent participants by 31.2% (15.6% to 50.1% more). Two studies were excluded from the meta-analysis due to alternate reporting of outcome data; one showed significant impact on adherence, one did not.	4	VERY LOW[1,2,3]
Medication adherence (continuous) Follow-up: 1-12 months	We are uncertain whether educational interventions improve medication adherence when using continuous measures of adherence. Five studies (1165 participants) using continuous measures of adherence were included in a meta-analysis. Standardised mean difference was 0.16 (95% CI -0.12 to 0.43), indicating that the mean adherence score in the intervention group was 0.16 standard deviations higher (0.12 lower to 0.43 higher) than the usual care group. Five studies were excluded from the meta-analysis; three due to alternate reporting of outcome data (none showed significant impact on adherence), while two did not report results.	10	VERY LOW[1,2,4]

Outcome	Description	No.	Quality
Health-related quality of life Follow-up: 3-12 months	Educational interventions may not lead to change in health-related quality of life, with all six studies showing no significant impact. Meta-analysis was not possible due to differences in scales used and differences in the reporting of results.	6	MODERATE[1]
ED/Hospital admissions Follow-up: 4-28 weeks	Educational interventions may not reduce ED/hospital admissions. Three studies (554 participants) were included in a meta-analysis. Risk ratio was 1.02 (95%CI 0.71 to 1.48), indicating no statistically significant change in the absolute number of patients admitted to ED/hospital.	4	MODERATE[5]
Mortality Follow-up: N/A	No studies were found that evaluated the effect of educational interventions on mortality.	-	-

CI: Confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

1. One mark deducted due to high or unclear risk of bias across multiple domains

2. One mark deducted due to variations in intervention, provider, setting, duration and outcome measures.

3. One mark deducted due to imprecision – only two studies in meta-analysis (one had very wide confidence interval and low events), plus the number of adherent patients (i.e. events) were not clearly reported in the two studies excluded from meta-analysis.

4. One mark deducted due to two studies not having available results

5. One mark deducted due to variations in duration of follow-up

3 Summary of findings: behavioural interventions alone

Behavioural interventions aimed at improving medication-taking ability and/or medication adherence compared with usual care for older community-dwelling patients taking multiple medications.

Patient or population: Older patients using at least four regular prescription medications (and/or their carers)
Settings: Community setting (including discharge from a hospital or other health care facility to the community)
Intervention: Interventions involving behavioural components only
Comparison: Usual care

Outcomes	Impacts	No of studies	Quality of the evidence (GRADE)
Medication-taking ability Follow-up: N/A	No studies were found that evaluated medication-taking ability.	-	-
Medication adherence (dichotomous) Follow-up: 3-18 months	We are uncertain whether behavioural interventions improve the proportion of people who are adherent. Four studies (528 participants) were included in a meta-analysis. Risk ratio was 1.22 (95%CI 1.07 to 1.38), indicating behavioural interventions increased the absolute number of adherent participants by 10.5% (3.3% to 18.1% more).	4	VERY LOW[1,2,3]
Medication adherence (continuous) Follow-up: 6-12 months	We are uncertain whether behavioural interventions improve medication adherence when using continuous measures of adherence. Three studies were identified, but results could not be pooled in a meta-analysis due to differences in reporting. Two of the studies have significant impacts on medication adherence.	3	VERY LOW[1,2,4]
Health-related quality of life Follow-up: 3 months	We are uncertain whether behavioural interventions have an effect on health-related quality of life. Only one study was identified, which found the intervention resulted in worsening quality of life using the Minnesota Living with Heart Failure Questionnaire.	1	VERY LOW[1,5,6]

ED/Hospital admissions	We are uncertain whether behavioural interventions reduce ED/hospital admissions. Two studies (70 participants) were included in a meta-analysis. Risk ratio was 0.21 (95% CI 0.08 to 0.55), indicating behavioural interventions may reduce the absolute number of patients admitted to ED/hospital by 42.9% (49.9% to 24.4% fewer).	2	VERY LOW[1,7]
Follow-up: 3-6 months			
Mortality	No studies were found that evaluated the effect of behavioural interventions on mortality.	-	-
Follow-up: N/A			

CI: Confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

1. One mark deducted due to high or unclear risk of bias across multiple domains

2. One mark deducted due to variations in intervention, provider, setting, duration and outcome measures.

3. One mark deducted due to low participant numbers and wide confidence interval for studies included in meta-analysis.

4. One mark deducted due to low participant numbers.

5. One mark deducted due to indirectness of evidence as the Minnesota Living with Heart Failure Questionnaire is specific for heart failure populations and results may not be generalizable to the general population of older people.

6. One mark deducted due to low participant numbers

7. Two marks deducted due to low participant numbers, low number of events and very wide confidence intervals in meta-analysis.

Background

Description of the condition

Older people, conventionally defined as those aged 65 years and above, often have multiple chronic health problems that require ongoing healthcare interventions (Hilmer 2007; WHO 2000). An expanding evidence base supporting multidrug regimens in the management of many chronic diseases means that polypharmacy (use of multiple medications) is often unavoidable in older people. Polypharmacy has a range of definitions, but is commonly defined as the use of four or more medications (Department of Health (UK) 2001; Patterson 2014). About two-thirds of people aged over 60 years who live in community settings use four or more medications daily (Elliott 2014). There is also a substantial subgroup who are prescribed an average of 10 or more different medications, which is sometimes referred to as hyperpolypharmacy (Elliott 2014).

Medication-taking ability refers to a person's ability to accurately follow a prescribed medication regimen. It includes knowing what medications to take and when to take them, and being able to correctly administer the medication (Maddigan 2003). Managing multiple long-term medications can be a complex and challenging task, especially for older people who may experience a decline in the cognitive and physical abilities required for taking medication (Barbas 2001; Beckman 2005). More than a quarter of older people experience difficulties in opening medication packages, including opening bottles and removing medication from blister packs (Philbert 2014). Older people with visual impairment are more than twice as likely to require help in managing their medication as those without visual impairment (McCann 2012). Many older people receive assistance from informal or non-professional carers with taking medication (ACSQHC 2012). Thus, interventions that aim to improve medication-taking ability in older adults may need to target carers as well as consumers.

Medication adherence refers to the extent to which a person's medication-taking behaviour corresponds with agreed treatment recommendations from a healthcare provider (WHO 2003). Non-adherence refers to deviations from that agreed treatment, and includes under-utilisation, over-utilisation and incorrect use of medication. There are two broad types of non-adherence: unintentional non-adherence – which may be due to factors such as forgetfulness, lack of understanding, physical problems or the complexity of the regimen; and intentional non-adherence – which occurs when a person decides not to take their treatment as instructed (Wroe 2002). A person is generally considered adherent if they take between 80% and 120% of their prescribed medication over a given time period (WHO 2003). Non-adherence to medications has been reported in up to 50% of older people in different countries and settings (George 2006; Gilbert 1993; Gray 2001; Hemminki 1975; Lau 1996; Lee 2010; Mansur 2008; McElnay 1997; Okuno 1999; Sewitch 2008; Spagnoli 1989; Stoehr 2008; Thorpe 2009; Vik 2006). The World Health Organization (WHO) has recognised the importance of enhancing adherence as a strategy to tackle chronic health conditions effectively (WHO 2003).

Consequences of poor medication-taking ability and non-adherence may include suboptimal response to treatment, recurrence of illness, adverse drug events (ADEs), increased healthcare service utilisation, unplanned hospitalisations, increased morbidity and mortality, and increased healthcare costs (Balkrishnan 2003; Col 1990; DiMatteo 2002; Howard 2003; Leendertse 2008; Tafreshi 1999). Among older adults, ADEs are a significant and increasing problem (Burgess 2005; Elliott 2014). Almost a quarter of preventable ADEs in older people are attributable to consumer errors (Field 2007; Gurwitz 2003). Between US$ 100 and US$

300 billion of avoidable healthcare costs have been attributed to non-adherence in the US annually (IMS 2013).

Medication-taking ability and adherence are influenced by a range of factors related to healthcare consumers, their therapies, medical conditions, and social-, healthcare provider-, and health system-related factors (Balkrishnan 1998; Jin 2008; WHO 2003). Age itself is generally not an independent predictor of poor medication-taking ability or non-adherence (DiMatteo 2004; Vik 2004). Nevertheless, the prevalence of risk factors for medication use problems increases with age (Col 1990). These include polypharmacy (Gray 2001; Vik 2006), medication regimen complexity (Corsonello 2009; Jansa 2010; Vik 2006), cognitive and functional decline (Gray 2001; Hutchison 2006; Spiers 1995; Vik 2006), inadequate contact with health professionals (George 2006), depressive symptoms (Vik 2006), poor social support (DiMatteo 2000; Spiers 1995), and absence of assistance with administration of medications (Vik 2006). The risk factors for suboptimal use of medications by older people have been studied extensively in cross-sectional studies (George 2006; Gilbert 1993; Gray 2001; Hemminki 1975; Jerant 2011; Lau 1996; McElnay 1997; Okuno 1999; Sears 2012; Spagnoli 1989; Tavares 2013; Vik 2006). Many adverse health outcomes may be preventable if appropriate measures are taken to address these risk factors and optimise medication-taking ability and adherence (George 2008; Jokanovic 2016; Sorensen 2004).

Description of the intervention

A range of simple to complex behavioural and educational interventions, alone or in combination, have been tested for improving the medication-taking ability and adherence of consumers (George 2008). Behavioural strategies include:

- alarm/beeper,
- calendar/diary,
- reminder chart/medication list,
- large print labels,
- packaging change,
- pillbox/calendar pack (also known as dose administration aid [DAA]),
- contracting (verbal or written agreement),
- adherence monitoring with or without feedback,
- reminders (mail, telephone, email),
- inpatient programs of self-administration of medications,
- simplification of medication regimens,
- skill building (supervised, group),
- tailoring (routinisation), and
- follow-up (home visit, scheduled clinic visit, video/teleconferencing).

Educational strategies comprise group (in-patient, family, and support group) and/or individual (verbal, audio-visual, visual, written, telephone, mail) education provided by physicians, pharmacists, nurses, allied health professionals and others.

How the intervention might work

Behavioural and educational interventions, used alone or in combination, are intended to improve older peoples' (and/or their carers') ability to manage medications and adhere to medication regimens.

These interventions may also lead to: improvements in knowledge about medications and confidence regarding medication management; greater satisfaction with treatment; better

health-related quality of life (HRQoL); reductions in the incidence of ADEs; and reductions in health service utilisation.

Why it is important to do this review?

Older people taking multiple medications represent a large and growing proportion of consumers seen by health professionals in clinical practice. They are also the group most likely to experience ADEs. Evidence from well-designed studies testing interventions to improve medication-taking ability and adherence in older people prescribed multiple long-term medications could provide valuable information for practitioners, researchers, and consumers to help optimise medication use among older people living in the community.

Interventions to improve medication adherence have been widely investigated (Bosch-Capblanch 2007; Campbell 2012; Chong 2011; Conn 2009; Conn 2015; Haynes 2008; Kripalani 2007; Krueger 2003; Linn 2011; McDonald 2002; Nieuwlaat 2014; Peterson 2003; Roter 1998; Ruppar 2008; Russell 2006; Sapkota 2015; Schedlbauer 2010; Schlenk 2004; Van Eijken 2003; Van Wijk 2005; Viswanathan 2012; Williams 2008). Most studies, and therefore most reviews, have focused on one health condition and/or the use of one medication or one medication class. However, older people form a heterogeneous population in terms of their medication consumption and disease patterns; therefore studies recruiting relatively homogenous samples of people experiencing one specific disease or consuming one type of medication have limited generalisability. We found only one systematic review focusing on older people taking multiple medications (George 2008), which analysed adherence only, and is now outdated.

To date, no systematic review has included measures of medication-taking other than adherence, such as ability to manage medications. Standardised methods for measuring the ability of people to manage medications have been developed (Elliott 2009; Elliott 2015), some of which have been used in studies of medication use in older people (Lam 2011). Two of the most well-studied assessment tools for evaluating medication taking are the Drug Regimen Unassisted Grading Scale (DRUGS) (Edelberg 1999), which utilises a person's own medications, and the Medication Management Ability Assessment (MMAA) (Patterson 2002), which uses a simulated medication regimen.

Our review will focus on interventions to improve medication-taking ability or adherence, or both, in older adults who are prescribed multiple medications, or their carers (who are not health professionals).

This review will complement previous Cochrane reviews looking at interventions for improving medication adherence in the general population (Nieuwlaat 2014), including the impact of dose reminder packaging (Mahtani 2011), and interventions for improving clinical outcomes in people with multi-morbidities (Smith 2016). The appropriateness of people's medication regimens is dependent on a number of factors and will not be considered as part of this review, but only their ability to take (or use) the medications and their adherence to the agreed regimen. There has been a previous Cochrane review of interventions targeted at health professionals, designed to improve the appropriateness of prescribing and polypharmacy (Patterson 2014).

Objective

To evaluate the effectiveness of interventions designed to improve medication-taking ability and/or medication adherence in older community-dwelling people (or their carers) who are being treated with multiple long-term, prescribed medications.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), cluster RCTs and quasi-RCTs as specified by the Cochrane Consumers and Communication Review Group (CCCRG 2014).

Types of participants

We included studies in which:

- most participants (80% or more) were aged 65 years and over, or the mean/median age was over 65 years. If studies were identified that did not meet these criteria, but had relevant data regarding older people that could be extracted separately, these were also included.
- participants were living in the community or were discharged from a hospital or other healthcare facility to the community (living in the community includes in a person's own home or retirement village/independent living unit, with or without additional support; it did not include situations in which professional carers or nurses administer the person's medications, such as in nursing homes, residential care facilities or full nursing care in the home).
- participants used at least four long-term regular prescription medications, or the group mean/median was more than four (irrespective of the participants' number of medical conditions).

Studies that involved carers of consumers who met these criteria were also included. Carers were defined as "people who provide unpaid care and support to family members and friends who have disability, mental illness, chronic condition, terminal illness or general frailty" (ACSQHC 2012).

Types of interventions

We included studies that tested single interventions or combinations of interventions directed at the consumer or their carer that sought to improve medication-taking ability and/or adherence by the consumer.

Examples included:

- support for behaviour change,
- provision of medication aids (e.g. DAAs, medication lists);,
- medication regimen simplification,
- remote monitoring of medication use with or without feedback,
- facilitation of communication and decision making about medications,
- provision of information or education, and
- acquisition of skills and competencies.

This list of interventions is not exhaustive. Therefore the search strategy (see Appendix 1) also focused on terms that described the outcomes of interest to avoid missing potentially-relevant studies that tested novel interventions.

We included the following comparisons:

- interventions to improve medication-taking ability and/or adherence versus standard or usual care, and

- one form of intervention to improve medication-taking ability and/or adherence versus another − including simple versus complex interventions.

In future updates we will also consider including interventions to improve medication-taking ability and/or adherence versus no intervention, but no studies were identified in this review.

Types of outcome measures

Primary outcomes

This review focussed on two outcomes directly related to the medication-taking behaviour of older adults (or their carers): ability to manage medications and adherence to medication regimens. To be eligible for inclusion, studies had to have assessed at least one of these outcome measures for at least four regular prescribed medications (which could be either the person's own medications or, for assessment of ability to manage medication, a validated, simulated medication regimen instrument) (Elliott 2009). These two outcomes were evaluated separately.

Ability to manage medications

This outcome assessed participants' (or carers') ability to manage medications, using objective and/or subjective measures:

1. Objective measures: direct observation using standardised assessment instruments/methods (e.g. Drug Regimen Unassisted Grading Scale (DRUGS), Medication Management Ability Assessment (MMAA), device technique checklists (Elliott 2006; Elliott 2009; Patterson 2002).
2. Subjective measures: self-reported ability or self-efficacy (e.g. Self-efficacy for Appropriate Medication Use Scale [SEAMS]) (Risser 2007).

Adherence to medication regimens

This outcome assessed consumer adherence to their prescribed medication regimens, using objective and/or subjective measures:

1. Objective measures: refill data, pharmaceutical claims data, electronic monitoring, biological assay, measure of used/unused medications (e.g. pill count).
2. Subjective measures: self-report of missed/used doses, validated questionnaires (e.g. Morisky scale; Morisky 1986).

If an included study measured adherence and/or ability using more than one type of outcome measure, then the most reliable measure was extracted (i.e. objective measures were preferentially reported over subjective measures).

Secondary outcomes

The following secondary outcomes were analysed from studies that also measured at least one of the primary outcomes listed above:

- consumer (or carer) knowledge about their medications;
- consumer (or carer) satisfaction with the intervention;
- health-related quality of life (HRQoL);
- adverse clinical health outcomes (e.g. unplanned hospital or emergency department presentations, general practitioner visits, ADEs);

- condition-specific outcomes (e.g. cardiovascular events, blood pressure, blood glucose levels, lung function); and
- cost effectiveness of the intervention.

Timing of outcome assessment

For adherence outcomes the minimum duration of follow-up was four weeks. For medication-taking ability outcomes a follow-up period of at least 48 hours after the intervention was required.

If an included study measured adherence and/or ability more than once, then the outcome measure with the longest follow-up was extracted.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases using search strategies tailored to each database:

- Cochrane Central Register of Controlled Trials (CENTRAL, *Cochrane Library*, to 2017);
- MEDLINE (OvidSP) (1966 to 2017);
- Embase (OvidSP) (1973 to 2017);
- PsycINFO (OvidSP) (1967 to 2017);
- CINAHL Plus (1981 to 2017); and
- International Pharmaceutical Abstracts (IPA) (1971 to 2017).

The search strategies are presented in <u>Appendix 1</u>.

There was no language restriction (provided the title and abstract were in English).

Searching other resources

For grey literature, we searched:

- the Joanna Briggs Institute Evidence Based Practice Database; and
- conference proceedings (Scopus®).

We checked the reference lists of included studies and previously published relevant systematic reviews to locate potential studies that were not identified via electronic searches.

We also searched the following online trial registries for ongoing and recently-completed studies:

- WHO International Clinical Trials Registry Platform (ICTRP);
- ClinicalTrials.gov;
- ClinicalTrials.com;
- TrialsCentral;
- Australian New Zealand Clinical Trials Registry (ANZCTR);
- United Kingdom Clinical Research Network (UKCRN);
- Networked Digital Library of Theses and Dissertations (NDLTD); and
- International Standard Randomised Controlled Trial Number (ISRCTN) registry.

Non-English language studies were translated and included if they met the eligibility criteria. Studies that were translated are noted in the <u>Characteristics of included studies</u> tables.

Data collection and analysis

Selection of studies

Abstracts were screened independently by two review authors (AC and KP, LK or JG) and full text of any papers identified as potentially relevant by at least one author was retrieved. Two authors independently screened full-text articles for inclusion or exclusion (AC and RE, KP, LK or JG), with discrepancies resolved by discussion and by consulting a third author if necessary to reach consensus (RE or JG). Review authors were not responsible for the screening of studies in which they were involved or associated. All potentially-relevant papers excluded from the review at this stage were listed as excluded studies, with reasons provided in the Characteristics of excluded studies table. We also provided citation details and any available information about ongoing studies, and collated and reported details of duplicate publications, so that each study (rather than each report or manuscript) was the unit of interest in the review. We reported the screening and selection process in an adapted PRISMA flow chart (Liberati 2009).

Data extraction and management

Two review authors extracted data independently from included studies (AC and, RE, KP, LK or JG). Any discrepancies were resolved by discussion until consensus was reached, or through consultation with a third author where necessary (RE or JG). We developed and piloted a data extraction form using the Cochrane Consumers and Communication Review Group Data Extraction Template (cccrg.cochrane.org/author-resources). Data extracted included the following study details: aim of the intervention, study design, study population, intervention details, control/comparison group(s), outcome(s), and follow-up period(s). All extracted data were entered into Review Manager (RevMan 2014, v5.3) by one review author (AC), and was checked for accuracy against the data extraction sheets by an independent person.

Assessment of risk of bias in included studies

We assessed and reported on the methodological risks of bias of included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and Cochrane Consumers and Communication guidelines (CCCRG 2014), which recommended explicit reporting of the following individual elements for RCTs: random sequence generation; allocation sequence concealment; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data, selective outcome reporting; and other sources of bias. We considered blinding separately for different outcomes where appropriate (for example, blinding may have the potential to differently affect subjective versus objective outcome measures). We judged each item as being at high, low or unclear risk of bias as set out in the criteria provided by Higgins 2011, and provided a quote or information from the study report and a justification for our judgement for each item in the 'Risk of bias' table.

Studies were deemed to be at the highest risk of bias if they were scored at high or unclear risk of bias for either the sequence generation or allocation concealment domains, based on growing empirical evidence that these factors are particularly important potential sources of bias (Higgins 2011).

We assessed and reported quasi-RCTs as being at high risk of bias on the random sequence generation item of the 'Risk of bias' tool. For cluster-RCTs we also assessed and reported risk of bias associated with an additional domain: selective recruitment of cluster participants.

In all cases, two authors independently assessed the risk of bias of included studies, with any disagreements resolved by discussion to reach consensus. We contacted study authors for additional information about the included studies, or for clarification of the study methods as required. We incorporated the results of the 'Risk of bias' assessment into the review through standard tables, and systematic narrative description and commentary about each of the elements, leading to an overall assessment of the risk of bias of included studies and a judgement about the internal validity of the review's results.

Measures of treatment effect

The primary outcomes were considered as dichotomous variables where possible. That is, the person (or carer) was assessed as able to manage medications or not, and similarly to have satisfactory (80% to 120%) or not satisfactory adherence (<80% or >120%). If a study did not report its outcome as dichotomous, then continuous outcomes were extracted and analysed.

For dichotomous outcomes, we analysed data based on the number of events and the number of people assessed in the intervention and comparison groups. We used these to calculate the risk ratio (RR) and 95% confidence interval (CI). Given the heterogeneity in study measures, for continuous measures we analysed data using the standardised mean difference (SMD) and 95% CI approach using the inverse variance method in Review Manager 5.

Unit of analysis issues

For included cluster-RCTs we checked for unit of analysis errors. If errors were found, and sufficient information was available, we re-analysed data using the appropriate unit of analysis, by taking into account the intracluster correlation coefficient (ICC). We obtained estimates of the ICC by contacting authors of included studies. Where this was not possible we reported effect estimates and annotated "unit of analysis error". In future updates, we may impute missing ICCs using estimates from external sources, but this was not required for any trials in this review.

Of the six cluster RCTs, three reported ICC but did not report their effective sample sizes. We recalculated effective sample sizes based on information reported in each study and divided the reported sample size by the design effect (Higgins 2011). We reported the adjusted sample sizes in meta-analyses, and reduced the weightings given to these studies.

Muth 2016 reported an ICC of 0.00, thus no adjustment was required.

Moral 2015 reported an ICC of 0.05 and had an average cluster size of 5.4 for intervention and 6.0 for control. There were 70 participants in the intervention group and 84 participants in the control group, which we adjusted to 57 (intervention) and 67 (control) for all outcomes.

Willeboordse 2017 reported an ICC of 0.08 but was not included in any meta-analyses, thus effective sample sizes were not calculated.

For the three studies that did not report an ICC (Bernsten 2001, Volume 2001 and Wood 1992), authors were contacted for further information. As no response was received, no adjustments could be made. Sensitivity analyses were conducted excluding these studies to adjust for possible unit of analysis errors.

Dealing with missing data

We attempted to contact study authors to obtain missing data (participant, outcome, or summary data). Where possible we conducted analyses of participant data on an intention-to-treat basis; otherwise data were analysed as reported. We reported on levels of lost to follow-up and assessed this as a potential source of bias.

For missing outcome or summary data we planned to impute missing data where possible and report any assumptions, but this was not required or possible for any included studies.

We conducted sensitivity analyses that excluded studies presenting data with lost to follow-up greater than 20% for the primary outcome, including total reported lost to follow-up and differential lost to follow-up between groups. This was due to potential serious threats to validity associated with high proportion of participants lost to follow-up (Sackett 2000).

Assessment of heterogeneity

We identified substantial variations in types of interventions, populations studied, study designs and settings. Where studies were considered similar enough to enable data pooling using meta-analysis, we assessed the degree of heterogeneity by visual inspection of forest plots and examining the chi² test for heterogeneity. Heterogeneity was quantified using the I² statistic. An I² value of 50% or more was considered to represent substantial levels of heterogeneity, but this value was interpreted in light of the size and direction of effects and the strength of the evidence for heterogeneity, based on the p value from the chi² test (Higgins 2011). Where heterogeneity was present in pooled effect estimates we explored possible reasons for variability by conducting subgroup analyses.

Where we detected substantial clinical, methodological or statistical heterogeneity across included studies, we did not report pooled results from meta-analysis but instead used a narrative approach to data synthesis.

Assessment of reporting biases

We assessed reporting bias qualitatively based on the characteristics of the included studies (e.g. if only small studies with positive findings were identified for inclusion), and information obtained from contacting authors of studies suggested that there might have been relevant unpublished data or studies.

Funnel plots to investigate publication bias were not conducted due to insufficient studies per outcome and intervention type, and presence of multiple studies not suitable to be included in meta-analyses.

In future updates, if we identify sufficient studies (at least 10) for inclusion in the review we will construct a funnel plot to investigate small study effects and formally test for funnel plot asymmetry, with the choice of test made based on advice in Higgins 2011, and bearing in mind that there may be several reasons for funnel plot asymmetry when interpreting the results.

Data synthesis

We conducted meta-analyses on extracted data for some outcomes. Due to the variability in the interventions of included studies, we used a random-effects model for all meta-analyses.

For studies not included in meta-analyses, and for outcomes that we were unable to pool data, we have presented data in tables and narratively summarised the results for each outcome.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted to investigate heterogeneity of mixed interventions for medication adherence. Three planned subgroup analyses were conducted:

- duration of intervention (short versus long);
- type of outcome measure (objective versus subjective); and
- health professional group/system delivering the intervention (e.g. pharmacist versus nurse versus medical professional versus automated).

Additional planned subgroup analyses to investigate heterogeneity were not able to be conducted due to insufficient studies or poor reporting of participant characteristics. In future updates, should more studies be included (especially for other outcomes or other intervention types), then we plan to also look at the following:

- duration of follow-up (short, medium and long term) as described in 'Timing of outcome assessment';
- person managing the medication (consumer versus carer);
- number of medications (up to 10 versus 11 or more medications); and
- frailty and/or functional ability (e.g. level of home-assistance required) and/or cognitive function/ability.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes that excluded studies assessed to have losses to follow-up of greater than 20%. We had planned to also conduct sensitivity analyses that excluded studies with high risk of bias, however there were too few included studies assessed as at low risk of bias. Future updates of this review should conduct these sensitivity analyses if sufficient studies are identified.

'Summary of findings' table

We prepared 'Summary of findings' tables to present the results of the meta-analyses, based on the methods described in chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We presented the results of meta-analyses for the major comparisons of the review and for each of the primary outcomes, as outlined in Types of outcome measures. We provided a source and rationale for each assumed risk cited in the tables and used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria to rank the quality of the evidence using the GRADEprofile (GRADEpro) software (Schünemann 2011). Where meta-analysis was not possible, we have presented results in a narrative 'Summary of findings' table format, such as that used by Chan 2011.

Results

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies; and Characteristics of studies awaiting classification.

Results of the search

The database search yielded 23,066 titles. We found 50 additional records through grey literature search. After removing duplicates, we screened 15,382 studies and reviewed 375 full text articles. We excluded 308 that did not meet the inclusion criteria and recorded our reasons for exclusion. We included 50 independent studies described in 53 articles; 40 studies were randomised controlled trials (RCTs), 4 were considered quasi-RCTs (Begley 1997, Shimp 2012, Volume 2001 and Winland-Brown 2000) and 6 were cluster-RCTs (Bernsten 2001, Moral 2015, Muth 2016, Volume 2001, Willeboordse 2017 and Wood 1992). Eight studies are awaiting classification as they are ongoing or unpublished studies with incomplete information to allow determination of eligibility (see Characteristics of studies awaiting classification). Six studies are ongoing (see Characteristics of ongoing studies). Refer to Figure 1 for PRISMA diagram.

Figure 1
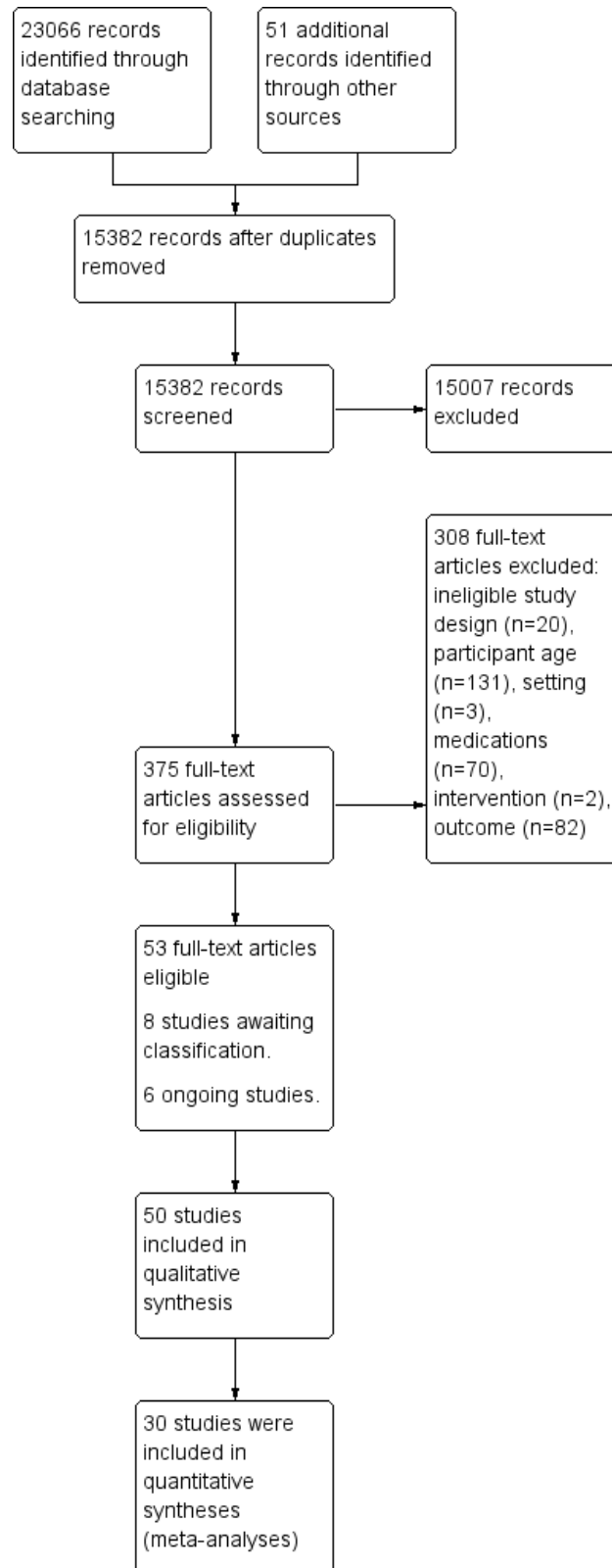
Study flow diagram

Included studies

Participants

There were a total of 14,269 participants across the 50 studies. Fifteen studies involved less than 100 participants, and six studies involved more than 500 participants. In 38 studies the intervention was directed at patients, in one study the intervention was directed at family caregivers (George 2016) and in eleven studies the intervention involved both patients and caregivers. The mean/median age of included patients ranged from 65.6 to 87.0 years and 52.4% (6893/13143) participants were females (three studies did not provide clear details on gender). Mean/median number of medications ranged from 4.2 to 16.3, but the definition of 'medication' varied greatly between studies and was poorly described in 24 studies (48%). Eighteen studies clearly referred to prescribed medications, but many restricted the count to regular and/or oral medications only.

Non-prescription/over-the-counter (OTC) medications were included in the total count in five studies (Haag 2016, Khdour 2009, Krska 2001, Lingler 2016, Marek 2013) and reported separately for three studies (Begley 1997, Chrischilles 2014, Volume 2001). Four studies did not provide mean/median but were included based on published range of number of medications being taken (Winland-Brown 2000), inclusion criteria (Hale 2016) or additional information provided by authors (Blalock 2010, Shively 2013) that indicated mean/median number of medications would be greater than four. One study was included as the subgroup of people taking >8 medications met our inclusion criteria (Truelove 2015).

Sixteen studies had some measure of frailty and/or functional ability for included participants, but the variations in scales used prevented comparison. Twenty studies included a measure of cognitive function of participants or listed the proportion of people with cognitive impairment, but heterogeneous nature of reporting cognitive impairment prevented comparison. Seventeen studies excluded people with cognitive impairment and 13 did not specify any details. Total mean/median chronic conditions (or co-morbidities) was mentioned in only 10 studies, and ranged from three to nine chronic conditions.

Setting

Included studies were carried out across four continents: North America, Europe, Asia and Australia (see Table A). The majority of studies were conducted in the USA (21), UK (8), Canada (5) and Australia (3). Ten studies were conducted in European countries: Spain (4), Croatia (1), Denmark (1), Germany (1), the Netherlands (1), Portugal (1) and Switzerland (1). Two studies were conducted in Asian countries, China (1) and Singapore (1). One study was conducted across seven countries (Bernsten 2001).

The health care settings for the studies were categorised based on where the interventions were initiated in the patient's healthcare journey. Twenty-six studies were initiated at the interface between hospital and community, either in hospital (2), immediately prior to discharge (11), post-discharge (6) or in hospital outpatient clinics (7). Twenty-four studies were initiated in the community/primary care setting including general practice/medical clinics/centres (11), community pharmacies (5), home health care services (2), a university clinic (1), an independent living facility (1) and in the home (4; 2 delivered online, 2 involving visiting health professionals).

Table A: Study design, setting and participants

Study ID	Study Design	Target participants	Country	Stage of the patients' healthcare journey/health care setting where the intervention was initiated	
				Hospital-community interface	*Community/Primary care*
Al-Rashed 2002	RCT	Patient	UK	Discharge	
Begley 1997	RCT	Patient	UK	Post-discharge	
Bernsten 2001	Cluster-RCT	Patient	7 Countries		Pharmacy
Blalock 2010	RCT	Patient	USA		Pharmacy
Bond 2007	RCT	Patient	UK		Pharmacy
Cargill 1992	RCT	Patient + Carer	USA	Outpatient clinic*	
Chrischilles 2014	RCT	Patient	USA		Home (online)
Cohen 2011	RCT	Patient	USA		Medical centre
Cossette 2015	RCT	Patient	Canada	ED-discharge	
George 2016	RCT	Carer	USA		Home (online)
Grymonpre 2001	RCT	Patient	Canada		Health clinic
Haag 2016	RCT	Patient	USA	Post-discharge	
Hale 2016	RCT	Patient	USA	Post-discharge	
Hanlon 1996	RCT	Patient + Carer	USA		General medicine clinic*
Holland 2007	RCT	Patient + Carer	UK	Post-discharge	
Khdour 2009	RCT	Patient	UK	Outpatient clinic	
Krska 2001	RCT	Patient	UK		General practice clinic
Lee 2006	RCT	Patient	USA	Outpatient pharmacy*	
Lim 2004	RCT	Patient	Singapore	Outpatient clinic	
Lingler 2016	RCT	Patient + Carer	USA		Community
Lipton 1994	RCT	Patient + Carer	USA	Discharge	
Lopez Cabezas 2006	RCT	Patient	Spain	Discharge	
Manning 2007	RCT	Patient	USA	Discharge	
Marek 2013	RCT	Patient	USA		Home health care service
Marusic 2013	RCT	Patient	Croatia	Discharge	

Study ID	Study Design	Target participants	Country	Stage of the patients' healthcare journey/health care setting where the intervention was initiated	
				Hospital-community interface	*Community/Primary care*
Messerli 2016	RCT	Patient	Switzerland		Pharmacy
Moral 2015	Cluster-RCT	Patient	Spain		General practice
Morales Suarez-Vurela 2009	RCT	Patient + Carer	Spain	Home health care service	
Murray 1993	RCT	Patient	USA	Outreach centre	
Muth 2016	Cluster-RCT	Patient	Germany		General practice
Nascimento 2016	RCT	Patient + Carer	Portugal		Diabetes clinic
Naunton 2003	RCT	Patient + Carer	Australia	Post-discharge	
Nazareth 2001	RCT	Patient + Carer	UK	Discharge	
Olesen 2014	RCT	Patient	Denmark		Community
Pandey 2017	RCT	Patient	Canada	Post-discharge	
Pereles 1996	RCT	Patient	Canada	In-patient	
Rich 1996	RCT	Patient	USA	Discharge	
Saez de la Fuente 2011	RCT	Patient + Carer	Spain	Discharge	
Shimp 2012	RCT	Patient	USA		University clinic
Shively 2013	RCT	Patient	USA		Primary care clinic
Taylor 2003	RCT	Patient	USA		General practice clinic
Truelove 2015	RCT	Patient	Australia		General practice clinic
Vinluan 2015	RCT	Patient	USA	Discharge	
Volume 2001	Cluster-RCT	Patient	Canada		University clinic
Willeboordse 2017	Cluster-RCT	Patient	Netherlands		Pharmacy
Williams 2012	RCT	Patient	Australia		General practice clinic
Winland-Brown 2000	RCT	Patient	USA		Independent living facility
Wood 1992	Cluster-RCT	Patient	UK	In-patient	
Wu 2006	RCT	Patient + Carer	China	Outpatient clinic	
Young 2016	RCT	Patient	USA	Discharge	

* Unclear whether health service provided primary or secondary care or both.

Interventions

A range of simple to complex interventions were used across the included studies (Table B). Due to the heterogeneous nature of the interventions, we categorised them into three broad groups: educational interventions, behavioural interventions and mixed interventions (both educational and behavioural). These categories have been used in a previous systematic review of interventions to improve medication taking in elderly patients prescribed multiple medications (George 2008).

Fourteen studies involved educational interventions comprising medication/health education (provided in writing or verbally) and/or medication review only, seven studies involved behavioural interventions only, and 29 studies had both educational and behavioural elements.

Educational interventions identified included 38 studies delivering patient or carer education regarding medications and/or health conditions, and 26 studies involving a review of patient's medications.

A range of behavioural interventions were used (either alone or in combination), including 24 studies utilising follow-up or monitoring, seven studies included regimen simplification (Begley 1997, Bernsten 2001, Lim 2004, Lipton 1994, Murray 1993, Olesen 2014 and Rich 1996), five studies included motivational interviewing (Khdour 2009, Moral 2015, Olesen 2014, Shively 2013, Williams 2012) and two studies included a three-step self-administration of medications program (Pereles 1996, Wood 1992). DAAs were utilised by all participants in six studies, including simple pill boxes (Lee 2006, Marek 2013, Morales Suarez-Vurela 2009, Winland-Brown 2000), unit-of-use packages (Murray 1993), automated dosing devices (Marek 2013, Winland-Brown 2000) and remotely monitored electronic devices (Hale 2016). Two studies utilised DAAs for some participants as required (Cargill 1992, Naunton 2003) and two studies provided participants with electronic pill reminder devices (Olesen 2014, Young 2016). Other types of interventions included text message adherence reminders (Pandey 2017), a four-ingredient poly-pill (Truelove 2015), use of online personal health records (Chrischilles 2014) and a 3D (durable display at discharge) medication discharge tool which involved patients affixing a tablet/capsule of each medication onto the 3D tool (Manning 2007).

Most interventions were delivered by pharmacists (31 studies), nurses (17 studies) and physicians (15 studies), either alone (31 studies) or in multidisciplinary teams of two or more health professionals (15 studies). Two studies were delivered online (Chrischilles 2014, George 2016), one study involved text message reminders (Pandey 2017) and one study involved a remotely monitored electronic device (Hale 2016). Interventions varied in duration, ranging from one-off (Al-Rashed 2002, Blalock 2010, Haag 2016, Lim 2004, Manning 2007, Marusic 2013, Muth 2016, Nascimento 2016, Naunton 2003, Saez de la Fuente 2011, Willeboordse 2017) to two years (Wu 2006), and were most commonly delivered in the home (face-to-face or phone calls), hospital, medical centre or community pharmacy. Four studies were delivered across two settings (Lipton 1994, Moral 2015, Nazareth 2001, Rich 1996) and 11 studies involved both face-to-face meetings and phone calls (Cargill 1992, Cossette 2015, Khdour 2009, Lingler 2016, Lipton 1994, Lopez Cabezas 2006, Olesen 2014, Shively 2013, Vinluan 2015, Williams 2012, Young 2016)

Table B: Intervention features

Study ID	Type of intervention								Provider of intervention				Location or delivery mode of intervention	Duration/frequency of intervention
	Educational				Behavioural									
	Education	Medication review	Regimen simplification	Follow-up/ monitoring	Motivational interviewing	DAA	Patient med card/list	Other	Pharmacist	Nurse	Physician	Other		
Al-Rashed 2002	X						X		X				Hospital	One-off
Begley 1997	X		X						X				Home	12mths (5 times)
Bernsten 2001	X	X	X	X					X				Pharmacy	18mths continuous
Blalock 2010	X	X									*		Pharmacy/health centre	One-off
Bond 2007	X	X		X					X		*		Pharmacy	One-off + as needed
Cargill 1992	X	X		X (G3)		*				X			Home + phone	One-off (+ 1-2wks for Group 3)
Chrischilles 2014	X							X				X	Online	12mths continuous
Cohen 2011	X			X					X	X		X	Medical centre	6mths (Weekly for 4 weeks, then monthly)
Cossette 2015	X			X						X			Hospital + phone	At discharge + 2-4 days and 7-10 days post-discharge
George 2016	X								X			X	Online	1mth continuous
Grymonpre 2001	X	X							X		*	X	Home/clinic	One-off + as needed
Haag 2016		X							X	*			Phone	One-off
Hale 2016				X		X			X				Home	90days continuous
Hanlon 1996	X	X							X			X	General medicine clinic	12mths (Before/after GP visits)
Holland 2007	X	X		X					X		*		Home	2wks & 6-8wks post-discharge
Khdour 2009	X	X			X				X				Outpatient clinic + phone	9mths (4 times)

Study ID	Education	Medication review	Regimen simplification	Follow-up/monitoring	Motivational interviewing	DAA	Patient med card/list	Other (behavioural)	Pharmacist	Nurse	Physician	Other (provider)	Location or delivery mode of intervention	Duration/frequency of intervention
Krska 2001		X							X		*		Medical centre or home	One-off + as needed
Lee 2006	X	X		X		X			X				Outpatient pharmacy clinic	6mths (every 2mths)
Lim 2004	X	X	X						X	*	*	*	Outpatient clinic	One-off
Lingler 2016	X	X		X						*		*	Home + phone	16 weeks (2-3 visits + 2-3 calls)
Lipton 1994	X	X	X	X					X		*		Hospital + home or phone	3 mths (5 times)
Lopez Cabezas 2006	X			X					X				Hospital + phone	12 mths (9 times)
Manning 2007	X						X	X		X			Hospital	One-off
Marek 2013	X			X		X				X			Home	12 mths
Marusic 2013	X	X									X		Hospital	One-off
Messerli 2016	X	X							X				Pharmacy	Twice (0 & 28wks)
Moral 2015				X	X					*	*		Home + health centre	6mths (4 times)
Morales Suarez-Vurela 2009				X		X				X			Unclear	2mths (3 times)
Murray 1993			X			X			X				Home or clinic	6mths (Monthly)
Muth 2016		X									X	*	GP clinic	One-off
Nascimento 2016	X	X				*			?				Home	One-off
Naunton 2003	X	X		X					X				Home	One-off
Nazareth 2001	X	X		X					X		*		Hospital + home	Twice (0 + 7-14days)
Olesen 2014	X	X	X	X	X			X	X				Home + phone	9mths (4 times)
Pandey 2017								X		*		X	Text message	12mths continuous

Study ID	Type of intervention — Educational				Type of intervention — Behavioural				Provider of intervention				Location of intervention	Duration of intervention
	Education	Medication review	Regimen simplification	Follow-up/ monitoring	Motivational interviewing	DAA	Patient med card/list	Other	Pharmacist	Nurse	Physician	Other		
Pereles 1996	X			X				X	X	X		X	Hospital	Continuous (mean 21.6 days)
Rich 1996	X	X	X	X						X	X		Hospital + home	Unclear
Saez de la Fuente 2011	X		X	X					?			X	Hospital	One-off
Shimp 2012	X	X							X				University	Twice
Shively 2013	X	X		X	X					X			Phone + ?clinic	6 mths (6 times)
Taylor 2003	X	X		X					X		*		Medical clinic	12mths (at GP visits)
Truelove 2015								X			X		GP clinic or aboriginal medical centre	18mths continuous
Vinluan 2015	X	X		X					X	X			Hospital + phone	90days (5 times)
Volume 2001	*	X							X				Pharmacy	One-off + as needed
Williams 2012	X	X		X	X					X			GP clinic	One-off
Willeboordse 2017	*	X							X		X		Home + phone	One-off + 12wks follow up
Winland-Brown 2000						X				X			Independent living facility	6mths (continuous)
Wood 1992	X			X				X	X	X			Hospital	Up to 3wks
Wu 2006	X			X				X	X	X			Phone	2yrs (6-8 times)
Young 2016	X			X				X	X	?			Hospital + phone	12 weeks (10 times)

* indicates an intervention (e.g. provision of DAA) or a healthcare provider that contributed to the intervention for some participants only;

? indicates intervention provider or location unclear;

G3 means group 3 only.

Primary outcomes

Medication-taking ability was measured in five studies (Table C). Four studies used objective measures, including a five item dexterity test that assessed skills such as opening child resistant closures on containers (Begley 1997), a medication-taking behaviour score (Cargill 1992), the Medication Management Instrument for Deficiencies in the Elderly (MedMaIDE) (Lingler 2016) and performance on an inpatient self-administration of medications program and/or pharmacist assessment (with input from other team members) of ability to self-administer medications (Pereles 1996). One study used a subjective measure, a self-reported assessment of safety in taking medication (Manning 2007). Medication-taking ability was typically measured at short follow-up points (e.g. 7-14 days, Manning 2007), except for one study which had an extended measure at 12 months (Begley 1997).

Medication adherence was measured in 48 studies (Table C). Twenty studies used an objective measure of adherence such as pill count (Begley 1997, Cargill 1992, Cohen 2011, Lee 2006, Lopez Cabezas 2006, Marusic 2013, Moral 2015, Murray 1993, Olesen 2014, Pereles 1996, Rich 1996, Williams 2012, Winland-Brown 2000, Wood 1992), prescription claims/refills (Al-Rashed 2002, Grymonpre 2001, Messerli 2016, Shimp 2012, Vinluan 2015) or machine-recorded correct doses (Marek 2013). Twenty-eight studies used a subjective measure of adherence; 16 of these used an original or modified version of the Morisky medication adherence scale, a validated measure of adherence (Bernsten 2001, Chrischilles 2014, Cossette 2015, George 2016, Haag 2016, Hale 2016, Khdour 2009, Morales Suarez-Vurela 2009, Muth 2016, Nascimento 2016, Saez de la Fuente 2011, Volume 2001), Medication Adherence Rating Scale (Bond 2007, Holland 2007, Muth 2016), Brief Medication Questionnaire (Blalock 2010) and Medical Outcome Study specific Adherence Scale (Shively 2013). Four studies used structured interviews to enquire about adherence (Hanlon 1996, Lipton 1994, Nazareth 2001, Willeboordse 2017) and six studies asked participants a single question about forgotten or missed doses (Lim 2004, Naunton 2003, Taylor 2003, Truelove 2015, Wu 2006, Young 2016). One study (Pandey 2017) used a patient-completed daily log-book of medication consumption and one study (Krska 2001) had pharmacist review for pharmaceutical care issues including potential or actual adherence issues. The longest follow-up time-points of post-intervention adherence outcomes ranged from 1 month to 18 months, with the median time-point being six months.

Table C: Summary of outcomes

Study ID	Primary Outcome — Medication-taking ability — Objective	Primary Outcome — Medication-taking ability — Subjective	Primary Outcome — Adherence — Objective	Primary Outcome — Adherence — Subjective	Longest follow-up time-point measured (~months)	Secondary outcome — Knowledge	Secondary outcome — Satisfaction	Secondary outcome — HRQoL	Secondary outcome — Adverse event	Secondary outcome — Condition outcome	Secondary outcome — Cost effectiveness	Secondary outcome — Other
Al-Rashed 2002			x		3	x						
Begley 1997	x		x		12	x			x			
Bernsten 2001			*	x	18	x	x	x	x		x	
Blalock 2010				x	12					x		
Bond 2007				x	12	x	x	x	x	x	x	
Cargill 1992	x		x	x	12							
Chrischilles 2014				x	1-1.5				x			x
Cohen 2011			x	x	6			x	x	x		
Cossette 2015				x	1		x		x			
George 2016				x	1		x					
Grymonpre 2001			x		6	x						
Haag 2016				x	1				x			
Hale 2016				x	3			x	x			
Hanlon 1996				x	12	x	x	x	x			
Holland 2007				x	6		x	x	x			
Khdour 2009				x	12	x		x	x			
Krska 2001				x	3			x		x		
Lee 2006			x		6					x		
Lim 2004				x	2	x	x		x			
Lingler 2016	x				2		x		x			x
Lipton 1994				x	3				x			
Lopez Cabezas 2006			x		12			x	x		x	
Manning 2007		x			0.5	x	x	x	x			
Marek 2013			x		12							

Study ID	Primary Outcome Medication-taking ability Objective	Primary Outcome Medication-taking ability Subjective	Primary Outcome Adherence Objective	Primary Outcome Adherence Subjective	Longest follow-up time-point measured (~months)	Knowledge	Satisfaction	HRQoL	Adverse event	Condition outcome	Cost effectiveness	Other
Marusic 2013			x		1				x			
Messerli 2016			x		6.5	x			x			
Moral 2015			x		6							x
Morales Suarez-Vurela 2009				x	2							
Murray 1993			x		6				x			
Muth 2016				x	3			x	x			
Nascimento 2016				x	6					x		
Naunton 2003				x	3		x		x			
Nazareth 2001				x	6	x	x		x			
Olesen 2014			x		12				x			
Pandey 2017				x	12							
Pereles 1996	x		x		1	x						
Rich 1996			x		1				x			
Saez de la Fuente 2011				x	1.5				x			
Shimp 2012			x		12							
Shively 2013				x	6				x			
Taylor 2003				x	12	x	x	x	x	x		x
Truelove 2015				x	18							
Vinluan 2015			x		3				x			
Volume 2001				x	12		x	x				
Willeboordse 2017				x	6		x	x	x			
Williams, 2012			x		9					x		
Winland-Brown 2000			x		6				x			
Wood 1992			x		3							
Wu 2006				x	2				x			
Young 2016				x	6				x			

Secondary outcomes

Knowledge about medications was measured in 13 studies. Knowledge was mostly assessed by asking participants about one or more of the following: name of medication, appearance of medication, purpose of medication, dose, dose frequency/interval, side effects, drug interactions, special comments or cautions (Al-Rashed 2002; Begley 1997; Bernsten 2001; Grymonpre 2001; Hanlon 1996; Lim 2004; Manning 2007; Messerli 2016; Nazareth 2001; Pereles 1996; Taylor 2003). One study asked participants on a five-point Likert scale if they "knew more about their medicines compared to a year ago" (Bond 2007) and another study assessed medication knowledge as part of a larger chronic obstructive pulmonary disease (COPD) knowledge questionnaire (Khdour 2009).

Satisfaction with the intervention was measured in 13 studies. Six studies used a previously validated measure (George 2016, Hanlon 1996, Lopez Cabezas 2006, Nazareth 2001, Volume 2001, Willeboordse 2017), but no two studies used the same measure. Satisfaction was most commonly assessed using a 5-point (Bernsten 2001, Bond 2007, Hanlon 1996, Manning 2007) or 7-point (George 2016, Volume 2001, Willeboordse 2017) Likert-type scale, which included between one (Manning 2007, Willeboordse 2017) and 15 items (Bond 2007). One study (Lopez Cabezas 2006) used a 0-10 analogue scale, and four studies did not adequately describe the measure used (Lingler 2016, Holland 2007, Naunton 2003, Taylor 2003).

Health-related quality of life (HRQoL) was measured in 14 studies. The two most common measures were the validated Short Form health survey involving 36 items (SF-36) used in eight studies (Bernsten 2001, Bond 2007, Cohen 2011, Hanlon 1996, Krska 2001, Marek 2013, Taylor 2003, Volume 2001) and the European Quality of life 5 dimension instrument (EQ-5D) used in five studies (Bond 2007, Holland 2007, Lopez Cabezas 2006, Muth 2016, Willeboordse 2017). Other measures used by individual studies included the 12-item Short Form health survey (SF-12, Willeboordse 2017), and disease-specific quality of life measures including the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (Hale 2016, Holland 2007) and the St George's Respiratory Questionnaire (SGRQ) (Khdour 2009)

Adverse clinical health outcomes were measured in 28 studies and included measures such as ED and/or hospital admissions (Al-Rashed 2002; Bernsten 2001; Cossette 2015; Haag 2016; Hale 2016; Holland 2007; Khdour 2009; Lipton 1994; Lopez Cabezas 2006; Marusic 2013; Messerli 2016; Muth 2016; Naunton 2003; Nazareth 2001; Olesen 2014; Rich 1996; Saez de la Fuente 2011; Shively 2013; Taylor 2003; Vinluan 2015; Winland-Brown 2000; Wu 2006; Young 2016), mortality (Holland 2007; Lopez Cabezas 2006; Naunton 2003; Nazareth 2001; Olesen 2014; Saez de la Fuente 2011; Vinluan 2015; Wu 2006), adverse drug reactions (Chrischilles 2014; Hanlon 1996; Lim 2004; Marusic 2013; Murray 1993; Willeboordse 2017) and physician visits (Al-Rashed 2002; Khdour 2009; Nazareth 2001; Winland-Brown 2000).

Condition specific outcomes were measured in six studies and included changes in blood pressure (Lee 2006, Taylor 2003, Williams 2012), diabetes control − glycosylated haemoglobin (HbA1c)/blood glucose (Nascimento 2016, Taylor 2003, Williams 2012), LDL-cholesterol (Lee 2006, Taylor 2003), falls (Blalock 2010), international normalised ratio (INR) of time taken for blood to clot (Taylor 2003) and renal function (Williams 2012). Two studies reported composite measures of reaching multiple 'health' targets (Bond 2007, Cohen 2011).

Cost-effectiveness of the intervention was measured in three studies (Bernsten 2001, Bond 2007,Lopez Cabezas 2006) using the costs of the intervention, medicines, hospitalisations and/or health consultations and one study (Lipton 1994) using US Medicare part B costs and total hospital inpatient costs.

Other outcome measures extracted included medication management problems from a list of eight problems (Chrischilles 2014), medication deficiency checklist (Lingler 2016), medication errors (Moral 2015) and medication misadventures (Taylor 2003).

Excluded studies

We excluded 308 studies in total, see Characteristics of excluded studies. Twenty studies were excluded because the study design did not meet Cochrane criteria for an RCT, cluster RCT or quasi-RCT. One hundred and thirty-one studies were excluded on the basis of age of participants. Seventy studies were excluded based on the number of regular prescription medications, including 10 studies where the number of medications was unknown (and contact with authors was unsuccessful) and 10 studies where authors did not collect information on number of medications. Seventy-five studies were excluded because they did not include a measure of medication-taking ability or medication adherence as an outcome, and eight studies were excluded as the follow-up period of outcome measure was too short (i.e. <48hrs for medication-taking ability, or <4 weeks for adherence). One study was excluded because the intervention did not target consumers, and three studies were excluded because participants were not community-dwelling.

Risk of bias in included studies

See Characteristics of included studies table, Figure 2 and Figure 3 for a summary assessment of the risk of bias of the included studies.
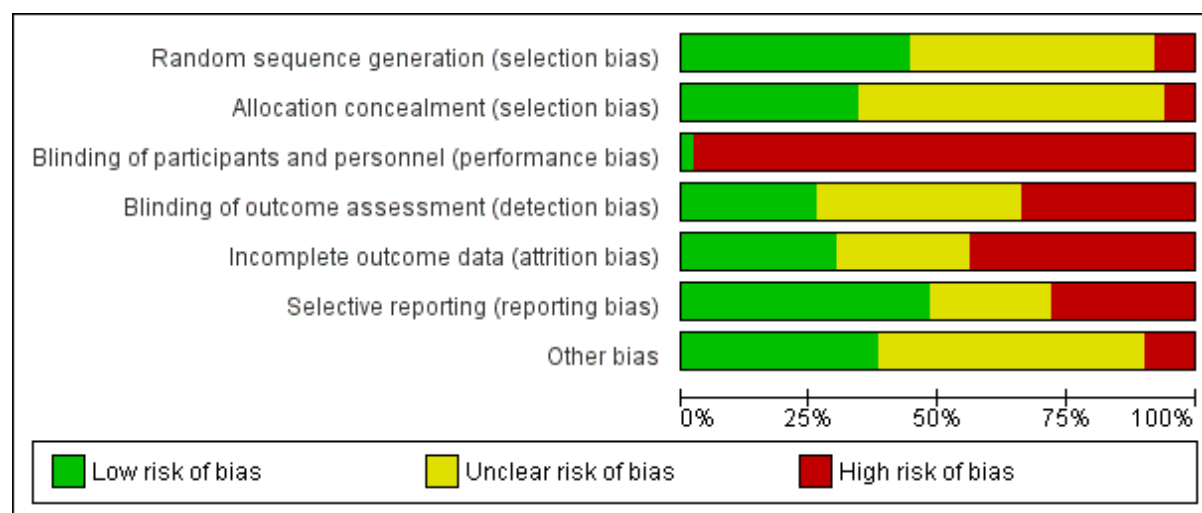
Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation (selection bias)

The risk of bias for random sequence generation was low in 22 studies (44%), unclear in 25 studies (50%) and high in three studies (6%). For concealment of allocation, risk of bias was low in 17 studies (34%), unclear in 29 studies (58%) and high for 4 studies (8%). Selective recruitment of cluster participants was assessed for the six cluster RCTs – three were considered at high risk (Moral 2015, Willeboordse 2017, Wood 1992), two were considered at low risk (Muth 2016, Wood 1992) and one was considered at unclear risk of recruitment bias (Bernsten 2001).

Blinding (performance bias and detection bias)

Blinding of both participants and personnel could not be achieved through the study design in 49 of the 50 studies (98%), leading to high risk of performance bias. One study (George 2016) was considered to have low risk of performance bias as the intervention was delivered online and both intervention and control participants viewed the same interface, thus they were unaware of their allocation.

Seventeen studies (34%) stated that there was no blinding of outcome assessment and were considered as having high risk of detection bias. Twenty studies (40%) were assessed as 'unclear' risk of detection bias due to insufficient details regarding method of outcome assessment. The studies with unclear detection bias included one study where data collection was performed "where possible" by a member of staff other than the intervention pharmacist (Bernsten 2001), one study involving caregiver-reported patient adherence where caregivers were assumed to be unaware of allocation (George 2016), and two studies where assessors were reported as blinded but contamination from unblinded participants was thought to be highly likely (Saez de la Fuente 2011 and Young 2016). Thirteen studies (26%) were assessed as low-risk of detection bias; five involved an objective measure of the primary outcome (Grymonpre 2001, Marusic 2013, Messerli 2016, Rich 1996 and Williams 2012), and eight involved subjective measures but were collected/analysed by blinded investigators (Bond 2007, Chrischilles 2014, Cossette 2015, Haag 2016, Hanlon 1996, Lipton 1994, Manning 2007, Nazareth 2001).

Incomplete outcome data (attrition bias)

Twenty-two (44%) studies were considered to have incomplete outcome data, and therefore high risk of attrition bias – 19 of these cases were due to high loss to follow-up. A further three (6%) studies were assessed as high risk of attrition bias due to: inconsistency between average number of medicines and the number assessed for adherence (Grymonpre 2001), inconsistency between number of patients with adherence reported and the number who saved their medication boxes enabling accurate pill count (Williams 2012), and lack of details regarding attrition of control group (Shimp 2012). Thirteen studies were assessed as having unclear risk of bias mainly due to low to moderate attrition which may have had an impact on the results or insufficient details on number of, or reasons for attrition. Incomplete outcome data was minimal and/or adequately addressed in 15 studies (low risk of bias).

Selective reporting (reporting bias)

Fourteen studies (28%) were considered to have high risk of reporting bias. Twelve were due to missing outcome data (Begley 1997, Blalock 2010, Cohen 2011, Krska 2001, Lim 2004, Lopez Cabezas 2006, Messerli 2016, Morales Suarez-Vurela 2009, Murray 1993, Olesen 2014, Shimp 2012 and Winland-Brown 2000), one study did not clearly specify how data were obtained (Vinluan 2015) and one study changed inclusion criteria mid-way through the study to increase recruitment (Williams 2012).

Twelve studies (24%) were considered to have unclear risk of reporting bias due to minor deviations from the methods (Bond 2007, Grymonpre 2001, Lipton 1994, Wood 1992), missing information in the methods (Bernsten 2001, Willeboordse 2017), missing baseline data (Lee 2006) and unclear reporting of results (Cargill 1992, Lingler 2016, Marek 2013, Moral 2015, Willeboordse 2017).

While 24 studies (48%) were assessed as having low risk of selective reporting, 15 of these did not have a published protocol or trial registration thus it was difficult to accurately assess reporting bias.

Other potential sources of bias

Four studies were identified as having high risk of other types of bias. One study (George 2016) was assessed as having high risk as it was a research thesis and had not been published in a peer-reviewed journal, two studies were considered to have high risk due to poor intervention fidelity (Chrischilles 2014, Nazareth 2001), and one study measured adherence only for the first three medications mentioned by the patient (Lipton 1994).

Twenty-seven studies were considered to have unclear risk of other types of bias. Sixteen studies did not reach their specified target sample size (Bernsten 2001, Blalock 2010, Bond 2007, Cossette 2015, Hale 2016, Khdour 2009, Lopez Cabezas 2006, Marek 2013, Messerli 2016, Moral 2015, Morales Suarez-Vurela 2009, Pereles 1996, Truelove 2015, Volume 2001, Willeboordse 2017 and Wu 2006). Three studies had unbalanced participant groups likely influencing outcomes (Haag 2016, Murray 1993, Winland-Brown 2000). Four studies had potential conflicts due to funding arrangements (Holland 2007, Shimp 2012) or participant compensation (Messerli 2016, Shively 2013) which may have biased the results of the study. Two studies had limited information regarding intervention fidelity (Manning 2007, Nascimento 2016) and four studies had concerns regarding the assessment of adherence (Nascimento 2016, Rich 1996, Pandey 2017, Williams 2012).

The authors also noted that 10 studies did not declare a funding source. However, given the differences in journal requirements and the age of those studies this was not considered as a risk of bias for this review.

Effects of interventions

<u>COMPARISON 1: Intervention versus usual care</u>

Primary outcome - medication-taking ability

Educational interventions: No studies identified

Behavioural interventions: No studies identified

Mixed educational and behavioural interventions were identified in five studies, which showed mixed impact on medication-taking ability (Table 1, low certainty evidence). Two studies (Cargill 1992, Lingler 2016) demonstrated improvement in medication-taking ability following an educational intervention with home and/or telephone follow-up directed at both patients and caregivers. In Lingler 2016, higher Medication Management Instrument for Deficiencies in the Elderly (MedMaIDE) scores were observed at 2 months in the intervention group (unpublished results: mean ± SD: intervention 0.595 ± 0.725 vs usual care 0.297 ± 0.777). In Cargill 1992, the intervention group receiving additional follow-up telephone calls (group 3) showed a greater improvement in medication-taking ability compared to usual care, as measured by a behaviour score at 4-6 weeks (mean scores presented visually, group 3 change p=0.01). Two studies (Manning 2007 and Pereles 1996) directed at the patient showed no significant difference in medication-taking ability. In Manning 2007, a medication chart with tablets/capsules affixed and medication discharge

education had no significant impact on the number of self-reported mistakes with taking medication. In Pereles 1996, an inpatient self-administration of medication program was reported to have no impact on the number of participants able to self-administer their medications; however, different methods of assessing the outcome were used for the intervention and control group. One study involving patient-focused education and regimen simplification did not report results (Begley 1997).

Subgroup analysis was not possible due to the small number of eligible studies.

Primary outcome - adherence

Forty-eight studies included a measure of adherence, and were analysed based on the type of intervention: educational, behavioural or mixed. Meta-analyses were possible for 31 studies: 18 involving dichotomous measures (Analysis 1.1) and 13 involving continuous measures (Analysis 1.2). The seventeen studies not included in meta-analyses are briefly summarised in Table 2 and in the following sub-sections.

Educational interventions were identified in fourteen studies, seven studies were included in meta-analyses. Two studies (Haag 2016; Marusic 2013) involving dichotomous measures of adherence and five studies (George 2016; Grymonpre 2001; Messerli 2016; Muth 2016; Nascimento 2016) involving continuous measures of adherence were included in the meta-analyses. Analysis 1.1.1 indicated educational interventions do increase the proportion of adherent patients (RR 1.66, 95% CI 1.33 to 2.06), however results were strongly influenced by Marusic 2013. Analysis 1.2.1 showed that educational interventions had no significant impact on adherence (SMD 0.16, 95% CI -0.12 to 0.43), but there was substantial heterogeneity. Sensitivity analysis performed after removing one study with high attrition (George 2016) did not alter the result (SMD 0.16, 95% CI -0.14, 0.47).

Seven studies (Table 2) could not be included in the meta-analyses due to incomplete data or reporting of results in formats that could not be meta-analysed (e.g. median and IQR). One intervention (Krska 2001) significantly increased the number of participants who had pharmaceutical care issues (e.g. non-adherence) resolved and four interventions had no significant impact on adherence (Bond 2007, Hanlon 1996, Volume 2001, Willeboordse 2017). Two studies had no results available (Blalock 2010, Shimp 2012).

In total, three of the 14 educational interventions had positive effects on adherence, and all three were delivered as one-off interventions. In Krska 2001 and Nascimento 2016, pharmacists provided individualised medication management education and medication reviews at home, with Nascimento 2016 also providing therapeutic education on diabetes care. In Marusic 2013, physicians who were specialists in clinical pharmacology provided pre-discharge counselling (e.g. medication indications, dosages, administration, importance of compliance, possible ADRs) to participants 24 hours before discharge. Adherence was measured using different measures and at different time points in each study; pharmacist assessment of pharmaceutical care issues including actual or potential adherence issues at three months (Krska 2001), pill count at 30 days (Marusic 2013) and subjectively using a Portuguese/Spanish variation of the Morisky adherence measure at six months (Nascimento 2016).

Behavioural interventions were identified in seven studies, of which five were suitable for inclusion in meta-analyses. Four studies (Hale 2016; Moral 2015; Morales Suarez-Vurela 2009; Truelove 2015) used a dichotomous measure of adherence and the meta-analysis showed behavioural interventions do increase the proportion of adherent patients (Analysis 1.1.2, RR 1.22, 95% CI 1.07 to 1.38). Sensitivity analysis after removing one study with high attrition (Truelove 2015) did not alter the result (RR 1.22, 95% CI 1.02 to 1.45). The single

study using a continuous measure (Murray 1993) had a large effect on adherence (SMD 1.90, 95% CI 0.82 to 2.97).

Two studies were unable to be included in the meta-analyses due to non-reporting of standard deviations (Winland-Brown 2000) or reporting of percentage of days covered rather than percentage of adherent participants (Pandey 2017), but both reported positive impacts on adherence.

In total, four of the seven behavioural interventions had individual positive impacts on adherence. Two studies involved DAAs: Murray 1993 involved pharmacist-led regimen simplification to twice daily dosing intervals and provided medications in unit-of-use packaging (translucent plastic cups with lids containing all medications for that dosing time), while Winland-Brown 2000 used an automated dispenser with audible reminders. Truelove 2015 involved a cardiovascular four ingredient poly-pill and Pandey 2017 sent once daily text message adherence reminders to participants. Adherence was measured objectively at six months using pill count in two studies (Murray 1993, Winland-Brown 2000) and subjectively using patient log-book records at 12 months (Pandey 2017) or self-reported use of medication at 18 months (Truelove 2015).

Mixed educational and behavioural interventions were identified in 27 studies, 19 studies were included in meta-analyses. Twelve studies (Bernsten 2001; Cossette 2015; Khdour 2009; Lopez Cabezas 2006; Naunton 2003; Olesen 2014; Rich 1996; Saez de la Fuente 2011; Vinluan 2015; Wood 1992; Wu 2006; Young 2016) used a dichotomous measure of adherence and showed that mixed interventions do increase the proportion of adherent patients (Analysis 1.1.3, RR 1.22, 95% CI 1.08 to 1.37). A sensitivity analysis was conducted after removing two cluster RCTs that had potential unit of analysis errors (Bernsten 2001, Wood 1992), but this had little impact on the risk ratio (RR 1.25, 95% CI 1.09 to 1.44). A second sensitivity analysis performed after removing six studies with high attrition (Bernsten 2001, Cossette 2015, Lopez Cabezas 2006, Olesen 2014, Vinluan 2015, Wood 1992) strengthened the above finding further (RR 1.33, 95% CI 1.20 to 1.49). Seven studies (Begley 1997; Chrischilles 2014; Lee 2006; Lipton 1994; Nazareth 2001; Shively 2013; Williams 2012) used a continuous measure of adherence and showed no significant impact on adherence in a meta-analysis (Analysis 1.2.3, SMD 0.48, 95% CI -0.08 to 1.04). A sensitivity analysis after removing three studies (Lipton 1994, Nazareth 2001, Williams 2012) with high attrition did not alter the findings (SMD 0.54, 95% CI -0.45 to 1.53).

Of the eight studies not included in meta-analyses, two showed positive impact on adherence (Al-Rashed 2002, Pereles 1996), four showed non-significant results (Cargill 1992, Holland 2007, Lim 2004, Taylor 2003) and two did not have clearly reported results (Cohen 2011, Marek 2013).

In total, eleven of the twenty-seven mixed interventions had positive impacts on adherence. All 11 were conducted at the hospital-community interface (e.g. in hospital, at discharge, post-discharge or at outpatient clinics) and involved elements of education/counselling. Five studies involved pharmacist medication review (Khdour 2009, Lee 2006, Lipton 1994, Naunton 2003, Rich 1996) and three involved regimen simplification (Begley 1997, Lipton 1994, Rich 1996). Interventions varied in duration from one-off (Al-Rashed 2002, Naunton 2003, Saez de la Fuente 2011), to 3 months or less (Lipton 1994, Pereles 1996, Young 2016), 6-12 months (Begley 1997, Khdour 2009, Lee 2006) or 2 years (Wu 2006). Duration of the intervention in one study (Rich 1996) was unclear. Other behavioural interventions in these studies included blister-packed medication adherence aids (Lee 2006, and as needed in Naunton 2003), motivational interviewing (Khdour 2009) and a medication reminder card (Al-Rashed 2002).

There were sufficient mixed intervention studies identified to conduct three of the planned subgroup analyses:

1. *Duration of intervention:* short (≤3 months) versus long (>3 months). Interventions with short duration had a significant impact on dichotomous measures of adherence, but had moderate heterogeneity (Analysis 1.3, RR 1.40, 95% CI 1.13 to 1.74, I^2 = 53%). Meta-analyses of interventions with short duration using continuous measures of adherence (Analysis 1.3), and long interventions using either dichotomous or continuous measures showed no significant impact on adherence and had considerable heterogeneity and (Analysis 1.4).

2. *Type of outcome measure:* objective versus subjective. Interventions using subjective dichotomous measures of adherence showed a positive impact on adherence (Analysis 1.5, RR 1.26, 95% CI 1.09 to 1.46), but objective dichotomous measures did not (Analysis 1.5, RR 1.13, 95% CI 0.93 to 1.38). Interventions using continuous measures, both subjective and objective, did not have a significant impact on adherence (Analysis 1.6). A large degree of heterogeneity was seen in both Analysis 1.5 (I^2 = 62% for objective measures, I^2 = 75% for subjective measures) and Analysis 1.6 (I^2 = 97% for objective measures, I^2 = 90% for subjective measures).

3. *Health professional delivering the intervention:* pharmacist versus nurse versus multidisciplinary (≥2 health professionals). Pharmacist delivered interventions showed the greatest impact on adherence using both dichotomous (Analysis 1.7; RR 1.21, 95% CI 1.04 to 1.41) and continuous (Analysis 1.8; SMD 1.38, 95% CI 0.01 to 2.75) measures. Nurse-led interventions showed positive impact on adherence using dichotomous measures (Analysis 1.7; RR 1.19, 95% CI 1.02 to 1.38), but interventions using continuous measures favoured control (Analysis 1.8; SMD -0.13, 95% CI -0.53 to 0.27). Multidisciplinary interventions had no significant impact on adherence, although only two studies were included in each meta-analysis (Analysis 1.7; RR 1.38, 95% CI 0.88 to 2.16; Analysis 1.8; SMD 0.42, 95% CI -0.38 to 1.21).

Secondary outcome - medication knowledge

Thirteen studies included a measure of medication knowledge (Table 3). Meta-analysis was not possible due to large variations in outcome measures and reporting.

Educational interventions were identified in four studies. In Bond 2007, pharmacist-led medication management review (including assessment of medication appropriateness, adherence, lifestyle, and social support) conducted in the community pharmacy resulted in more patients agreeing that they knew more about their medications compared to that one year ago (intervention 73% vs usual care 65%). Two studies (Grymonpre 2001 and Hanlon 1996) showed no significant impact on medication knowledge. In Grymonpre 2001, home medication histories were obtained by trained staff and reviewed by pharmacists, the pharmacists then sent a letter summarising the information and recommendations to the patient's general practitioner. In Hanlon 1996, the intervention involved pharmacist education to the participant and medication review at a general medicine clinic before/after physician appointments. One study involving pharmacist medication review and counselling in the pharmacy (Messerli 2016) did not report results.

No *behavioural interventions* that included a measure of medication knowledge were identified.

Mixed educational and behavioural interventions were identified in nine studies. Five studies reported positive impacts on medication knowledge (Al-Rashed 2002, Khdour 2009, Manning 2007, Pereles 1996, Taylor 2003). Two studies used one-off pre-discharge education: Al-Rashed 2002 involved 30-minute pharmacist counselling session (focusing on indication, side effects, dose, dosage times, importance of adherence and provision of a medication card etc.), and Manning 2007 involved nurse education using a 3D medication discharge education tool where participants could affix a tablet or capsule of each medication onto the tool to assist with tablet identification. Three studies involved follow-up/monitoring: Pereles 1996 involved a three stage self-administration of medications program in hospital, Khdour 2009 involved medication review and motivational interviewing conducted four times over nine-months in an outpatient clinic or via phone, and Taylor 2003 involved pharmacist education and medication review at scheduled medical clinic visits over 12 months. Three studies reported no impact on medication knowledge – one involving medication review and regimen simplification conducted at home post-discharge for 12 months (Begley 1997), one involving medication review and regimen simplification conducted continuously for 18 months in the community pharmacy (Bernsten 2001), and one involving hospital pharmacist medication review with community pharmacist home visit follow-up 7-14 days post discharge (Nazareth 2001). One study did not report any follow-up results on medication knowledge (Lim 2004).

Secondary outcome - satisfaction

Thirteen studies included a measure of consumer satisfaction, but only 10 studies measured the outcome in both intervention and control groups (Bernsten 2001, Bond 2007, George 2016, Hanlon 1996, Lopez Cabezas 2006, Manning 2007, Nazareth 2001, Taylor 2003, Volume 2001, Willeboordse 2017). Three studies (Holland 2007, Lingler 2016, Naunton 2003) measured satisfaction in the intervention group only. Meta-analysis was not possible due to large variations in outcome measures (Table 4).

Educational interventions were identified in five studies, four of which had no significant impact on satisfaction (George 2016, Hanlon 1996, Volume 2001, Willeboordse 2017). One study (Bond 2007) involving community pharmacists providing consultations on medications, medication adherence, lifestyle and social support reported that participants had greater satisfaction in the intervention group compared to usual care, however the effect size was small.

No *behavioural interventions* that included a measure of satisfaction were identified.

Mixed educational and behavioural interventions were identified in eight studies. Three studies (Holland 2007, Lingler 2016, Naunton 2003) measured participant satisfaction only in the intervention group, with satisfaction levels ranging from 64% (Holland 2007) to 94% (Naunton 2003). Five studies measured participant satisfaction in both intervention and usual care groups; the between group differences were non-significant in four studies (Bernsten 2001, Lopez Cabezas 2006, Manning 2007, Nazareth 2001) and one study appeared to favour the usual care group; however, the satisfaction measure used was poorly described (Taylor 2003).

Secondary outcome - HRQoL

Fourteen studies included a measure of HRQoL (Table 5). Meta-analysis was not possible due to differences in scales used and differences in the reporting of results.

Educational interventions were identified in six studies (Bond 2007, Hanlon 1996, Krska 2001, Muth 2016, Volume 2001, Willeboordse 2017), and none of these had a significant impact on HRQoL.

Behavioural interventions were identified in only one study (Hale 2016). The intervention involved a remotely monitored electronic medication dose administration aid with alerts and follow-up calls if medications were missed. HRQoL was measured using the MLHFQ, with results showing that the intervention group had worse HRQoL (higher MLHFQ scores) at both baseline and 90 day follow-up compared to the usual care group (baseline: mean ± SD: 43.7 ± 25.9 vs 26.2 ± 23.1; 90 days: mean ± SD: 62.2 ± 20.6 vs 28.2 ± 22.3).

Mixed educational and behavioural interventions were identified in seven studies, with six showing no significant impact on HRQoL (Bernsten 2001, Cohen 2011, Holland 2007, Khdour 2009, Lopez Cabezas 2006, Taylor 2003). One study (Marek 2013) showed that nurse education, follow-up and weekly nurse-filled DAAs resulted in improved physical and mental summary scores on the SF-36 at 12 months compared to usual care (mean change (95% CI): physical: 1.390 (0.816, 1.963), mental: 1.686 (0.949, 2.423), $p<0.0001$).

Secondary outcome - adverse clinical health outcomes

Twenty-eight studies included a measure of adverse clinical health outcomes (Table 6)

ED/hospital admissions were measured in 23 studies, and 16 studies were included in the meta-analysis (Analysis 1.9). Four studies reported hospital and ED admissions separately, but only hospital admissions were chosen to be included in the meta-analysis (Hale 2016, Khdour 2009, Taylor 2003, Young 2016).

Educational interventions (Haag 2016, Marusic 2013, Messerli 2016) had no significant impact on admissions (RR 1.02, 95% CI 0.71 to 1.48).

Behavioural interventions (Hale 2016, Winland-Brown 2000) significantly reduced the risk of admissions (RR 0.21, 95% CI 0.08 to 0.55), although meta-analysis was conducted with only two studies and both had unclear risk of bias in multiple domains.

Mixed educational and behavioural interventions (Al-Rashed 2002, Cossette 2015, Khdour 2009, Lopez Cabezas 2006, Naunton 2003, Nazareth 2001, Olesen 2014, Rich 1996, Taylor 2003, Vinluan 2015, Young 2016) significantly reduced the risk of admissions (RR 0.73, 95% CI 0.56 to 0.95), however the level of heterogeneity was high ($I^2 = 73\%$)

Seven studies were not included in the meta-analysis, one educational intervention (Muth 2016) and six mixed interventions (Bernsten 2001, Holland 2007, Lipton 1994, Saez de la Fuente 2011, Shively 2013, Wu 2006). Two studies (Bernsten 2001, Saez de la Fuente 2011) had unclear participant numbers, one (Holland 2007) reported only total admissions and not number of participants admitted, two reported mean (SD) number of days in hospital (Lipton 1994, Muth 2016), one reported mean (SD) admissions (Shively 2013); and one reported median (IQR) hospital visits (Wu 2006). None of the interventions in these seven studies had a significant effect on ED/hospital admissions.

In total, four out of 23 individual studies had results favouring the intervention – one behavioural (Winland-Brown 2000) and three mixed (Al-Rashed 2002, Khdour 2009, Taylor 2003) interventions. Two studies involved pharmacist-led education and medication review with (Khdour 2009) or without (Taylor 2003) motivational interviewing conducted in an outpatient clinic (Khdour 2009) or medical clinic (Taylor 2003). One study involved an automated medication dispenser with audible adherence reminders in the participant's home (Winland-Brown 2000). One study involved pharmacist pre-discharge counselling and provision of a medicine reminder card conducted in hospital (Al-Rashed 2002).

Mortality was reported in eight studies, all involving *mixed behavioural and educational interventions* led by pharmacists. Meta-analysis involving seven studies (Holland 2007, Lopez Cabezas 2006, Naunton 2003, Nazareth 2001, Olesen 2014, Vinluan 2015, Wu 2006)

showed that interventions had no significant effect on mortality (Analysis 1.10, RR 0.97, 95% CI 0.70 to 1.36). No individual study had a significant impact on mortality, with three appearing to favour the intervention, and four appearing to favour usual care. One study (Saez de la Fuente 2011) was excluded from the meta-analysis due to unclear participant numbers.

Adverse drug reactions (ADRs) were reported in six studies. Three *educational interventions* included a measure of ADRs; two had no significant effect (Hanlon 1996, Marusic 2013), while one (Willeboordse 2017) found that the percentage of solved medication-related problems was significantly higher in the intervention group (Regression coefficient 22.6 (95%CI 14.1–31.1), P < 0.001). One *behavioural intervention* (Murray 1993) was identified and had no significant impact on ADRs. Two *mixed educational and behavioural interventions* were identified – one had no significant impact (Chrischilles 2014) while the other (Lim 2004) found that total ADRs were higher at two months following an intervention involving education, medication review and regimen simplification (total 13 vs 6), but residual ADRs from baseline were lower (4/13 vs 4/8).

Physician visits were reported in four studies. Two studies (Al-Rashed 2002, Khdour 2009), both involving *mixed educational and behavioural interventions*, showed a significant reduction in number of unplanned physician visits. Two studies, one behavioural (Winland-Brown 2000) and one mixed (Nazareth 2001), showed no significant impact on number of physician visits.

Secondary outcome - condition-specific outcomes

Seven studies included a condition-specific outcome measure (Table 7). Meta-analysis was not possible due to variations in outcome measures.

Three studies involved educational interventions: Blalock 2010 reported no significant impact on the number of participants experiencing ≥1 fall; Bond 2007 found no significant impact on the number of a participants reaching health targets (total score for 8 targets, e.g. physical activity, diet and weight); but Nascimento 2016 achieved significant reduction in fasting blood glucose and HbA1c levels among intervention participants when compared to usual care.

No studies were identified that involved only behavioural interventions.

Four studies involved mixed interventions. Two studies involving multidisciplinary (Cohen 2011) or pharmacist (Taylor 2003) education in a medical clinic with follow-up had significantly higher numbers of people reaching goal levels for blood pressure, HbA1c, and LDL cholesterol). Two additional studies (Lee 2006, Williams 2012) measured multiple health targets; although the results were in favour of the intervention they were not statistically significant.

Secondary outcome – cost-effectiveness

Four studies, one educational (Bond 2007) and three mixed (Bernsten 2001, Lipton 1994, Lopez Cabezas 2006) interventions, included a measure of cost-effectiveness (see Table 8). Three studies showed the intervention resulted in a reduction in mean/median costs per patient. These involved pharmacist medication review conducted as a one-off (Bond 2007) or with repeated/continuous follow-up for 18 months, either in the pharmacy (Bernsten 2001) or in hospital with home follow-ups (Lopez Cabezas 2006). One study (Lipton 1994) which involved one-off face-to-face medication review and education in hospital with telephone follow-up post discharge for 3 months showed that intervention patients had higher Medicare

Part B Charges and total hospital inpatient charges as measured at six months compared to usual care patients.

Secondary outcome - other

Four studies included other outcome measures potentially related to measures of medication-taking ability.

One study (Moral 2015), involving a behavioural intervention of motivational interviewing and follow-up by physicians and nurses, found that the average number of medication errors was significantly lower in the intervention group compared to the usual care group (0.429 vs 1.145, p=0.047).

Three studies involving mixed interventions showed that the number of medication management problems (Chrischilles 2014), the presence of medication errors and problems (Lingler 2016) and the number of participants with at least one medication misadventure (Taylor 2003) did not differ between the intervention and usual care groups.

COMPARISON 2: Intervention versus intervention

Six studies involved a comparison between interventions as part of a three-arm RCT design (Begley 1997, Cargill 1992, Marek 2013, Murray 1993, Olesen 2014, Winland-Brown 2000).

Primary outcome - medication-taking ability

Two studies included measures of medication-taking ability. One study (Begley 1997) involving pharmacist home interview with counselling (intervention) or without counselling (modified usual care) reported no significant difference in dexterity between groups at 12 months (data were not reported). One study (Cargill 1992) involving a 20 minute nurse teaching session and review of medications with or without additional follow-up telephone calls reported no significant difference in medication-taking behaviour at 4-6 weeks (score out of 100 read from graph: mean 84 vs 86).

Primary outcome - adherence

Six studies involved a measure of medication adherence. In Begley 1997, pharmacist home interview with counselling had greater impact on pill-count adherence than home interview alone (mean ± SD percentage 89 ± 19 vs 75 ± 21). In Cargill 1992, there was no difference in pill count adherence between the nurse teaching session group and the group which received nurse teaching with additional telephone follow-ups (mean 74% vs 76%). In Marek 2013, pill-count adherence was similar across both the medication dispensing machine and simple medication boxes groups (98.8% vs 97.4%). In Murray 1993, pill count adherence was higher in the group that received regimen simplification and unit-of-dose medication packaging compared to regimen simplification alone (92.6% vs 82.6%; p=0.02). In Winland-Brown 2000, nurse filled pillboxes were associated with higher number of missed pills as measured via pill count than the automated dispenser with audible adherence reminders (mean 15.1 vs 1.7; p<0.001, however time interval is unclear). In Olesen 2014, adherence was measured using different methods in different groups and thus not comparable.

Secondary outcome - medication knowledge

One study (Begley 1997) involving pharmacist home interview with counselling (intervention) or without counselling (modified usual care) reported no significant difference in medication knowledge between groups at 12 months (mean 70% vs 68%), as measured by comparing patient answers to hospital discharge and GP instructions regarding medication name, purpose, dose, dosage frequency and side effects.

Secondary outcome - satisfaction

None of the studies identified assessed consumer satisfaction.

Secondary outcome - HRQoL

One study (Marek 2013) compared a medication dispensing machine with audio and visual prompts for adherence with nurse filled simple weekly medication boxes. There was no significant difference in improvement in participant physical or mental summary scores between the two groups as measured using SF-36 (mean (95%CI): physical: 0.095 (-0.450, 0.640), mental: 0.241 (-0.459, 0.940)).

Secondary outcome - Adverse clinical health outcomes effects

Three studies reported measures of adverse clinical health outcomes. In Winland-Brown 2000, hospitalisations (4/16 vs 3/24 patients) and mean number of physician visits (1.5/month vs 1/month) were higher in the weekly pre-filled pill box group compared to the automated dispenser with audible reminders. In Murray 1993, both the intervention and modified usual care group (regimen simplification without unit-of-use medication packages) had similar numbers of self-reported side effects over six month follow-up (1/9 vs 2/12). Authors of Olesen 2014 were contacted who reported that data on unplanned admissions and mortality were not collected for the electronic reminder device group.

Secondary outcome - Condition specific outcomes

No studies identified.

Secondary outcome – cost-effectiveness

No studies identified.

Discussion

Summary of main results

Our systematic review identified a range of simple to complex interventions for improving medication-taking ability and medication adherence in older adults prescribed multiple medications.

Our overall findings suggest that mixed educational and behavioural interventions may improve the proportion of people who are adherent to their prescribed medications, but may have little or no impact on adherence when measured as a continuous variable. However, these results must be interpreted with a degree of caution, recognising the variations in intervention design, duration, follow-up and risk of bias of included studies. We were unable to determine the impact of mixed interventions on medication-taking ability due to the small number of eligible studies, and large variations in design and quality of those studies. No studies involving educational only or behavioural only interventions for improving medication-taking ability were identified, and the quality of evidence for educational only or behavioural only interventions for improving medication adherence was very low.

Within mixed interventions for improving medication adherence, several important findings were identified. Firstly, sub-group analyses based on health professional(s) providing the intervention found that pharmacist-led interventions were more effective than those delivered by nurses or multi-disciplinary teams of two or more health professionals. Secondly, each of the individual studies that had a significant impact on medication adherence (11 out of 27 studies) were delivered at the hospital-community/primary care interface (e.g. in hospital, at discharge, post-discharge or at outpatient clinics). Thirdly, meta-analyses found that studies using dichotomous rather than continuous adherence measures, subjective rather than objective adherence measures and those interventions with duration 3 months or less were more effective. These findings may inform design of interventions in future research, and reinforce the need to have more robust research using objective, continuous measures of adherence are required.

A number of secondary outcomes were evaluated, but the results were mixed and heterogeneity and concerns regarding risk of bias limited our ability to draw firm conclusions. Large variations in outcome measures limited our ability to pool results for meta-analyses for most of the secondary outcomes such as medication knowledge and intervention satisfaction. There were a limited number of studies that measured condition-specific outcomes (7 studies), ADRs (6 studies) and cost-effectiveness of interventions (4 studies). There was some evidence to suggest that mixed interventions may reduce the number of ED/hospital admissions and may improve patient knowledge regarding their medication, however further high quality studies are required to confirm this finding.

Overall completeness and applicability of evidence

Most of the studies in this review are relatively new, with almost half (24/50) being published since 2010. This trend most likely reflects the increasing prevalence of multiple medication use in older adults and the global efforts to improve medication adherence. In contrast, three of the five interventions evaluating medication-taking ability were published last century.

Studies were identified from four continents. The majority of studies were from high-income countries, with the greatest proportions emanating from the USA (21), UK (8) and Canada (5). The results of this review may be more applicable to older adults residing in developed countries, mostly Western countries, with only two studies identified in non-Western countries (1 each from China and Singapore).

Reporting of medication use was generally poor and inconsistent. This may have resulted in exclusion of potentially eligible studies where authors did not collect and/or clearly report the number of medications the participants were taking. There were also variations in the types of medications reported across studies, with some only reporting prescription medication, some only reporting regular medication and some reporting all medications (e.g. regular, when required, prescription and non-prescription medications). It was also unclear at times whether the interventions targeted all medications taken by participants, and whether assessment of medication-taking ability or medication adherence applied to all medications or only a subset. There is a need for clearer reporting of medication use in intervention studies targeting medication-taking ability or medication adherence. Similarly, there needs to be clearer reporting of factors that may affect medication-taking ability and medication adherence, including co-morbidities, quality of life, frailty, and functional and cognitive impairment.

There were a limited number of studies that evaluated adverse clinical health outcomes. Adverse clinical health outcomes should be measured for any intervention that may result in changes in a person's medication intake, including any changes (decrease or increase) in medication adherence. ED and hospital admissions were reported in 23 studies, however it was often unclear how many were unplanned admissions and/or medication-related admissions. Only six studies reported the number of participants experiencing ADRs and four studies reported the number of primary care physician visits, the most likely surrogate for minor to moderate medication-related problems.

Studies that evaluated the cost-effectiveness of interventions to improve medication-taking ability or medication adherence were scarce. Future studies should include appropriate measures of cost-effectiveness of interventions to assist decision makers in allocating health care resources efficiently.

Quality of the evidence

We evaluated the certainty of the body of evidence using the GRADE approach for the two primary outcomes – medication-taking ability and medication adherence, and three key secondary health outcomes – HRQoL, ED/hospital admissions and mortality. Overall there were serious concerns relating to risk of bias and inconsistencies resulting in low or very low quality evidence for all outcomes except for the effect of educational interventions on HRQoL and ED/hospital admissions which was considered moderate quality.

Most studies had unclear or high risk of bias across multiple domains, particularly relating to random sequence generation and allocation concealment. Nearly all studies (98%) also had high risk of performance bias, but we acknowledge that double blinding (of participants and clinicians) is often impossible in pragmatic health services research. More than half of the included studies also had unclear or high risk of detection bias, attrition bias and/or reporting bias. Studies were commonly given an 'unclear' risk of bias rating due to poorly described methods or results. Thus future studies should strongly consider prospective registration, publication of study protocol with detailed methodology and description of outcome measures, and be conducted and reported more rigorously.

Serious concerns relating to inconsistencies were identified due to the heterogeneous and complex nature of the interventions (components, provider, setting, duration) and variations in outcome measures. While interventions were broadly grouped as educational, behavioural or mixed interventions, the high heterogeneity was still evident in the meta-analyses and limited the internal validity of our results.

Concerns relating to imprecision were also present for behavioural interventions where there were often low participant numbers, low event rates and/or wide confidence intervals.

Potential biases in the review process

Differing terminologies for medication-taking ability and medication adherence may have limited the number of studies found, despite us using broad search terms and searching the grey literature and reference lists of included studies. As mentioned previously, poor reporting of medication use may also have resulted in us missing potentially eligible studies.

Agreements and disagreements with other studies or reviews

Our review is the first to evaluate interventions for improving medication-taking ability in older adults prescribed multiple medication. Reviews of instruments to assess medication-taking ability (Elliott 2009) and self-efficacy for medication management (Lamarche 2018) have been published, but no reviews of interventions utilising these instruments have been published to date.

There have been several reviews investigating medication adherence, however only four reviews to date have evaluated interventions for improving medication adherence in older people taking multiple medications. Two of these reviews were conducted over a decade ago (George 2008, Williams 2008), and two have been published more recently – one focusing on theory-based interventions (Patton 2017) and the other included both cross-sectional analyses of prevalence of medication adherence and clinical trials/systematic reviews of interventions targeting adherence (Zelko 2016). Our findings are consistent with these reviews as all four concluded that high quality evidence is scarce, and that inconsistencies in methodology, interventions and outcome measures have made it difficult to draw any firm conclusions regarding the most effective interventions for improving medication adherence.

Our concerns regarding risk of bias of included studies were also consistent with a previous Cochrane systematic review investigating interventions for enhancing medication adherence (Nieuwlaat 2014). Nieuwlaat et al. evaluated all RCTs of interventions to improve adherence with prescribed medications (i.e. not restricted to older adults or multiple medications), and found that only 17 of 182 included studies had the lowest risk of bias for study design features and their primary clinical outcome.

Authors' conclusions

Implications for practice

Our review highlights a significant gap in the literature regarding high quality evidence on interventions for improving medication-taking ability and medication adherence in older adults prescribed multiple medications. Low quality evidence suggests that healthcare providers should consider a combination of educational and behavioural strategies, tailored to their patient's need, to optimise medication use. Healthcare providers and policy makers may also consider that our findings suggest that pharmacist-led interventions, particularly those initiated at the hospital-community interface (e.g. at transitions of care), have the greatest impact on medication adherence, however further evidence confirming clinical benefits and cost-effectiveness are required.

Implications for research

There is a need for further well-designed RCTs to investigate the effects of interventions for improving medication medication-taking ability and medication adherence in older adults prescribed multiple medications. Priority should be given to adequately powered trials using validated, objective measures of medication-taking ability and medication adherence. The effect of interventions on clinical outcomes and cost-effectiveness should also be evaluated.

Researchers should strongly consider prospective trial registration and publication of protocols using standard reporting checklists such as the Standard Protocol Items: Recommendations for Interventional Trials (An-Wen 2013). This will help to ensure clearer and more consistent reporting of outcome variables and participant characteristics that may impact medication-taking ability and medication adherence.

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Contributions of authors

- Writing of protocol and review: AC, RE, JG
- Screening of titles and abstracts: AC, RE, KP, LK, JG
- Assessment of studies for inclusion: AC, RE, KP, LK, JG
- Quality assessment: AC, RE, KP, LK, JG
- Data extraction: AC, RE, KP, LK, JG
- Data entry into RevMan: AC
- Data analysis: AC in consultation with RE and JG
- Disagreement resolution: AC, RE, JG

Declarations of interest

Amanda J Cross: None declared.

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Review authors may also have been authors of studies eligible for inclusion in this review. To avoid bias, selection of such studies were performed by other independent members of the review team.

Differences between protocol and review

The Medline search strategy was updated by John Kis-Rigo, the information specialist with the Cochrane Consumers and Communication Group after the protocol was published but prior to the database search being run. The updated search strategy contained additional terms to minimise potential for missed studies.

Interventions were grouped as educational, behavioural or mixed which was not specified in our protocol. We felt this grouping was necessary to help describe and understand the large number of heterogenous studies, and this grouping had been used in a previous systematic review of interventions to improve medication adherence (George 2008).

Risk factor(s) for poor medication-taking ability and/or medication adherence targeted by the intervention(s) were not extracted. This information was, in general, poorly reported within the included studies as medication-taking ability and/or medication adherence was not always the primary outcome of the included studies. We attempted to extract potential participant factors that may affect medication use (e.g. number of medications used, frailty, cognitive impairment and number of co-morbidities), however even this was limited by poor reporting in the included studies. Analysis of specific risk factors targeted by interventions should be considered in future updates of this review where further high-quality studies are identified.

Characteristics of studies

Characteristics of included studies

Al-Rashed 2002

Methods	Aim of study: 1. To evaluate if pharmaceutical counselling pre-discharge from hospital (in combination with a medication and information discharge summary (MIDS) and a medicine reminder card) can improve a patient's therapeutic management post-discharge and reduce unnecessary visits to their doctor or hospital readmission. 2. To investigate if a pharmaceutical domiciliary visit can reinforce in-patient counselling. Study Design: RCT (2 inpatient wards: 1 intervention, 1 control) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: UK Setting: Hospital discharge Inclusion criteria: >65 years, prescribed 4 or more regular items, discharged to own home, abbreviated mental score >7 (/10), first language English, assessed by pharmacist as at risk of problems with their medicines when discharged home. Number of participants randomized: 89 (45 intervention, 44 control) Number of participants included in analysis: 83 (43 intervention, 40 control) Age: Mean (SD): 80.2 (5.7) years intervention, 81.1 (5.8) years control Gender: female: 36% (n=16) intervention, 45% (n=20) control Ethnicity: Not specified Number of medications: Regular medications at discharge mean (SD): 7.1 (1.8) intervention, 7.1 (2.3) control Frailty/functional impairment: Not specified Cognitive impairment: All participants had abbreviated mental score>7/10 Co-morbidities: Not specified
Interventions	Group 1: *Pharmaceutical counselling pre-discharge:* Approximately 30min pre-discharge counselling by clinical ward pharmacist, including indication, side-effects, doses, dosage times and importance of compliance. Counselling conducted using medicine reminder card Group 2: *Usual care:* Nurse went through discharge medication at point of discharge. Co-intervention: Both groups received MIDS and medicine reminder card and 14 days of medication. All patients received home visit by pharmacists at 15-22 days and were questioned on medication use. Any incorrect information provided to participants was corrected. Provider: Pharmacist (hospital) Where: Hospital (inpatient ward) When & how often: Intervention provided once, within 24 hours of discharge

	Intervention personalised: Yes
Outcomes	Timing of outcome assessment: 3 months post-discharge *Medication adherence (objective)*: percentage of total medications to which participants are compliant (compliance considered 85-115%), using home medicines stock and refill prescriptions. *Knowledge about medicines (objective)*: percentage of correct answers on a pharmacist delivered questionnaire (drug use, dose, dosage interval) *Adverse clinical health outcomes (objective)*: number of general practitioner visits and hospital readmissions
Notes	Trial registration: NA Consumer involvement: Not specified Funding source: Not specified Drop-out: Prior to first visit: Intervention = 2 (1 died, 1 withdrew), Control = 4 (2 died, 1 nursing home, 1 withdrew)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Of the two care of the elderly wards one was randomly chosen for the study group patients and the other for the control group patients. Unclear how this was chosen.
Allocation concealment (selection bias)	Unclear risk	Unclear how patients were allocated to wards and if this was affected by study
Blinding of participants and personnel (performance bias)	High risk	Participants and research staff unblinded
Blinding of outcome assessment (detection bias)	High risk	Research pharmacist not blinded
Incomplete outcome data (attrition bias)	Unclear risk	Excluded/declined patients not reported, 6/89 attrition (6.7%)
Selective reporting (reporting bias)	Low risk	Outcomes listed in methods reported
Other bias	Low risk	None apparent

Begley 1997

Methods	Aim of study: To evaluate the influence of domiciliary pharmacist visits on medication management in a sample of elderly people recently discharged from hospital to their own homes. Study Design: RCT (3 hospitals, unit of allocation: individual) Number of arms/groups: 3
Participants	Description: patient/consumer Geographic location: UK Setting: Community (post discharge)

	Inclusion criteria: ≥75 yrs, ≥3 prescribed drugs, ≥2 doses/day, under care of participating consultant, consented to participate, discharge to own home Number of participants randomized: 222 (A;75, B:75, C: 73) Number of participants included in analysis: 190 (A: 61, B: 63, C: 66) Age: Median (Range) = A: 84 (75-94), B: 81 (75-96), C: 82 (76-92) Gender: Female A: 61%, B: 65%, C: 56% Ethnicity: Not specified Number of medications: Mean (SD) prescribed: A: 4.6 (1.8), B: 4.8 (1.6), C: 5.5 (1.9), Mean (SD) OTC: A:2.6 (0.7), B: 4.1 (1.4), C: 2.2 (1.8) Frailty/functional impairment: Not specified Cognitive impairment: Abbreviated mental test mean (SD): A: 8.4 (1.5), B; 8.8 (1.1), C: 7.9 (1.3) Co-morbidities: Not specified
Interventions	Group 1: *Domiciliary pharmacy medication management visit:* Interview consisted of six sections: patient information, drug knowledge, patient dexterity, abbreviated mental test, medication management, compliance. Following interview, intervention group (A) received structured counselling on correct use, storage and compliance (including simplifying regimen, emphasising importance of compliance, positive reinforcement). Group 2: *Group (B)*: control, with home interview but no counselling. Group 3: *Group (C)*: control with no home visit (i.e. usual care). Co-Intervention: N/A Provider: Pharmacist (investigator) Where: Home (post-discharge) When & how often: Home visits for A & B occurred at baseline, 2 weeks, 1 month, 3 months and 12 months Intervention personalised: Yes - counselling tailored to needs of patient
Outcomes	Timing of outcome assessment: 12 months *Medication adherence (objective):* percentage of medications to which participant is compliant using pill count. Researcher counted remaining number of tablets and measured volume of liquid. To improve reliability and accuracy, patients were asked to retain all used medicine containers for removal by the investigator. *Medication taking ability (objective):* dexterity medication management. 5 task dexterity test (e.g. opening child resistant closure) *Medication taking ability (subjective):* hoarding and storage. Percentage of correct answers when patients questioned about medicines in their home that they no longer take and storage of medicines. *Knowledge about medicines (subjective):* drug knowledge. Percentage of correct answers. Patients asked about name, purpose,

		dose, dosage frequency and side effects. Accuracy compared to hospital discharge or GP instructions.
Notes		Trial registration: N/A Consumer involvement: Not specified Funding source: Not specified Drop-out: 4 withdrew (refused), 28 lost to follow-up (7 death, 7 hospitalised, 10 nursing home, 4 moved out of area)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Recruitment staff blinded to identity of groups, allocated patients consecutively to group A, B or C. No random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Allocated sequentially by blinded recruiter
Blinding of participants and personnel (performance bias)	High risk	Unable to blind participants, patients knew what they were getting (respondent bias)
Blinding of outcome assessment (detection bias)	High risk	Intervention delivered by same pharmacist taking outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	Lost to follow-up, only reported completed patients, rates seem similar across groups but breakdown of reasons not available for each group
Selective reporting (reporting bias)	High risk	Some outcomes not reported at follow-up (e.g. dexterity) and some only in visual format making them difficult to assess (hoarding/storage). Unclear if results for adherence are patient reported or pill count, only gives 'difference' not raw scores of both
Other bias	Low risk	Required sample size achieved (61 per group)

Bernsten 2001

Methods	Aim of study: To investigate the impact of a coordinated community pharmacy-based pharmaceutical care programme for elderly patients on a range of health and economic outcomes. Study Design: Cluster-RCT with repeated measures (unit of allocation: pharmacy) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: 7 European Countries (Denmark, Germany, The Netherlands, Northern Ireland, Portugal, Republic of Ireland and Sweden). *Sturgess 2003 paper describes subgroup of Ireland data only.*

	Setting: Community pharmacy Inclusion criteria: ≥65yrs, ≥4 prescribed medications, orientated with respect to self, time and place, community dwelling and regular visitors to a recruited pharmacy. Exclusion criteria: housebound, resident in a nursing/residential home. Number of participants randomized: Intervention: 104 pharmacies, 1290 patients, Control: 86 pharmacies, 1164 patients, *Ireland subgroup: 191 patients (110 vs 81)* Number of participants included in analysis: 18 months: 1340 (704 intervention, 636 control), *Ireland subgroup: 110 patients (75 & 35)* Age: Median (IQR): I: 74(8), C: 74 (8), *Ireland subgroup:* mean ± SD 73.1 ± 5.0 vs 74.2 ± 6.3 Gender: female: 57.9% intervention, 57.3% control, *Ireland subgroup:* female 63.6% vs 61.0% Ethnicity: Not specified Number of medications: prescribed medications mean ± SD: intervention: 7.1 ± 2.5, control: 7.0 ± 2.5, *Ireland subgroup:* 5.87 ± 1.86 vs 6.66 ± 1.99 Frailty/functional impairment: Not specified Cognitive impairment: Not specified Co-morbidities: Not specified
Interventions	Group 1: *Structured community pharmaceutical care:* Intervention pharmacists attended ≥1 study day, and a study manual. Pharmacists assessed participants to identify actual and potential DRPs (e.g. poor compliance, poor knowledge, ADRs, interactions, sub-optimal) using a structured approach. Pharmacists then formulated an intervention (education, implementing compliance strategies, simplification, etc) and monitoring plan per patient. Group 2: *Usual care:* control pharmacist provided normal services Co-Intervention: N/A Provider: Pharmacist (community) Where: Community pharmacy When & how often: Assessment and intervention was a continuous process throughout the 18 months. Intervention personalised: Personalised intervention and monitoring plan
Outcomes	Timing of outcome assessment: 18 months *Medication adherence (subjective): Percent self-reported compliant.* Self-completed questionnaire using 4 item, 4 point Likert scale (forgetting doses, choosing not to take a dose because feeling well, choosing not to take a dose because of perceived non-benefit and choosing to take more of a medicine than prescribed because of feeling the need for it) - based on previously validated Morisky scale. Patients compliant if never experienced any aspects of non-compliance. *Medication adherence(objective): Ireland subgroup only: Refill compliance*: Refill compliance rates calculated from patient medication records, percentage of patients compliant

	Knowledge about medicines (objective): Percentage correct knowledge. Interview-based questionnaire calculating % correctness (looking at 4 areas: indication, number of dosage units taken per dose, number of doses per day and awareness of potential adverse effects). Higher scores = better knowledge *Satisfaction with intervention (subjective):* Self-reported using investigator administered questionnaire - Satisfaction with services and general opinion of pharmaceutical care. % who agree/mainly agree *Health-related quality of life (subjective):* SF-36 (validated) - 8 dimensions. *Adverse clinical health outcomes (subjective):* One or more hospitalisations in past 18 months, Self-reported using investigator administered questionnaire. *Cost-effectiveness (objective):* health care related resource usage. Direct costs of the study including: additional time spent by pharmacists; contacts with GPs, specialists and nurses; and costs of hospitalisation and medications.
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: European Commission (BIOMED 2) funded coordination of RCT (+ lots of others for financial/logistic support), *Ireland subgroup:* Northern Pharmacies Trust, Northern Ireland and European Commission Drop-out: at 18 months: 1114 (45%) patients (586 intervention, 528 control) due to unwillingness, illness, moving away, pharmacy withdrawal and death. *Ireland subgroup:* withdrew: 41 (15 & 26), illness: 2 (1 & 1), pharmacy withdrew: 30 (15 & 15), patient death: 8 (4 & 4) *ICC value unclear, authors contacted for further information but no response. Thus unit-of-analysis error exists.*

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Pharmacies assigned as control or intervention, "where possible control and intervention sites were matched as closely as possible" - limited details Sturgess 2003: Restricted randomisation technique to match community pharmacies in similar pairs. Half participating pharmacies then randomly assigned as intervention sites, other half as control sites. No details on randomisation technique
Allocation concealment (selection bias)	High risk	Pharmacies randomised, participants attended their normal pharmacy. Unclear whether allocation was concealed from pharmacies until after randomisation.

Blinding of participants and personnel (performance bias)	High risk	Unable to blind, patients and pharmacies aware. Non-blinding may have influenced service delivery by the pharmacists
Blinding of outcome assessment (detection bias)	Unclear risk	Data collection interviews were performed, where possible, by a member of staff other than the pharmacist (e.g. pharmacy assistant). Suspect staff would still be aware of allocation.
Incomplete outcome data (attrition bias)	High risk	Two countries did not complete 18 month follow-up (stopped at 6 months), one country conducted 18 month follow up at 24months. High withdrawal and those that withdrew were older and had poorer QoL. Sturgess 2003: Large attrition - 191 Baseline, 147 at six months, 119 at 12 months, 110 at 18 months
Selective reporting (reporting bias)	Unclear risk	Reported as per methods. However methods didn't discuss how to deal with large attrition.
Other bias	Unclear risk	Target sample size was 480 per country - not reached. Large variance in follow-up. Recruitment bias (selective recruitment of cluster participants): Unclear whether allocation was concealed from pharmacies until after recruitment. Potential for risk of bias as patients with good relationship with pharmacists and knowledge of intervention may have preferentially joined the study

Blalock 2010

Methods	Aim of study: To assess the effects of a community pharmacy-based falls-prevention program targeting high-risk older adults on the rates of recurrent falls, recurrent injurious falls, and filling prescriptions for medications that have been associated with an increased risk of falls. Study Design: RCT (1yr look back, and 1 yr follow-up after RCT, unit of allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: Community pharmacy Inclusion criteria: Those at high risk of falling ($\geq$ 65 years, $\geq$1 fall not attributable to syncope within the 1 year preceding, $\geq$4 chronic prescription medications, $\geq$1 CNS-active medication). Exclusion criteria: housebound, in long-term care facility, not able to read and write in English, or exhibited significant cognitive impairment Number of participants randomized: 186 (93 intervention/93 control) Number of participants included in analysis: 93 & 93 (ITT), 73 & 113 (as treated) Age: Mean (SD): I 75.5 (7.0) vs C: 74.1 (6.8)

	Gender: Female: 78.5% intervention vs 65.4% control Ethnicity: White: 91.4% intervention vs 86.0% control Number of medications: unclear (inclusion criteria ≥4 chronic prescription) Frailty/functional impairment: Use of cane or walker: 37 (39.8%) vs 43 (46.2%) (p-0.37) Cognitive impairment: not specified Co-morbidities: High risk conditions (dizziness, diabetes, incontinence, arthritis, Parkinson, stroke): Mean (SD): 1.65 ±1.19 intervention vs 1.58±1.06 control
Interventions	Group 1: *Enhanced pharmacologic care.* Invitation to participate in free, face-to-face medication consultation (~45min) with community pharmacy resident. Pharmacist reviewed medications and identified potential problems (emphasis on CNS-active medications) using structured algorithms. If problem identified and patient interested in making change, pharmacist contacted physician to seek prescriber approval of the recommended changes. Group 2: *Usual care:* no medication consultation Co-Intervention: Both groups received 2 brochures on prevention of falls Provider: Pharmacist (community) Where: Local health care centre When & how often: once Intervention personalised: Yes personalised medication review
Outcomes	Timing of outcome assessment: Baseline and 12 months *Medication adherence (subjective): BMQ (validated),* 5-item regimen screen that assesses how medication is used *Condition specific outcomes (subjective):* One or more falls. calculated using Monthly fall calendar, patients recorded each fall "a sudden, accidental change in position where you land on the ground, floor, or an object"
Notes	Trial registration: NA Consumer involvement: Not specified Funding source: National Center for Injury Prevention and Control at the Centers for Disease Control and Prevention. Drop-out: 20 didn't receive intervention, 27 dropped out (17 vs 10), 9 unable to contact (6 vs 3), 5 died (3 vs 2) *Further information required*: BMQ results (email correspondence with author - unsuccessful)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized to either intervention or control - unclear how

Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Unable to blind, patients knew if they had the intervention
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of blinding
Incomplete outcome data (attrition bias)	Unclear risk	ITT, although no BMQ data so difficult to assess if/how ITT was done
Selective reporting (reporting bias)	High risk	"BMQ was readministered at 4 monthly intervals, ending 12 months after the baseline assessment" - results not listed. However BMQ listed as a data source not outcome in methods.
Other bias	Unclear risk	Initial sample size was 262, "interim power analyses were conducted when it became apparent that it would be difficult to reach target sample size." Sample size changed to 95 per group. Sample size based on falls risk

Bond 2007

Methods	Aim of study: To test the hypothesis that a comprehensive MEDMAN service would i) increase the proportion of patients receiving treatment according to the National Service Framework in England and Wales; ii) improve overall patient health status, and iii) be cost effective Study Design: RCT (pharmacy/GP, unit of allocation: individual) Number of arms/groups: 2
Participants	Description: Patient/consumer Geographic location: UK Setting: Community Pharmacy (+ primary care (GP)) Inclusion criteria: Patients registered with GP, >17 years, and with CHD (previous MI, angina, CABG and/or angioplasty). Pharmacies: only pharmacies with private consultation area were eligible to participate. Exclusion criteria: illiterate/innumerate, history of alcohol/drug misuse, terminal/serious illness, severe mental illness and unable to provide informed consent or otherwise unsuitable for the trial as determined by GP. Number of participants randomized: 1493 (I: 980, C: 513) Number of participants included in analysis: Questionnaires analysed: 712 vs 373, clinical records analysed: 868 vs 466 Age: mean ± SD intervention 68.7 ± 9.2 vs control 68.8 ± 9.1 Gender: F: 307 (32.6%) vs 147 (29.4%) Ethnicity: Not specified

	Number of medications: Prescribed medications median (IQR) of 738 intervention: 7 (5-10) Frailty/functional impairment: Not specified Cognitive impairment: Not specified Co-morbidities: Not specified
Interventions	Group 1: *Community Pharmacy Medicines Management (MEDMAN):* patients received a study registration card and letter asking them to visit their nominated pharmacy to initiate service. Initial consultation informed by the extracted medical data supplied by the researchers. Further consultations provided according to pharmacist-determined patient need. Consultations included assessments of the following: therapy, medication compliance, lifestyle (e.g. smoking, exercise, diet) and social support (e.g. difficulties collecting prescriptions and opening bottles). Recommendations were recorded on a referral form which was sent to the GP, who returned annotated copies to the pharmacists. Group 2: *Usual care* from GP & community pharmacy Co-Intervention: N/A Provider: Pharmacist (community) Where: Community pharmacy When & how often: Initial consultation then as pharmacist-determined need Intervention personalised: Yes - assessment of therapy, compliance, lifestyle, social - and further consultations as needed
Outcomes	Timing of outcome assessment: Baseline and 12 months *Medication adherence (subjective):* 12 statements about medicine taking were summated to derive self-reported compliance score (range 12-60). 12-item scale extended scope of MARS questionnaire, introduced a time dimension and rephrased some questions to make them more patient friendly. *Knowledge about medicines (subjective):* Patients were asked whether they "knew more about their medicines compared with a year ago" on five point Likert scale. Dichotomous, those that said agree/strongly agree. *Satisfaction with intervention (subjective):* Responses to 15 positive and negative statements regarding their most recent pharmacy visit. Overall score 15-75 (higher better) *Health-related quality of life (subjective):* SF-36 and EuroQoL-5D *Condition specific outcomes (objective):* Patients reaching CHD targets. Total score for patients reaching 8 targets (aspirin, lipid, BP, smoking, alcohol, physical activity, diet and BMI). *Cost-effectiveness (objective): H*ealth economics analysis. Total NHS-related study cost: NHS resource use based on information extracted from GP-held records at baseline and follow-up. NHS costs included cost of intervention and other treatment (e.g. medicines, hospital, other health consultations)
Notes	Trial registration: N/A Consumer involvement: Not specified

	Funding source: Department of Health for England and Wales, managed by National Pharmaceutical Association, the Royal Pharmaceutical Society of Great Britain, the Company Chemist Association and the Co-operative Pharmacy Technical Panel, led by PSNC Drop-out: prior to intervention: 3 died, 49 withdrew (total 52, 39 vs 13), post intervention: 38 vs 9 withdrew, 20 vs 19 died *Unpublished data included:* Full trial report provided by authors.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomized 2:1 (Intervention:Usual care) independently of research team using a password protected computer programme in permuted blocks stratified by practice
Allocation concealment (selection bias)	Low risk	Patients consented prior to randomization and randomization done independent of research team
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind participants or staff of intervention. Pharmacies not told which control patients had nominated their pharmacy.
Blinding of outcome assessment (detection bias)	Low risk	Audit clerks and researchers conducting statistical analyses were blinded to patient randomization. Self-reported data collected by postal questionnaire.
Incomplete outcome data (attrition bias)	Low risk	81% & 79% of questionnaires analysed. Intention to treat but patients with missing data excluded. Potential selection bias resulting from loss to follow-up or missing data was tested, and adjusted for, using the Heckman selection correction. Where evidence of selection bias was found, the unbiased effect of the intervention is reported. 98 & 99% of clinical record forms analysed
Selective reporting (reporting bias)	Unclear risk	Krska paper not as per protocol
Other bias	Unclear risk	Didn't reach required sample size, Sample size calculation: 1920 (1280 vs 640)

Cargill 1992

Methods	Aim of study: To provide information on identification of patients at highest risk for problems related to medication non-compliance and behaviours problematic in the home setting, and their response to teaching interventions. To optimize elderly patients medication-taking compliance by strengthening the home medication administration system. To reinforce the nursing role as facilitator of maximum health status.

	Study Design: RCT (unit of allocation: individual) Number of arms/groups: 3
Participants	Description: both patient/consumer and carer Geographic location: USA Setting: Outpatient clinic (general medicine servicing Veteran's Administration) Inclusion criteria: ≥60 years, metropolitan area accessible to home visits. Number of participants randomized: 70 Number of participants included in analysis: 70 Age: Range: 62-97years, Mean: 72 Gender: Not specified Ethnicity: Not specified Number of medications: Prescription, non-topical, non-inhalant, non-liquid: Mean: 7.5 Frailty/functional impairment: Not specified Cognitive impairment: Not specified Co-morbidities: Not specified
Interventions	Group 2: *Nurse teaching session:* 20 minute teaching session, including review of medications timed to patient's schedule and any allowed flexibility. A pill cassette was dispensed if feasible for the patient; Group 3: *Nurse teaching session and follow up phone call:* 20 minute teaching session (as above) plus additional follow-up telephone call 1-2 weeks after visit in which the nurse reviewed the medication regimen verbally with the patient Group 1: *Usual care* Co-Intervention: N/A Provider: Nurse Where: Home± phone call (group 3) When & how often: Once (+ follow-up at 1-2 weeks in group 3) Intervention personalised: Personalised review of medications was timed to patient's schedule, pill cassette dispensed if feasible
Outcomes	Timing of outcome assessment: baseline & 4-6 weeks *Medication adherence (objective):* Pill count percentage compliance. Percentage of pills taken vs those prescribed to be taken using pill count *Medication taking ability (objective):* Behaviour score /100 for congruency between supply of medications on hand and prescribed medications (/40), verbalising correct regimen (/30), maintaining each prescribed med (/20), appropriate use of OTC (/10). Points deducted for sequestering old scripts, inappropriate use of alternative meds, or mixing meds together.
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Not specified Drop-out: N/A

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	No mention of blinding, assume patients and nurses knew allocation in order to perform intervention
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of blinding
Incomplete outcome data (attrition bias)	Low risk	No attrition mentioned
Selective reporting (reporting bias)	Unclear risk	Raw data not reported, only in graph
Other bias	Low risk	None apparent

Chrischilles 2014

Methods	Aim of study: To examine the impact of a personal health record (PHR) on medication-use safety among older adults Study Design: RCT (Single-centre open-label parallel group study with unequal randomization (3:1), unit of allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: Patient's home (online) Inclusion criteria: Age 65+, used a computer in past month to visit websites or to send/receive email and responded to questionnaire Number of participants randomized: 1163 Number of participants included in analysis: 1075 (802 vs 273) Age: Mean ± SD 72.5 ± 6.0 vs 72.0 ± 6.3 Gender: Female: 461 (57.5%) vs 150 (54.9%) Ethnicity: Non-Hispanic white: 782 (99%) vs 267 (98.2%) Number of medications: Mean ± SD: Prescription: 4.1 ± 3.2 vs 4.2 ± 3.2, OTC: 4.1 ± 2.8 vs 4.3 ± 3.1 Frailty/functional impairment: Physical health (SF-12): 45.9 ± 10.6 vs 46.1 ± 10.3 Cognitive impairment: Memory problems: 80 (10%) vs 31 (11.4%) Co-morbidities: Medical conditions (from list of 19): 3.6 ± 2.3 vs 3.6 ± 2.2
Interventions	Group 1: *Personal Health Record (PHRs):* participants sent an invitation to use study PHR for a period of 1 year and a quick-start guide. Users can enter, view and print their current and past medicines, allergies, health conditions and health event tracking over time. PHR also had user-friendly medication safety messages based on the Assessing Care of Vulnerable Elders project

	(ALCOVE-3) medication use quality indicators. PHR displayed a message when a user entered a medication with an associated ALCOVE-3 safety concern (drug-drug interactions e.g. warfarin, dosage concerns e.g. acetaminophen, important lab monitoring e.g. loop diuretics, risk awareness e.g. NSAIDs & bleeding, drugs that should be avoided e.g. barbiturates). Three levels of increasing detail - brief alert, summary level and detailed explanation. Participants who didn't log in were sent a reminder letter 3-4 weeks after initial invitation. Group 2: *Usual care:* No access to study PHR Co-Intervention: N/A Provider: Online Where: Online (With baseline and follow-up questionnaires mailed) When & how often: Continuous for 1 yr at patients discretion Intervention personalised: Individual medication specific messages
Outcomes	Timing of outcome assessment: Baseline & 6 months *Medication adherence (Subjective): Modified Morisky self-reported adherence.* Answers never, rarely, sometimes, often or always (instead of the original yes/no). Mailed questionnaire. *Adverse clinical health outcomes (subjective):* Experienced medication side effects in past 3 months (yes/no - reported as percentage of participants experiencing side effects) *Other (subjective):* Medication management problems: Mean (SD) number of medication management problems. List of 8 problems: including questions on multiple prescribers, multiple pharmacies, mail-order prescriptions, confusion whether medication was taken, taking medication without knowing indication, problems affording medications, feeling that medications aren't working and feeling that medications aren't doing what they were intended to do.
Notes	Trial registration: NCT02012712 Consumer involvement: PHR was developed and refined using participatory design and focus group sessions with older adults as well as evaluation in a usability laboratory. Funding source: Agency for Healthcare Research and Quality grant and National Institutes of Health grant. Drop-out: 23 prior to intervention, 65 lost to follow-up Fidelity: 61.2% attempted to log on to PHR, 55.2% performed some activity with PHR. More than 40% entered at least one medication into PHR.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized in a 3:1 ratio using computerized random numbers. Groups comparable.

Allocation concealment (selection bias)	Low risk	Notification of study group assignment was sent by mail to all trial participants by an investigator with no clinical involvement in the trial.
Blinding of participants and personnel (performance bias)	High risk	Not blinded - participants knew allocation
Blinding of outcome assessment (detection bias)	Low risk	Mailed questionnaires and online results, no outcome assessors
Incomplete outcome data (attrition bias)	Low risk	1075 of 1163 included in analysis, ITT
Selective reporting (reporting bias)	Low risk	Reported as per methods
Other bias	High risk	61.2% attempted to log on to PHR, 55.2% performed some activity with PHR. More than 40% entered at least one medication. - so poor fidelity of intervention. Reimbursed for completing baseline and follow-up questionnaires.

Cohen 2011

Methods	Aim of study: To assess whether Veterans Affairs Multi-disciplinary Education and Diabetes Intervention for Cardiac risk reduction Extended for 6 months could improve attainment of target goals for hypertension, hyperglycaemia, hyperlipidaemia, and tobacco use in patients with type 2 diabetes compared to primary care after 6 months of intervention Study Design: RCT (1:1 randomisation, unit of allocation individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: medical centre (Veterans Affairs medical centre) Inclusion criteria: Veterans with type 2 diabetes HbA1c>7% and LDL-C >100mg/dl, coronary artery disease LDL>70mg/dl and BP >130/80 in previous 6 months. Exclusion criteria: Gestational diabetes, unable to attend group sessions, psychiatric instability or organic brain injury that precluded them from diabetes self-care Number of participants randomized: 103 Number of participants included in analysis: 99 (50 & 49) Age: Mean ± SD I: 69.8 ± 10.7, C: 67.2 ± 9.4 Gender: Female: 0% (n=0) vs 4% (n=2) Ethnicity: Not specified Number of medications: Total not available (added means = 4.20 vs 4.15). Hypertension meds = 2.02 ± 1.09 vs 1.86 vs 1.12, diabetes: 1.38 ± 0.81 vs 1.47 ± 0.82, Cholesterol: 0.80 ± 0.49 vs 0.82 vs 0.53 Frailty/functional impairment: Not specified

	Cognitive impairment: Not specified Co-morbidities: Heart failure: 16 vs 10.2%, Smoker 14 vs 8.2%, Stroke 4 vs 4.1%, Coronary heart disease: 48 vs 46.9%, COPD: 14 vs 20.4, mood disorder 14 vs 14.3%
Interventions	Group 1: *VA MEDIC-E:* 4 weekly group sessions followed by 5 monthly booster group sessions. Each 2 hr session included 1 hr multidisciplinary diabetes specific healthy lifestyle education and 1hr pharmacotherapeutic intervention performed by a clinical pharmacist (diabetes educator). Family/friends encouraged to participate. 90 minute booster sessions were less structured. Group 2: *Usual care* (clinic visits with primary care providers, averages once every 4 months) Co-Intervention: N/A Provider: Weekly Multidisciplinary (pharmacist, dietician, pharmacist/PT, nurse) + monthly booster clinical pharmacist Where: Medical centre room When & how often: 4 once-weekly + 5 monthly booster Intervention personalised: Sessions were group based - however pharmacist sessions were more informal and allowed for open discussion about each individuals risk factor control, obstacles, solutions.
Outcomes	Timing of outcome assessment: baseline and six months *Medication adherence (objective): Medication possession ratios:* total days supply of medication received divided by total number of expected medication intake days *Health-related quality of life (subjective):* Change in VR-36 (SF-36 for veterans) *Condition specific outcomes (objective):* Achievement of glycaemic & cardiac risk factor goals. Percentage of participants achieving SBP<130, LDL<100, A1c<7%
Notes	Trial registration: NCT00409240 Consumer involvement: Not specified Funding source: Sandra A. Daugherty Foundation Drop-out: 4 prior to intervention, 3 died *Further information required*: total number of medications and complete data regarding medication adherence. (email correspondence with author - successful, but authors had no further data available)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Assigned in a 1:1 ratio, no details on randomisation method
Allocation concealment (selection bias)	Unclear risk	No details on allocation specified

Blinding of participants and personnel (performance bias)	High risk	Unable to blind participants/personnel, assume intervention would impact behaviour
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of blinding
Incomplete outcome data (attrition bias)	Low risk	103 randomised, 99 included in analysis. 4 revoked consent (3 vs 1). 3.8% attrition
Selective reporting (reporting bias)	High risk	Raw data missing for adherence. MPR for total medications quoted but total number of medications not reported
Other bias	Low risk	None noted

Cossette 2015

Methods	Aim of study: To evaluate the effectiveness of an ED-based nursing intervention. To report the impact of an intervention on the secondary outcomes of perceived continuity of care, illness perceptions, self-care capacities, psychological symptoms and medication adherence. Study Design: RCT (unit of allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Canada Setting: Hospital discharge (Emergency department) Inclusion criteria: at risk of ED return because ≥ 1 ED visit in past year, ≥6 medications. Exclusion criteria: inability to speak French or English, cognitive problems (e.g. dementia), patients already receiving regular follow-up (e.g. at a specialised clinic in hospital). Number of participants randomized: 265 (132 vs 133) Number of participants included in analysis: 203 (108 vs 95) Age: mean ± SD: 67.06 ± 10.42 vs 67.33 ± 9.11 Gender: Female: 38.9% vs 48.4% Ethnicity: Not specified Number of medications: medications on arrival in ED: Mean (SD) 9.2 (2.79) vs 9.95 (3.47) Frailty/functional impairment: Not specified Cognitive impairment: Cognitive impairment (e.g. dementia) excluded Co-morbidities: Not specified
Interventions	Group 1: Nursing ED intervention: Three encounters: one a discharge, two telephone follow-ups at 2-4 days and 7-10 days post-discharge. Potential patient concerns assessed using a 19-item clinical disease management tool (worries about returning home, disease management, treatment management, ADL/iADL, emotions/cognition, informal resources and the health care system). If patients rated as 'at risk' then they received tailored nurse intervention (e.g. teaching, advice, feedback, referring to external

	resources). Patients could also call the nurse between planned encounters if they had questions or concerns. Group 2: *Usual care* + project nurse repeated advice given by bedside nurse that patients should contact regular healthcare resources if needed (e.g. hotlines, GPs, cardiologists). Co-Intervention: N/A Provider: Nurse (project nurse: bachelors degree + 5 yrs experience in clinical cardiac care) Where: Face-to-face in ED and telephone follow-up When & how often: 3 times (discharge, 2-4 days & 7-10 days) Intervention personalised: Yes - each person received different package care
Outcomes	Timing of outcome assessment: 30 days post discharge *Medication adherence (subjective): Morisky Self-Reported Medication Taking Scale* (validated). Patients indicated whether (1) or not (0) they forgot (item 1), omitted (item 2), were careless (item 3), or stopped their medication when feeling better (item 4). In this study results dichotomised as 0 (never miss Rx) vs 1 or more (1 or more missing Rx) *Adverse clinical health outcomes (objective): ED revisits.* Percentage of participants readmitting to emergency room.
Notes	Trial registration: ISRCTN88422298 Consumer involvement: Not specified. Funding source: Fonds de la Recherche Quebec Sante, Quebec Network on Nursing Intervention Research & Montreal Heart Institute foundation and research centre Drop-out: 62 (24/38) lost to follow-up

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence generated by independent statistician using PROC PLAN procedure
Allocation concealment (selection bias)	Low risk	Statistician provided opaque envelopes containing assignment to project nurse who was blinded until opening envelope
Blinding of participants and personnel (performance bias)	High risk	Unable to blind - patient and nurse unblinded
Blinding of outcome assessment (detection bias)	Low risk	Research assistant who collected outcome measure data by telephone was blinded
Incomplete outcome data (attrition bias)	High risk	Missing patients - 203/265 reached at time of outcome assessment. Unbalanced losses also 24 (18%) vs 38 (29%)
Selective reporting (reporting bias)	Low risk	Reported as per methods

| Other bias | Unclear risk | Trial ceased early due to unlikely achievement of primary outcome. Sample size not reached |

George 2016

Methods	Aim of study: To examine the efficacy of a web based intervention that utilized Bandura's theory of self-efficacy and targeted dementia family caregivers Study Design: RCT (sub study of larger study, unit of allocation: individual) Number of arms/groups: 2
Participants	Description: carer Geographic location: USA Setting: Community Inclusion criteria: Carer: (a) women ≥18 years (b) assisted a community-dwelling biological or "chosen" earlier-generation relative by (c) accompanying/providing transportation to a medical appointment of this relative ≥1x/yr, (d) engaging in ≥1 caregiving activities related to prescription drugs: Ordering, retrieving, organizing or administering medication, routinely reminding the older adult to take medications, or sharing in decision-making with care recipient and physician to begin, hold, increase, decrease, or discontinue a medication and who (e) endorsed a score of ≥ 2, "somewhat distressed," on two items of the Family Caregiver. Care-recipients (i.e. patients) were required to have a caregiver reported diagnosis of dementia. Exclusion criteria: Care-recipients: lifetime reported history of (b) schizophrenia, (c) bipolar disorder, (d) suicide attempts, (e) Huntington's Disease, (f) Korsakoff's Disease, (g) Multiple Sclerosis, (h) HIV, (i) traumatic brain injury or (j) drug/alcohol dependence Medication Administration Hassles Scale Number of participants randomized: 53 (28 vs 25) Number of participants included in analysis: 35 (18 vs 17) completed program Age: mean age years ± SD: Carers: 53 ± 10.7 vs 53.92 ± 9.05, Patients: 83.03 ± 9.12 vs 83.00 ± 6.83 Gender: All carers female (n=53, 100%), Patients: female: 22 (78.6%) vs 19 (76%) Ethnicity: Carers: Caucasian: 25 (89.3%) vs 15 (60%), African American: 2 (7.1%) vs 6 (24%), Latina: 0 (0%) vs 1 (4%), Multiracial: 1 (3.6%) vs 3 (12%) Number of medications: total prescription medications: 7.03 ± 3.47 vs 7.76 ± 3.91 Frailty/functional impairment: ADL score: 1.29 ± 1.61 vs 0.80 ± 1.15 Cognitive impairment: All had carer reported dementia, CDR: 1.46 ± 0.81 vs 1.44 ± 0.79 Co-morbidities: Total not-specified

Interventions	Group 1: Narrative Health Education *Narrative* online education: Participants entering the experimental condition's website also encountered a still screen shot with four clickable content areas. In the centre of the page, they saw a clickable section titled "introduction" - which linked to a video. When participants entered any content area, they saw another screen containing two columns - one with resources and a single video of an "expert" (pharmacist, nurse, psychologist or social worker) providing brief supplementary information, the second column titled "story" included brief video episodes, each less than four minutes in length, showing ethnically diverse care dyads encountering various medication related challenges as the weeks progressed. Group 2: Narrative Health Education *Didactic* online education: still screen shot with four clickable content areas. When participants entered any content area, they saw another screen containing one column. This column was titled "resources" and contained PDF didactic handouts with information about that content area, and a single video of an "expert" (pharmacist, nurse, psychologist or social worker) providing brief supplementary information. Co-Intervention: N/A Provider: Online delivery Where: Online delivery When & how often: Continuous for one month Intervention personalised: No
Outcomes	Timing of outcome assessment: Baseline and 1 month *Medication adherence (subjective)*: Morisky Medication Adherence: 8 item self-report by caregiver (caregiver answered questions about care recipient's level of adherence) = Yes/No answers, Yes = 1 indicating non-adherent behaviour, No = 0 indicating good medication adherence. Higher scores = poor adherence. *Satisfaction with intervention (subjective):* User Satisfaction regarding the use of the computer program questionnaire (USUCPQ): 8-item measure that assess user satisfaction with online health-based interventions. This measure is based on a 7 point Likert scale (o= very unsatisfied, 7 = very satisfied). Explores following domains of caregiver satisfaction a) convenience, b) entertainment, c) how interesting the content was, d) speed of the modules, e)usefulness, f) practicality, g) tolerability and h) how much information was presented. Maximum score 56.
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Express Scripts Research Award (July, 2013) Drop-out: 7 and 11 did not complete the program *Unpublished data: Full manuscript of thesis. Some data, particularly relating to the larger study, is not yet published.*

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Online random number generator used to evenly divide ID numbers into two groups before the study began.
Allocation concealment (selection bias)	Low risk	A lab member, unaffiliated with the project placed randomly assigned condition type into sealed envelopes with the ID number on the front. Once an individual was determined to be in the dementia group, the envelope with the correct participant number in the group was opened, and the individual was placed in the condition identified inside the envelope.
Blinding of participants and personnel (performance bias)	Low risk	Project coordinator accessed pre-intervention survey to determine dementia status, thus random assignment was not blind to project coordinator. Of note, all intervention materials and contact points were pre-determined and thus there was no possibility of differing participant assignment based on project coordinator knowledge of intervention condition. Both groups viewed same online interface - thus may have been unaware of allocation
Blinding of outcome assessment (detection bias)	Unclear risk	Care-giver self-reported adherence, but likely blinded so unsure of the impact this would have on outcome assessment
Incomplete outcome data (attrition bias)	High risk	High attrition: A third considered non-completers. No difference in dropout rates between groups. Participants who dropped out were reporting poorer medication management adherence and higher level of overall medication related hassles. No significant differences in dropout rates emerged between the didactic and narrative vignette
Selective reporting (reporting bias)	Low risk	Results as per methods
Other bias	High risk	Thesis only - not published in peer reviewed journal. Poor fidelity as 33% didn't log on to complete the program

Grymonpre 2001

Methods	Aim of study: To measure the impact of a community-based geriatric pharmaceutical care model on specific process measures. Study Design: RCT (unit of allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Canada Setting: Primary care clinic (interdisciplinary community health clinic) Inclusion criteria: ≥65yrs, non-institutionalised, ≥2 medications (prescribed or non-prescribed)

	Number of participants randomized: 135 (69 intervention vs 66 control) Number of participants included in analysis:114 (56 vs 58) Age: mean ± SD 76.9 ± 8.4 vs 77.2 ± 8.8 Gender: female: 75% vs 83% Ethnicity: 100% Caucasian Number of medications: prescribed medications mean ± SD 5.9 ± 3.1 vs 6.5 ± 3.4 Frailty/functional impairment: Not specified Cognitive impairment: Not specified Co-morbidities: Not specified
Interventions	Group 1: *Geriatric pharmaceutical care model:* Home medication history (HMH) conducted by trained staff or volunteers using standardised instrument, reviewed by pharmacist to identify and document potential and actual drug-related issues. Pharmacist letter provided to physician summarising info and recommendations. Group 2: *Usual care with home medication history but no pharmacist intervention.* HMH was reviewed by pharmacist for any immediate concerns and those with "life-threatening" drug related problems were required to withdraw. Co-Intervention: N/A Provider: Pharmacist Where: private office or at their home When & how often: Once (and then as required) Intervention personalised: Yes - depending on nature of drug related problems
Outcomes	Timing of outcome assessment: Baseline and 6 months *Medication adherence (objective): Prescription refill adherence*: Refill adherence was based on provincial prescription claims database, medication percentage adherence by comparing one year pre and one year post intervention date prescription claims database. Percentage adherence = sum of days supply in interval x 100/actual number of days in interval between first and last fill. *Knowledge about medicines (objective):* Knowledge of purpose: Knows purpose of prescribed drugs (yes/no), expressed per prescribed drug.
Notes	Trial registration: Not specified Consumer involvement: Not specified Funding source: Not specified Drop-out: 15 withdrew (10 vs 5), 4 died (2 vs 2), 1 NH, 1 unable to contact Fidelity: pharmacist was able to evaluate and make recommendations on 66 of the 69 test clients at baseline

Risk of bias table

Bias	Authors' judgement	Support for judgement

	<u>Cognitive impairment</u>: Dementia excluded <u>Co-morbidities</u>: Not specified
Interventions	<u>Group 1</u>: *Medication therapy management (MTM):* MTM consultation with a pharmacist by telephone 3-7 business days after hospital discharge. Intervention complemented existing CTP (care transition program). Pharmacist completed comprehensive review of all prescription, non-prescription and herbal medications, to identify, resolve and prevent DRPs (e.g. PIM, ADEs, prescribing omissions). Recommendations sent via secure messaging function within electronic medical record to CTP provider. <u>Group 2</u>: *Usual care* - defined as the pre-existing CTP without pharmacist intervention. <u>Co-Intervention</u>: Pre-existing CTP program: Home visit by nurse practitioner within 3 business days after discharge. As part of the visit, the nurse practitioner reviewed the patient's medications and made changes as deemed appropriate. The changes were implemented directly or were discussed with the patient's primary care provider, depending on clinical judgment. <u>Provider</u>: Pharmacist <u>Where</u>: Telephone (phone call to patients home) <u>When & how often</u>: Once, 3-7 days after discharge <u>Intervention personalised</u>: Yes
Outcomes	<u>Timing of outcome assessment</u>: Baseline and 5 weeks (or 30 days) *Medication adherence (subjective)*: *Adapted Morisky Medication Adherence Scale (MMAS):* Self-reported using questionnaire over phone. 6 yes/no questions - number of No's (No = indicating good adherence behaviour). Validated *Adverse clinical health outcomes (objective): ED visits or hospital readmission:* Readmissions assessed by blinded, independent pharmacists
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Grant # UL1 TR000135 from National Center for Advancing Translational Sciences, NIH and US DHHS Drop-out: 1 withdrew, 2 died

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study statistician used a random number generator to determine allocation sequence
Allocation concealment (selection bias)	Low risk	Randomization completed during phone call with study coordinator, who opened a sealed envelope that contained an indication of which group the patient was assigned to.

Blinding of participants and personnel (performance bias)	High risk	Trial was unblinded (participants & investigators) - but unable to blind
Blinding of outcome assessment (detection bias)	Low risk	All outcomes were assessed while blinded to the intervention or usual care group allocations
Incomplete outcome data (attrition bias)	Low risk	3 participants lost, balanced across groups
Selective reporting (reporting bias)	Low risk	All outcomes reported, including NS outcomes
Other bias	Unclear risk	2 of the 12 patients who were randomized to the usual care group had participated in MTM in the past 12 months

Hale 2016

Methods	Aim of study: To compare the MedSentry remote medication monitoring system versus usual care in older HF adult patients who recently completed a HF telemonitoring program. Study Design: RCT of people who had recently completed hospital based heart failure telemonitoring (individual allocation) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: community dwelling (hospital tele monitoring into the home) Inclusion criteria: using 3-10 different medications daily, no more than four specified times each day, able to sort and manage their own medications, had a telephone/mobile phone, live in greater Boston area, speak, read and write English Exclusion criteria: vision or hearing impaired (i.e. unable to hear an alarm), dementia or other conditions precluding informed consent, awaiting revascularization, cardiac resynchronization or heart transplant, or terminal illness. Number of participants randomized: 29 (13 vs 16) Number of participants included in analysis: 25 (11 vs 14) Age: mean $\pm$ SD = 68.4 $\pm$ 11.8 vs 74.4 $\pm$ 10.4 Gender: Female: 4 (36%) vs 5 (36%) Ethnicity: White: 9 (82%) vs 13 (93%) Number of medications: not specified, but all participants taking min 3 and max 10 different medications/day Frailty/functional impairment: NYHA functional classification: Class II or higher: 10 (91%) vs 2 (16%) Cognitive impairment: dementia excluded Co-morbidities: Not specified
Interventions	Group 1: *MedSentry Medication Management System*: (1) a remotely monitored electronic device ("device") that alerts participants when it is time to take their medications and (2) a monitoring centre with advisors who contact participants and

	caregivers when medications are not taken. The device is installed in the participant's home and data are transmitted to the monitoring centre via the Internet. The device is approximately the size of a small microwave oven. The top of the device consists of a series of small, removable bins arranged in a 7 by 4 configuration (seven days of the week and four medication times per day). A lid on the top of each bin detects when a bin is opened. The bottom of each bin is clear plastic. Cameras located under the bins transmit an image of the contents to the monitoring centre. First, the device provides a visual cue (blue lights around a bin) and an audio alarm to alert a participant when it is time to take their medication. If a dose is not taken within 30 minutes, an advisor at the monitoring centre calls the participant. After three attempts over a 45 minute time span to contact the participant, a voice message is left and a call is placed to an optional caregiver who has agreed to be contacted and to follow up with the participant. Participants were responsible for refilling the device and communicating medication changes to the monitoring centre. Group 2: *Usual care* Co-Intervention: N/A Provider: MedSentry device (with telephone calls if non-adherent to device administered medication) Where: Home When & how often: Continuous - 90 days Intervention personalised: Alerts based on individual medication regimens - otherwise no
Outcomes	Timing of outcome assessment: Baseline and 90 days *Medication adherence (subjective)*: Morisky Medication Adherence: 8-item questionnaire, scored from 0-8. 0= high adherence, 1-2=medium adherence, 3 or more = low adherence. *Health-related quality of life (subjective):* Minnesota Living with Heart Failure Questionnaire: 21 items that assess the impact of HF and HF treatment. Responses coded from 0 = does not apply to 5 = very much. Higher scores indicate greater impact (worse). *Adverse clinical health outcomes (mixed objective/subjective):* All cause unplanned hospitalizations and ED visits. Electronic medical records and patient questionnaire.
Notes	Trial registration: NCT01814696 Consumer involvement: Not specified Funding source: Presentcare, Inc Drop-out: 3 (2 vs 1) didn't complete enrolment, 1 control withdrew, 1 control excluded for randomisation error. Adherence measure also had missing participants not described (9 vs 13 baseline, 10 vs 12 follow-up). *Further information required*: mean/median number of medications (email correspondence with author - unsuccessful)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Patients who agreed to participate were randomized during the screening phone call. No further details
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Unclear risk	"Missing cases for some comparisons is because of incomplete responses on the closeout questionnaire". 3 didn't complete enrolment, 1 withdrew, 1 excluded for randomisation error.
Selective reporting (reporting bias)	Low risk	Appears to present results as planned
Other bias	Unclear risk	"recruitment was slow and the study was ended early before achieving the original goal of 35 participants per study arm"

Hanlon 1996

Methods	Aim of study: To evaluate the effect of sustained clinical pharmacist interventions involving elderly outpatients with polypharmacy and their physicians Study Design: RCT (unit of allocation: individual) Number of arms/groups: 2
Participants	Description: Both patient/consumer and carer Geographic location: USA Setting: primary care clinic (General Medicine Clinic (GMC) at Veterans Affairs Medical Center) Inclusion criteria: ≥65, evidence of polypharmacy (≥5), received primary care in GMC. Exclusion criteria: living in nursing home. Patients with cognitive impairment only eligible if a caregiver was available to be involved Number of participants randomized: 208 Number of participants included in analysis: 172 (88 int vs 84 control) Age: mean ± SD: 69.7± 3.5 vs 69.9 ± 4.1 Gender: Female: 1.9% vs 0% Ethnicity: % white: 79.0 vs 74.8

	<u>Number of medications</u>: Veterans Affairs prescribed medications 7.6 ± 2.8 vs 8.2 ± 2.7 <u>Frailty/functional impairment</u>: Not specified <u>Cognitive impairment</u>: percentage of participants: 7.6% vs 12.6% <u>Co-morbidities</u>: Mean chronic medical conditions: 9.2 ± 3.7 vs 9.0 ± 3.0
Interventions	<u>Group 1</u>: *Sustained clinical pharmacist involvement:* Usual and clinical pharmacist care. Pharmacist monitored drug therapy outcomes, medication list and identified DRPs prior to every scheduled GMC visit by reviewing medical record and meeting with patients/caregivers. Pharmacists provided written recommendations to primary physician. After physician visit pharmacist educated patients regarding any medication changes. Pharmacist also used compliance-enhancing strategies and written patient education materials to assist compliance. The clinical pharmacist also reviewed with patients and caregivers general principles of safe medicine use in the elderly and the importance of discussing their medications with their physicians. <u>Group 2</u>: *Usual care* (GMC) - clinic nurse reviewing medications before visit, physician/nurse review medications after visit. The clinical pharmacist neither spoke with, nor gave advice to, control patients or their physicians during the study period. Written drug therapy recommendations for control patients prepared before randomization were not discussed or given to their primary physician but were filed for review at the end of the study. <u>Co-Intervention</u>: N/A <u>Provider</u>: Pharmacist <u>Where</u>: Medical centre <u>When & how often</u>: Before/after GMC visits <u>Intervention personalised</u>: Yes
Outcomes	<u>Timing of outcome assessment</u>: Baseline and 12 months *Medication adherence (subjective)*: *Self-reported compliance*: proportion of medications for which the patients' adherence response agreed with the directions for their use on their action profile, obtained during telephone interviews *Knowledge about medicines (subjective):* Self-report knowledge of 'how they took each analysed medication and what the medication was for', proportion of correct responses *Satisfaction with intervention (subjective):* Health Care Attitude Questionnaire: 5 point Likert scales to rate 3 questions on pharmacy-related health care satisfaction, 1) directions received for taking medication, 2) explanation of SEs, 3) number and types of drugs they were taking *Health-related quality of life (subjective):* Assessed using *SF-36* by blinded interviewers *Adverse clinical health outcomes (subjective):* Patients asked if they had or had not had any possible ADEs (any side effects, unwanted reactions, or other problems with their medications)
Notes	Trial registration: Not specified

	Consumer involvement: Not specified Funding source: National Institute on Aging grant and academic award, and supported by Claude D. Pepper Older Americans Independence Center Drop-out: lost to follow-up 36 (17 vs 19)	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcomes assessed by a separate blinded clinical pharmacist
Incomplete outcome data (attrition bias)	High risk	Lost to follow-up (19%). Methods state ITT but not done for adherence outcomes?
Selective reporting (reporting bias)	Low risk	Appears to be as per methods
Other bias	Unclear risk	Physicians not randomized, potential to be differentially influenced. Sample size 100 per group "to detect an effect of 0.4" or 84 per group "to detect an effect size of 0.5".

Holland 2007

Methods	Aim of study: To test whether a drug review and symptom self-management and lifestyle advice intervention by community pharmacists could reduce hospital admissions or mortality in heart failure patients. Study Design: RCT (unit of allocation: individual stratified) Number of arms/groups: 2
Participants	Description: Both patient/consumer and carer Geographic location: UK Setting: Community pharmacy (after discharge from hospital) Inclusion criteria: >18 years, admitted as an emergency in which HF was an important ongoing clinical condition, prescribed ≥2 medications on discharge. Exclusion criteria: residential or nursing home, awaiting surgery for heart disease/transplant, or had terminal malignancy. Number of participants randomized: 339 (169 intervention vs 170 control)

	Number of participants included in analysis: 291 (148 vs 143) Age: mean ± SD: 77.6 ± 9.0 ± 76.4 ± 9.5 Gender: Female: 54 (36.2%) vs 53 (36.7%) Ethnicity: Not specified Number of medications: Number of prescribed items taken daily: mean ± SD: 7.9 ± 2.6 vs 7.7 ± 2.3 Frailty/functional impairment: Not specified Cognitive impairment: Abbreviated mental test: 9.2 ± 1.0 vs 9.3 ± 1.0 Co-morbidities: Not specified
Interventions	Group 1: *HeartMed (visits from community pharmacist):* Community pharmacist received discharge letter and arranged home visit within two weeks of discharge to meet with patient or carer. As appropriate, educated about heart failure, drugs, exercise, diet, smoking, sign & symptom daily cards, removed discontinued drugs, fed recommendations back to GP. Intervention delivered in line with advice from British Heart Foundation's booklet living with heart failure, which was also given to the patient. A follow-up visit occurred at 6-8 weeks to reinforce. Group 2:*Usual care* Co-Intervention: N/A Provider: Pharmacist (community) Where: Patients home When & how often: Twice - at 2 weeks and 6-8 weeks post-discharge Intervention personalised: Yes
Outcomes	Timing of outcome assessment: Baseline and 6 months *Medication adherence (subjective)*: *Medication adherence report scale (MARS)* scores from 5 (very poor adherence) to 25 (perfect adherence). Questionnaires mailed to patients *Satisfaction with intervention (subjective):* Satisfaction questionnaire at 3 months *Health-related quality of life (subjective): EQ-5D* - self assessed quality of life, 1 (perfect health) to -0.59 (worst imaginable health state) *Adverse clinical health outcomes (objective): Mortality* - number of deaths *Adverse clinical health outcomes (objective): Emergency admissions* - emergency admission data from Hospital Episode Statistics *Condition specific outcomes (subjective): Minnesota living with heart failure questionnaire*, 21 questions of 0-5 giving total score from 0 to 105. Higher scores implying worse condition. Change of 5 points is significant.
Notes	Trial registration: ISRCTN59427925 Consumer involvement: Not specified Funding source: British Heart Foundation project grant. Great Yarmouth and Southern Norfolk Primary Care Trusts covered excess treatment costs. Pfizer supported pharmacist training.

	Drop-out: 46 (20 vs 26) excluded prior to intervention, 2 (1 vs 1) lost to follow-up Fidelity: Of 149 intervention patients - 136 received first visit, 119 received second visit. 13 did not received intervention.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third party telephone randomisation based on a computer generated random allocation sequence. Stratified by New York Heart association class and recruitment site.
Allocation concealment (selection bias)	Unclear risk	participants told allocation after baseline, concealment unclear
Blinding of participants and personnel (performance bias)	High risk	No placebo possible, so participants were told which group they were in.
Blinding of outcome assessment (detection bias)	Unclear risk	Not specified
Incomplete outcome data (attrition bias)	High risk	High rate of failure to complete 6 month assessments (only 101/169 intervention and 103/170)
Selective reporting (reporting bias)	Low risk	As per methods
Other bias	Unclear risk	Pharmacist training funded by Pfizer - unclear what, if any, influence they had on content of training. Of 149 intervention patients - 136 received first visit, 119 received second visit. 13 did not received intervention.

Khdour 2009

Methods	Aim of study: To investigate the impact of a pharmacy led disease and medicine management programme (with a strong focus on self-management) in patients with COPD on clinical and humanistic outcomes. Study Design: RCT (one clinic, allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Ireland Setting: Outpatient clinic (COPD hospital clinic) Inclusion criteria: Confirmed diagnosis of COPD by hospital consultant for ≥1 yr, FEV1 of 30-80% of predicted normal value and >45 years old. Exclusion criteria: CHF, mod-severe learning difficulties (judged by hospital consultant), attended pulmonary rehab programme in last 6 months, severe mobility problems or terminal illness

	Number of participants randomized: 173 (86 vs 87) Number of participants included in analysis: 143 (71 vs 72) Age: Mean ± SD: 65.63 ± 10.1 intervention vs 67.3 ± 9.2 control Gender: Female: 55.8% vs 56.3% Ethnicity: Not specified Number of medications: Combined prescription & non-prescription: 8.3 ± 2.9 vs 8.0 ± 3.8 Frailty/functional impairment: Not specified Cognitive impairment: Not specified Co-morbidities: Comorbid conditions: n=41 (47.7%) vs n=44, (50.5%)
Interventions	Group 1: *Pharmacy-led COPD disease and medicine management programme:* Preliminary assessment with pharmacist to determine individual needs (data on disease knowledge, smoking, medication adherence, self-efficacy, exercise and diet). Intervention pharmacist then discussed drug therapy with consultant and provided education (adherence, inhaler technique, home exercises, management of COPD symptoms). The pharmacist demonstrated techniques and then observed patients carry out the techniques (a booklet on these techniques was given to take home). Pharmacist provided advice using motivational interviewing technique (e.g. quit smoking) and provided customisable action plan for exacerbations (include advice to GPs about antibiotics). The initial intervention lasted for approximately 1 hour (slightly longer for smokers). Group 2: *Usual care* (medical and nursing staff only - no pharmacist involvement) Co-Intervention: N/A Provider: Pharmacist Where: Outpatient clinic When & how often: Baseline & 6 months in person, phone call at 3 & 9 months Intervention personalised: Yes - tailored according to preliminary assessment
Outcomes	Timing of outcome assessment: Baseline and 12 months *Medication adherence (subjective)*: *Morisky Adherence* (measures adherence with 4 Yes/No response items: forgetting, carelessness, stopping when feeling better and stopping when feeling worse); yes=1, no=0 -> high adherence (scores 0-1) vs low adherence (scores 2-4) *Knowledge about medicines (objective): COPD knowledge questionnaire* (validated)- effectiveness of education in helping persons with COPD. 16 T/F questions, correct response = 1, range 0-16, higher score = better knowledge *Health-related quality of life (subjective): St George's Respiratory Questionnaire (SGRQ)* Total Score = SGRQ is 76-item supervised self-administered survey, scores symptoms, activity and impact to give global view of respiratory health. Scores 0-100, high = poor health

	Adverse clinical health outcomes (objective): ED visits, hospital admissions and unscheduled GP visits, assessed using questionnaire & computer records for past year
Notes	Trial registration: Not specified Consumer involvement: Not specified Funding source: Chest Heart and Stroke (N.Ireland) financial support Drop-out: 13 (7 vs 6) withdrew , 8 Died (3 vs 5), 9 lost to follow up (5 vs 4)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization carried out using the minimization method (see reference). Groups matched as closely as possible.
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Participants and research staff unblinded
Blinding of outcome assessment (detection bias)	High risk	Research pharmacist not blinded
Incomplete outcome data (attrition bias)	Low risk	Lost to follow up described and balanced
Selective reporting (reporting bias)	Low risk	Reported results for all outcome measures listed in methods section
Other bias	Unclear risk	Sample size based on SQRG - aimed for 180 patients (90 vs 90) - not reached

Krska 2001

Methods	Aim of study: To evaluate the effect of pharmacist-led medication review on outcomes such as presence of pharmaceutical care issues (PCIs), hospitalization, medication costs and HRQoL. Study Design: RCT (6 general medical clinics, individual patients randomised) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Scotland Setting: Primary care clinic (general medical practices) Inclusion criteria: ≥ 65yrs. ≥4 medications (via computerized repeat prescribing system, ≥2 chronic conditions. (note: A maximum of 70 patients from each practice were invited to participate) Exclusion criteria: Dementia, GP considered patient unable to cope with study Number of participants randomized: 381 Number of participants included in analysis: 332 (168 & 164)

	<u>Age</u>: mean ± SD (range) 74.8 ± 6.2 (65-90) intervention vs 75.2 ± 6.6 (65-93) control <u>Gender</u>: Female: 95 (56.5%) vs 106 (64.6%) <u>Ethnicity</u>: Not specified <u>Number of medications</u>: Medications actually being taken (prescription and non-prescription): mean ± SD (Range) 7.3 ± 2.7 (3-16) vs 7.6 ± 2.7 (3-17) <u>Frailty/functional impairment</u>: Not specified <u>Cognitive impairment</u>: Dementia excluded <u>Co-morbidities</u>: Chronic diseases: 3.9 ± 1.4 (2-8) vs 3.8 ± 1.4 (2-9)
Interventions	<u>Group 1</u>: *Pharmacist medication review & pharmaceutically care planning:* Pharmaceutical care plan drawn up using medical notes and home interview (actual and potential PCIs, actions planned, desired outputs). Copies of plan put in medical notes and given to GP. GP asked to indicate level of agreement to each PCI identified and with actions. Pharmacist then implemented agreed actions. <u>Group 2</u>: Interviewed and PCIs identified, no pharmaceutical care plan written or implemented, just *usual care* (but if serious PCI identified, independent medical assessor decided whether to withdraw patient = n=1) <u>Co-Intervention</u>: Patients interviewed at home about medications, health services, SF-36, medication costs. <u>Provider</u>: Pharmacist <u>Where</u>: GP practice/Home <u>When & how often</u>: One home visit <u>Intervention personalised</u>: Yes - individualised care plan
Outcomes	<u>Timing of outcome assessment</u>: baseline and 3 months *Medication adherence (subjective)*: *Potential/actual compliance* - Pharmacist review identified pharmaceutical care issues, including potential or actual compliance issues. Results as total number of issues at baseline, and number resolved at 3 months *Health-related quality of life: SF-36* (data not reported in paper)
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Grampians Healthcare NHS trust Drop-out: 24 & 25 (excluded after randomization -hospital, ill health, holidays), 1 withdrew

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Following stratification by number of drugs, no. of CV drugs and presence of NSAIDs, patients allocated randomly to intervention or control.
Allocation concealment (selection bias)	Unclear risk	Not specified

Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Low risk	Withdrawal explained. No differences in demography or medicine use between groups.
Selective reporting (reporting bias)	High risk	Not all results listed (e.g. HRQoL just says not significant)
Other bias	Low risk	None apparent

Lee 2006

Methods	Aim of study: To test the efficacy of a comprehensive pharmacy care program to improve medication adherence and its associated effects on BP and LDL-C. Study Design: RCT (Multiphase prospective study with Observational and RCT components, Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: outpatient pharmacy clinics (Outpatient medicine service of Army medical center and Armed Forces Retirement Home (independently living military health care beneficiaries)) Inclusion criteria: ≥65 years, ≥4 chronic medications daily, at increased risk for non-adherence. Exclusion criteria: if not living independently (assisted living or nursing home residents excluded), or if had serious medical condition with unlikely 1 year survival Number of participants randomized: 159 (83 vs 76) enrolled in RCT phase Number of participants included in analysis: 159 (83 vs 76) Age: mean SD 77 ± 10.5 vs 78 ± 6.2 Gender: Female: 21 (25.3%) vs 20 (26.3%) Ethnicity: White: 51 (61.4%) vs 43 (56.6%), Black: 29 (34.9%) vs 31 (40.8%) Number of medications: chronic medications: 9.1 ± 3.2 vs 8.3 ± 2.8 Frailty/functional impairment: Not specified Cognitive impairment: Taking medication for memory problems: 6 (3.8%) vs 2 (1.3%) Co-morbidities: ≥4 health problems: 52 (62.7%) vs 38 (50%)
Interventions	Group 1: *Comprehensive pharmacy care program:* clinical pharmacist meeting every 2 months and medications continued to be blister packed (phase 2) Group 2: Return to *usual care* (no adherence aid, new pill bottles with 90 day supply and 1 refill prescription given) Co-Intervention: Run-in: (months 1-2) = baseline data collection (adherence, BP, LDL-C). Phase 1 (months 3-8): prospective

	observational study of comprehensive pharmacy care program including individualized medication education, medications dispensed using adherence aid & regular follow-up with clinical pharmacist every 2 months Provider: Pharmacist Where: Pharmacy clinics at outpatient medical center and retirement home When & how often: 2 monthly clinical pharmacist follow-ups Intervention personalised: Yes
Outcomes	Timing of outcome assessment: baseline (end of phase 1, 8 months) and conclusion (end of phase 2, 14 months) *Medication adherence (objective)*: *pill count adherence*, Sustained mean medication adherence *Condition specific outcomes (objective): Blood pressure:* Change in Systolic and diastolic blood pressure, mmHg *Condition specific outcomes (objective): LDL-cholesterol:* Change in LDL-C, mg/dl
Notes	Trial registration: NCT00393419 Consumer involvement: Not specified Funding source: Competitive junior investigator grant from American Society of Health-System Pharmacists Research and Education Foundation Drop-out: 13 lost to follow-up (6 & 7), last observation carried forward

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized 1:1 ration using a computer generated random number sequence. Patients randomized in blocks based on level of baseline medication adherence (above or below 55%)
Allocation concealment (selection bias)	Low risk	Allocation was concealed to both patients and study personnel and revealed at end of phase 1
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind participants
Blinding of outcome assessment (detection bias)	High risk	Not possible to blind pharmacists assessing outcomes
Incomplete outcome data (attrition bias)	Low risk	Figure 1 shows participant flow, last observation carried forward for analysis
Selective reporting (reporting bias)	Unclear risk	Results at baseline not split based on intervention or control, hard to compare intervention effect
Other bias	Low risk	None apparent

Lim 2004

Methods	Aim of study: To evaluate the impact of a pharmacist consult clinic on health-related outcomes of elderly outpatients in a local setting. Study Design: RCT (randomized in blocks of 2 participants) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Singapore Setting: Outpatient clinic (Geriatric medicine hospital outpatient clinic) Inclusion criteria: participants who required drug therapy monitoring, evidence of polypharmacy (>3 regular meds or >9 doses per day), documented non-compliance, self-administered drugs that require psychomotor skill and coordination, on nasogastric tube feeding, >1 doctor managing care OR were hospitalised within last 6 months. Exclusion criteria: stable on follow-up, cognitive impairment & no care-giver to participate, life expectancy <6 months, medications supervised by other healthcare personnel Number of participants randomized: 136 (68 & 68) Number of participants included in analysis: 126 (64 & 62) Age: mean ± SD 79.6 ± 7.7 vs 80.5 ± 8.1 Gender: Female: 60.9% vs 69.4% Ethnicity: Chinese: 73.4% vs 83.9%, Malay 6.3% vs 6.5%, Indian: 12.5% vs 6.5%, Other: 7.8% vs 3.2% Number of medications: regularly scheduled medicines: Median (range): 6 (3-16) vs 7 (3-10) Frailty/functional impairment: ADL independent: 50.8 % vs 40.3% Cognitive impairment: Impaired cognition: 20.3% vs 21.0% Co-morbidities: Not specified
Interventions	Group 1: *Pharmacist consult in clinic* (10-30mins) - evaluate patients for MRPs by reviewing medical records, medication list and by interviewing patient and caregiver. Recommendations to simplify, reduce ADEs, decrease cost etc discussed with primary physician and accepted recommendations implemented. Pharmacist also counselled on medication knowledge, administration etc Group 2: Assumed *usual care* Co-Intervention: N/A Provider: Pharmacist Where: Outpatient clinic When & how often: Once at baseline Intervention personalised: Yes - Individualised based on medications and MRPs
Outcomes	Timing of outcome assessment: baseline and 2 months *Medication adherence (subjective)*: Self-reported compliance: patients asked if they 'forgot to take medication as directed'. Then categorised as compliant or not. Participants then classified as least compliant (compliant base, not at 2mth), not-compliant (not compliant at base or 2mth), compliant (compliant at 2mth)

	Knowledge about medicines (objective): Composite % Knowledge of dose (D), frequency (F) and indication (I), reported as percentage correct. *Adverse clinical health outcomes (subjective): Reported ADRs.* Asking patients if they experience side effects or unwanted reactions with their medications. Patients asked to name medication involved, and this was assessed by primary physician to ascertain if symptoms were indeed ADRs of the implicated medicine
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: National Healthcare Group research grant NHG-RPR/01027 Drop-out: 10 excluded prior to intervention (4 & 6), 9 withdrew (5 & 4), 17 lost-to follow up (8 & 9) *Further information required:* raw data on adherence and medication knowledge at follow-up (email correspondence with author successful, but further data was not available)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomly assigned using computer generated numbers in blocks of 2.
Allocation concealment (selection bias)	Unclear risk	Randomization carried out before consent (Zelen design)
Blinding of participants and personnel (performance bias)	High risk	Unblinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not specified
Incomplete outcome data (attrition bias)	Unclear risk	Figure 2 shows study profile, ITT concluded patients only
Selective reporting (reporting bias)	High risk	Raw values for outcomes not listed, 90% CI?, no sample size calculation
Other bias	Low risk	None apparent. Sample size 60/arm "to achieve a power of 80% to detect a 10% difference between the 2 groups in the knowledge outcome"

Lingler 2016

Methods	Aim of study: To develop and examine the efficacy of a tailored, problem-solving intervention on informal caregivers' management of medications for community-dwelling persons with memory loss. Study Design: RCT (unit of allocation: dyad) Number of arms/groups: 2

Participants	<u>Description:</u> Both patient/consumer and carers (recruited as dyads) <u>Geographic location:</u> USA <u>Setting:</u> Participants home <u>Inclusion criteria:</u> PATIENT: self- or caregiver-reported memory loss necessitating help with medication-taking, ≥2 co-morbid conditions requiring medication, living in community, provided informed consent. INFORMAL CAREGIVERS: family members or kin-like friends, ≥18 years, participate in management of patient's medications, exhibit ≥1 deficiency on any of 3 measures of their ability to effectively manage the patient's medications, and live within 75 miles of the University. Exclusion: paid caregivers or living in residential care setting. <u>Number of participants randomized:</u> 83 pairs (42 vs 41) <u>Number of participants included in analysis:</u> 76 pairs (37 & 39) <u>Age:</u> Mean ± SD: Patient: 79.67 ± 9.19 vs 80.15 ± 8.48, Caregiver: 66.00 ± 12.8 vs 67.80 ± 11.2 <u>Gender:</u> Female = Pt: 28 (67%) vs 22 (54%), Caregiver: 29 (69%) vs 29 (71%) <u>Ethnicity:</u> White: Pt 34 (81%) vs 37 (90%), C: 34 (81%) vs 37 (90%), Black: Pt 3 (7%) vs 3 (7%), C: 4 (10%) vs 3 (7%), Other: Pt: 5 (12%) vs 1 (2%), C: 4 (9%) vs 1 (2%) <u>Number of medications:</u> Total medications (including OTC, supplements etc): 10.79 ± 5.52 vs 10.61 ± 5.89 <u>Frailty/functional impairment:</u> Not specified <u>Cognitive impairment:</u> Baseline sample (n=91) Pt MMSE: 17.62, Carer Blessed: 2.97 <u>Co-morbidities:</u> Number of co morbidities: Pts 8.691 ± 3.57 vs 9.024 ± 4.21, Carers: 7.86 ± 3.69 vs 6.44 ± 3.59
Interventions	<u>Group 1:</u> *Maximising Medication Management by Caregivers of Persons with Memory Loss:* Guided by intervention manual, sessions with nurse or social worker interventionist addressed 7 basic aspects of the caregiver's role in managing medications during home/telephone discussions. Caregivers provided with self-study version of intervention manual. Initial 8 week intervention, then 4 bi-weekly calls over next 8 weeks. (Note: The mean length of home visits was 40.05 minutes (SD 13.22) and telephone sessions was 13.42 minutes (SD 6.34).) <u>Group 2:</u> *Usual care:* At baseline, received pamphlet on medication safety. Received home visits for purpose of data collection only (medication errors were corrected). At completion of study caregivers received intervention manual. <u>Co-Intervention:</u> For safety, if any errors were noted during medication reconciliation they were brought to the attention of both caregivers and prescribers regardless of group assignment. In addition, all participants received care as usual from their health care providers. <u>Provider:</u> Nurse or social worker <u>Where:</u> Patients home

	When & how often: 2 or 3 home visits 2 weeks apart, followed by 2 or 3 telephone sessions 7-10 days apart for 8 weeks. Then four bi-weekly phone calls for 8 weeks. Intervention personalised:
Outcomes	Timing of outcome assessment: Baseline and 2 months post intervention *Medication taking ability (objective): MedMaIDE*: Medication Management Instrument for Deficiencies in the Elderly uses interview and observation to assess ability to self-administer medications using three areas: knowledge of medications, how to take medications, and how to procure medications. Each medication is reviewed during administration. Scores 0-13, max total deficiency score is 13. *Satisfaction with intervention (subjective):* Set of Likert scaled questions (not specified) and eliciting open-ended comments during an exit interview at study completion *Other (objective):* Mediation Deficiency Checklist (MDC): 15 item, investigator developed instrument, uses caregiver interviews to assess for the presence of errors and problems (e.g. taking at the wrong time). Investigator developed tool (not validated)
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Program project grant: NIH/NINR P01 NR010949) Drop-out: 3 pairs withdrew (2 vs 1), 4 pairs lost to follow-up (3 vs 1) Fidelity: Good - independent rater randomly selected 10% of cases for an audit of protocol fidelity. Percentage of agreement 91.6%, quality of interaction 4.5/5 Unpublished data included: successful communication with authors, follow-up MedMaIDE results provided

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random group assignments were computer generated using permuted blocks within strata to ensure balance of nurse/social worker, r/ship of caregiver and race/ethnicity
Allocation concealment (selection bias)	Unclear risk	Order of consent/allocation not specified, no details on allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Unblinded - necessary because it was not feasible to blind participating caregivers to their group assignment

Blinding of outcome assessment (detection bias)	Unclear risk	No blinding specified, unclear who did outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	Minimal loss to follow-up, clearly detailed. Erlen paper: there are instances where data are missing, so number of participants may be different. We did not impute data for these participants.
Selective reporting (reporting bias)	Unclear risk	MedMaIDE results only presented in visual format, raw results not in results text
Other bias	Low risk	None apparent

Lipton 1994

Methods	Aim of study: To evaluate if the intervention would 1) enhance patients' compliance with drug regimens, 2) reduce polypharmacy, 3) lower health care expenditures for physician visits, ED visits and hospitalizations, and 4) reduce hospital readmission rates Study Design: RCT (unit of allocation: individual) Number of arms/groups: 2
Participants	Description: Both patient/consumer and carer Geographic location: USA Setting: hospital discharge (in hospital and post discharge via telephone or face-to-face in hospital or home) Inclusion criteria: ≥ 65 years, covered by Medicare, admitted to non-psychiatric ward, resided within 35 miles, English-speaking (or proxy), mentally competent (or proxy), access to telephone, discharged not to nursing home or hospice, ≥3 medications taken for chronic conditions at hospital discharge Number of participants randomized: 719 (not clearly stated, 52% of 1383 eligible) Number of participants included in analysis: 706 (350 vs 356) Age: Mean: 74.6 vs 74.4 Gender: Not specified Ethnicity: Not specified Number of medications: Chronic medications at second compliance assessment: 5.16 ± 2.62 vs 6.75 ± 2.92 Frailty/functional impairment: At least one sensory deficit: 29% vs 32% Cognitive impairment: Those not mentally competent had to have proxy Co-morbidities: Not specified
Interventions	Group 1: *Clinical pharmacist review and face-to-face consultations:* pharmacists review hospital records and drug regimens, then face-to-face consultation with patient. Post-discharge consultations at 1 week, 2-4 weeks, 2 months and 3 months post discharge, via telephone or in pharmacy at hospital or in home. Medication regimen simplification by discussion with physician for prescription, or with patient for non-prescription. Group 2: Usual care

	<u>Co-Intervention</u>: Both groups: booklets given at discharge to record medication information (e.g. drug purpose, dosage and schedule) <u>Provider</u>: pharmacist (clinical hospital pharmacist) <u>Where</u>: In hospital + hospital, home or telephone <u>When & how often</u>: Baseline, Post-discharge consultations at 1 week, 2-4 weeks, 2 months and 3 months post discharge <u>Intervention personalised</u>: Yes
Outcomes	<u>Timing of outcome assessment</u>:6-8 weeks, and 12-14 weeks post discharge *Medication adherence (subjective)*: Structured telephone interviews with a sub-sample. Data only collected for antiarrhythmics, antihypertensives, anticoagulants, cardiac anticonvulsants, antidiabetic NSAIDs, respiratory and GI drugs, and only for first three medications mentioned by patient. Adherence asked for the first three such medications mentioned by patient. 4 behavioural questions (excluding purpose) - calculated as total compliance score out of 100. perfect compliance = 100. Results as 1. Mean compliance scores (SD), 2. mean proportion with perfect(100%) scores. *Cost effectiveness (objective):* Medicare Part B Charges, Total days in hospital, Total hospital inpatient charges
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: John A Hartford Foundation (NYC) Drop-out: not specified

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients drew a folded slip of paper from a box containing equal numbers of experimental and control-designated slips
Allocation concealment (selection bias)	Low risk	Patients drew a folded slip of paper from a box containing equal numbers of experimental and control-designated slips
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind
Blinding of outcome assessment (detection bias)	Low risk	Interviewers not study pharmacists, interviews conducted by investigators. Both interviewers were blinded to study group assignment.
Incomplete outcome data (attrition bias)	High risk	Subgroup selected for sub study on adherence, no details on how selected. States no demographic differences but demographics not listed. 274 selected for interview but only 206 completed second assessment (25% attrition)

Selective reporting (reporting bias)	Unclear risk	Hospital readmission data not clear, compliance reported - but additional analyses that looked at compliance (excluding purpose) were not specified in methods
Other bias	High risk	Adherence measure only for first three medications mentioned by patient - patient may have preferentially selected medication they were more familiar with (thus more adherent with)

Lopez Cabezas 2006

Methods	Aim of study: To assess the efficacy of multifactorial educational intervention carried out by a pharmacist in patients with heart failure Study Design: RCT (2 hospitals, allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Spain Setting: Hospital discharge Inclusion criteria: patients admitted for definite heart failure (Framingham criteria - 2 major or 1 major + 2 minor criteria met simultaneously). *Falces 2008 describes subgroup of >70years.* Exclusion criteria: living out of the area of influence of the hospital, living in old people home, moved to a social-health center or other centers for acute patients, suffering any type of dementia or psychiatric disease, refusing participation Number of participants randomized: 134 (70 & 64), *subgroup >70yrs:* 103 (53 vs 50) Number of participants included in analysis: 134 (70 & 64), except adherence 63 (40 vs 23), *subgroup >70yrs:* 82 (45 vs 37) Age: 75.3 ± 8.4 vs 76.1 ± 9.4, *subgroup >70yrs: 79.0 ± 4.9 vs 80.1 ± 5.5* Gender: female: 41 (58.6%) vs 34 (53.1%), *subgroup >70yrs: 60.4% vs 56%* Ethnicity: Not specified Number of medications: type not specified, 7.1 ± 3.0 vs 7.1 ± 2.5, *subgroup >70yrs:* 7.5 ± 3.1 intervention vs 7.0 ± 2.1 control Frailty/functional impairment: New York Heart Association Functional Classification: I-II: 58 (84.1%) vs 54 (87.1%) Cognitive impairment: Dementia excluded Co-morbidities: total not reported
Interventions	Group 1: *Active information program:* Active information program (run by a pharmacist from the research team) consisted of a personal interview at the time of the discharge and subsequent telephone reinforcement. The intervention included information about the disease, diet education and information about the medications. Simple language was used, adapted to the cultural level of patients, with support of audio-visual and written didactic material. Monthly during the first 6 months of follow-up, and subsequently every 2

	months, patients were called to reinforce the intervention and to solve doubts or problems that may have arisen. Group 2: *Usual care* Co-Intervention: N/A Provider: Pharmacist Where: In person at discharge; and telephone to home When & how often: Discharge, monthly follow up for 6 months then 2-monthly follow up for 6 months Intervention personalised: Yes
Outcomes	Timing of outcome assessment: 12 months *Medication adherence (objective)*: *Pill count/*tablet accountability: % of Reliable patients (95-100% compliance) *Satisfaction with intervention (subjective):* Catalan Health Department satisfaction survey, asking the patient about the care and the information received and asking them to provide a global scoring from 0 to 10 *Health-related quality of life (subjective):* EuroQol, validated in Spanish and Catalan *Adverse clinical health outcomes (objective):* Hospital readmissions, percentage of patients with re-admission, *subgroup >70yrs: mortality* *Adverse clinical health outcomes (objective): number of deaths* *Cost-effectiveness (objective):* Financial evaluation: Hospitalization costs calculated for both groups, adding in intervention direct costs, delivered materials and time spent by the pharmacist
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Health Research Fund and European Regional Development Fund Drop-out: 12 months data for adherence only available for 40 & 23 patients, *subgroup >70yrs:* 20died (7 vs 13) Language translation: Yes - Falces 2008 was translated to English

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generation of the randomization sequence was the responsibility of the clinical epidemiology unit. Randomization lists generated by software and in blocks of 4.
Allocation concealment (selection bias)	Unclear risk	Allocation controlled by admissions department, recruitment carried out by cardiology department
Blinding of participants and personnel (performance bias)	High risk	Not blinded. Neither the physician nor the nurse responsible for the patient knew the allocation until the educational intervention, the day of discharge.

Blinding of outcome assessment (detection bias)	High risk	Compliance assessed by pharmacist. Pharmacist responsible for active info program knew allocation and this could have generated contamination problems
Incomplete outcome data (attrition bias)	High risk	No mention of reason for attrition, only 47% completed 12 month compliance. *Falces paper:* Compliance data only available for 49 patients (59%). Methods stated that those who didn't attend follow-up were to be considered non-compliant but results not presented this way. P-value figure not listed
Selective reporting (reporting bias)	High risk	Only reported 'reliable patients' - but compliance had three levels reliable, partially reliable and not reliable. Financial evaluation not a planned outcome. *Falces paper:* No reasons given for chosen variables in hazard ratio calculation
Other bias	Unclear risk	Sample size calculation: 67/group not reached, 3 years from final data to publication

Manning 2007

Methods	Aim of study: To determine if the 3D tool better than Medication Discharge Worksheet in terms of patient satisfaction, understanding and safety Study Design: RCT (exploratory RCT, 4 medical units, individual allocation) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: hospital discharge Inclusion criteria: >20 years, ≥3 discharge medications, returning to self-care at home (or to care of relative). Exclusion criteria: discharge to nursing home, hospital, or assisted living facility; unable to speak or read English; unable to hear over the telephone to participate in follow-up; or pregnant. Number of participants randomized: 337 Number of participants included in analysis: 138 (78 & 60) Age: mean ± SD 68.1 ± 5.65 intervention vs 67.6 ± 13.06 control, (total range 24-100) Gender: Unclear: % or mean (SD): Table 1: 0.51 ± 0.50 vs 0.38 ± 0.49 Ethnicity: Not specified Number of medications: not specified (discharge medications): 10.0 ± 4.42 vs 8.7 ± 3.93 (total range 4-31) Frailty/functional impairment: Not specified Cognitive impairment: Not specified Co-morbidities: Not specified
Interventions	Group 1: *3D (durable display at discharge) medication discharge education tool:* 3D tool including purpose, time to take medications, comments & cautions, and space for durable display (patients

	encourage to affix tablet/capsule of each medication onto the 3D tool in column labelled Display). Plus a section for 'home medications you should no longer take'. Subjects randomised to 3D upon returning home and after filling any new prescriptions were encouraged to affix (with clear adhesive tape) a tablet or capsule of each medications onto the 3D adjacent to the medication name, and under the column labelled Display. Group 2: *Usual care* - medication discharge worksheet (MDW) Co-Intervention: Before hospital dismissal, the primary nurse conducted her/his usual patient education session including usage of either MDW or 3D (per randomisation) Provider: 3D medication sheets (generated by study recruiter, reviewed by principle investigator or pharmacist co-investigator. Nurse did patient education) Where: Hospital discharge When & how often: Once Intervention personalised: Yes
Outcomes	Timing of outcome assessment: 7-14 days after discharge *Medication taking ability (subjective)*: *self-reported safety in taking medications*: "Since discharge, how many mistakes have you made taking your medications (score 0-4)?" *Knowledge about medicines (objective):* Assessment of knowledge of indication, dosage frequency and special comments or cautions. 0 (for no correct responses) to 3 (all correct responses). *Satisfaction with intervention (subjective):* How satisfied were you with the form you received from the nurse when she/he was talking to you about your medications? 5 point Likert scale: 1 (low) to 5 (high)
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Mayo Clinic Rochester MIDAS grant. Mayo foundation for education and research, small grants program Drop-out: 38 (did not remember form - so were not interviewed), 126 lost to follow-up (93 could not be reached, 12 excluded post-discharge, 4 couldn't hear during call, 5 incorrect phone number, 2 didn't receive MDW, 5 too ill, 4 refused, 1 no English) Fidelity: compliance with affixing medications to 3D is uncertain

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer generated random number algorithm
Allocation concealment (selection bias)	Unclear risk	Not specified

Blinding of participants and personnel (performance bias)	High risk	Not possible to blind
Blinding of outcome assessment (detection bias)	Low risk	Research assistant conducting follow up call was blinded to both study hypotheses and subject randomization
Incomplete outcome data (attrition bias)	High risk	Loss to follow up high (52% contacted by telephone of 337 enrolled), plus extra 38 that didn't remember the tool so were excluded from analysis. No statistically significant differences in patient loss at each level.
Selective reporting (reporting bias)	Low risk	hypotheses and outcomes listed as per methods
Other bias	Unclear risk	"Patient compliance with affixing medications to 3D is uncertain" - "analysed on intention-to-influence basis with knowledge that any non-compliance might diminish the apparent 3D benefit.

Marek 2013

Methods	Aim of study: The purpose of this study was to evaluate health status outcomes of frail older adults receiving a home-based nurse support program that emphasized self-management of medications using both care coordination and technology. Study Design: RCT (3 home health care agencies, individual allocation) Number of arms/groups: 3
Participants	Description: patient/consumer Geographic location: USA Setting: Discharge from home health care Inclusion criteria: ≥60, Medicare primary payer, impaired ability to manage medications and/or impaired cognitive functioning, working telephone & electricity. Exclusion criteria: terminal diagnosis or hospice care that would make attrition likely, use of other device for medications (e.g. pager) Number of participants randomized: 456 Number of participants included in analysis: 414 (152, 137, 125); completed 12 month follow-up: (98, 102, 101) Age: mean ± SD: MD.2: 79.6 ± 7.92 vs Planner: 79.6 ± 7.64 vs Control: 78.2 ± 7.25 Gender: n(%) Female: 104 (68.4) vs 93 (67.9) vs 77 (61.6) Ethnicity: n(%): White: 124 (81.6) vs 114 (83.2) vs 113 (90.4). Black: 28 (18.4) vs 22 (16.1) vs 12 (9.6). Hispanic: 2 (1.3) vs 6 (4.4) vs 3 (2.4) Number of medications: all medications: Mean ± SD: 11.01 ± 4.466; range 2-27 *(as listed in Lancaster 2014)* Frailty/functional impairment: physical performance test: 14.6 ± 5.06 vs 14.2 ± 5.16 vs 15.8 ± 6.14

	Cognitive impairment: MMSE: 25.5 ± 3.33 vs 25.0 ± 3.65 ± 26.3 ± 3.17 Co-morbidities: total co-morbidities not listed
Interventions	Both group 1 & 2: received nurse care coordination - education, tools for participants to manage their chronic conditions, enhanced communication with health professionals, monitoring signs & symptoms of disease. Nurse visited at least every two weeks + additional visits if change in medication or if hospitalised. Group 1:MD2: medication dispensing machine (releases preloaded medication in plastic reusable cups, at preprogramed intervals user presses large red button and a plastic cup containing medications in a chute. Audible and visual prompt for 45 mins, if medication not taken then notification to identified responder e.g. family member or nurse). Group 2: Medplanner: Medplanner (simple weekly medication box). Nurses filled medplanners and recorded number of medications remaining in the medplanners before refilling. Group 3: *Usual care* Co-Intervention: Each participant received a pharmacy screen on admission (pharmacist & advance practice nurse), which was sent to prescribing provider(s). Main purpose was to ensure medications were not harmful. Provider: Nurse care coordinators + medication device Where: In home When & how often: 12 months: contact minimum every 2 weeks as per intervention Intervention personalised: Individualised
Outcomes	Timing of outcome assessment: monthly for 12 months *Medication adherence (objective)*: *Percentage correct doses/month*: Average percent of correct doses per month in two intervention groups. Either machine recorded medication doses or nurse counted medications left in planner *Health-related quality of life (subjective): HRQoL*: Quarterly improvement in SF-36
Notes	Trial registration: NCT01321853 Consumer involvement: Not specified Funding source: National Institute of Nursing Research & University of Wisconsin-Milwaukee Self-Management Science Center Drop-out: excluded before baseline (22, 17, 3), didn't receive intervention (22, 11, 0), Lost to follow-up (32, 24, 24)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomised using computer program developed by a study statistician

Allocation concealment (selection bias)	Low risk	randomised before staff contacted potential patients
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind providers or patients. Higher attrition rate from MD.2
Blinding of outcome assessment (detection bias)	High risk	Not possible to blind providers and data collection. Research data collectors, however, did not deliver the intervention, and interrater reliability among data collectors was monitored closely.
Incomplete outcome data (attrition bias)	Unclear risk	Analysed based on intention to treat. Only 72.7% completed 12 month follow up
Selective reporting (reporting bias)	Unclear risk	adherence results not reported clearly, no MD2 vs control for HRQoL
Other bias	Unclear risk	Sample size 100 per group reached (but close) - noted actually completed numbers 98 vs 102 vs 101

Marusic 2013

Methods	Aim of study: To evaluate the effect of hospital pharmacotherapeutic counselling on the rates and causes of 30-day post-discharge hospital readmissions and ED visits. Study Design: RCT (individual allocation) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Croatia Setting: Hospital discharge Inclusion criteria: ≥65 years, hospital discharge to community with prescription for ≥2 medications for treatment of chronic disease. Exclusion criteria: cognitive or perceptual problems, diagnosis of terminal illness with life expectancy <1 month, discharge to long term care facility, inability to be followed up. Number of participants randomized: 160 Number of participants included in analysis: 160(80 & 80) Age: mean ± SD (range): 74.0 ± 6.7 (65-88) vs 73.9 ± 5.5 (65-87) Gender: female n (%) 43 (53.8%) vs 47 (58.8%) Ethnicity: Not specified Number of medications: prescribed medication mean ± SD (range): 6.6 ± 2.4 (2-13) vs 6.2 ± 2.6 (2-13) Frailty/functional impairment: not specified Cognitive impairment: cognition problems excluded Co-morbidities: Number of discharge diagnoses: 4.4 ± 1.6 (1-8) vs 3.9 ± 1.5 (2-8)
Interventions	Group 1: *Pharmacotherapeutic discharge counselling:* Pre-discharge counselling (30 mins) by qualified physician, specialist in clinical pharmacology, provided within 24 hours prior to discharge. Counselling included indications, dosage & admin times,

	importance of compliance, possible consequences of non-compliance, possible ADRs Group 2: Usual care (including discharge letter to be handed to GP) Co-Intervention: N/A Provider: Physician (specialist in clinical pharmacology) Where: Hospital When & how often: Once within 24hrs of discharge Intervention personalised: Yes
Outcomes	Timing of outcome assessment: 30 days *Medication adherence (objective)*: *Pill count* - patients asked to bring all remaining medications and empty packaging to follow-up visit. compliance = total number of doses taken by the patient since discharge/total number of doses to be taken since discharge x100. Reported as percentage of participants who are compliant (80-110%). If participants couldn't attend hospital then visit was arranged at their home. *Adverse clinical health outcomes (objective): hospital readmission/ED visit:* Number of patients with readmission or ED visit. *Adverse clinical health outcomes (objective): Number of patients with ADRs.* The probability that an ADR was drug related was estimated using the Naranjo ADR probability scale. ADRs that were fatal, life threatening or required hospital admission were considered serious ADRs.
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: No external funding Drop-out: Nil mentioned

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Manual shuffle of 80 intervention and 80 control cards in envelopes
Allocation concealment (selection bias)	Unclear risk	Sealed, unmarked envelope contained card with 'intervention' or 'control'. Unclear if opaque envelopes.
Blinding of participants and personnel (performance bias)	High risk	Patients and physicians were not blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcomes assessed by research assistant blinded to treatment assignment
Incomplete outcome data (attrition bias)	Low risk	no attrition
Selective reporting (reporting bias)	Low risk	Reported as per methods
Other bias	Low risk	sample size 80/group

Messerli 2016

Methods	Aim of study: To investigate the impact of the polymedication check (PMC) on patients on polypharmacy. Study Design: RCT (individual allocation) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Switzerland Setting: Community pharmacy Inclusion criteria: >18 years, ≥4 prescribed drugs over ≥ 3 months. Exclusion criteria: living in retirement home, prior PMC, receiving weekly dosing aids filled by the pharmacy or another person, cognitive impairment, move or death, insufficient knowledge of written & spoken German or French Number of participants randomized: 450 (218, 232) Number of participants included in analysis: 372 completed. 450 in analysis Age: mean ± SD 67.2 ± 11.52 vs 67.1 ± 11.56 Gender: female: 118 (54.1%) vs 125 (53.9%) Ethnicity: Not specified. Number of medications: Chronic oral medications (excluding on demand and self-medication): 6.8 ± 2.92 (range: 1-19) Frailty/functional impairment: Disabilities of the Arm, Shoulder and Hand (DASH-4) score: 4.9 ± 2.01 vs 4.9 ± 1.83 Cognitive impairment: Cognitive impairment excluded Co-morbidities: Not specified
Interventions	Group 1: *Polymedication check (PMC):* face-to-face counselling with pharmacist. Pharmacist screened all meds, checked for knowledge gaps and pharmaceutical care issues (e.g. handling, adherence). Pharmacist documented all resulting interventions (e.g. GP consultations, implementation of weekly dose reminder systems). Education and medication plan could also be provided where necessary. PMC occurred at T0 and T28 (28 weeks = study end). Group 2: *Usual care*: No intervention or T0 documentation. Did receive PMC at 28 weeks (study end) Co-Intervention: N/A Provider: Pharmacist (appropriately trained) Where: Community pharmacy (separate area i.e. consulting room) When & how often: T0 (intervention) and T28 (both) Intervention personalised: Yes - Personalised because medication specific
Outcomes	Timing of outcome assessment: Baseline (200 days prior to T0) and 28 weeks (T0=T28 = 196 days) *Medication adherence (objective)*: *Medication possession ratio (MPR)* - calculated by dividing the days supply of a medication dispensed by the number of days in the time interval of interest

	Knowledge about medicines (objective): Knowledge of medicines and daily use - phone questionnaire. 58 questions - included assessing knowledge *Adverse clinical health outcomes (subjective): GP/Hospital visits:* Self-reported patient's unplanned visits at the general practitioner or hospital
Notes	Trial registration: NCT01739816 Consumer involvement: Unclear - The PMC (polymedication check) is standardised so potentially consumers involved in the original development of the Swiss PMC Funding source: Investigator initiated project and partly funded by Swiss pharmacists association, pharmaSuisse Drop-out: 18 withdrew, 60 lost to follow-up

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The patients were assigned by 2 x 4 block randomisation into intervention or control group. Initially, each study pharmacist received two blocks containing eight dossiers (four intervention and four control) each packed in sealed and unlabelled envelopes. Unclear if envelopes opaque.
Allocation concealment (selection bias)	Unclear risk	Once the first patient had consented, the study pharmacist opened one envelope out of the first block to reveal what arm of the study the patient had been randomised to. Once all eight envelopes of block No. 1 had been assigned, the next block was used. Upon request, further blocks were available. Pharmacist would know allocation of some (e.g. if already opened 4 intervention then would know remaining was control).
Blinding of participants and personnel (performance bias)	High risk	Unable to blind, Hawthorne effect
Blinding of outcome assessment (detection bias)	Low risk	Patients filled out questionnaire, sealed in envelope and returned to pharmacy. Interviewers blinded to intervention and without any knowledge of the content of the PMC or the patients questionnaire at T0
Incomplete outcome data (attrition bias)	High risk	Table 2 summarises reasons for drop out, 34 lost because pharmacist revoked study participation because underestimated time commitment. But unexplained missing patients from both T0 and T28 analysis
Selective reporting (reporting bias)	High risk	MPR for antiplatelets and PPI listed, not mentioned in methods, no results presented for medication knowledge
Other bias	Unclear risk	Sample size calculation: 780 at T0 and 252 at T28 (not reached for adherence). Also study pharmacists received

		compensation for the delivery of each complete patient data set, and patients paid for time spent on telephones.

Moral 2015

Methods	Aim of study: To determine whether a face to face communicative strategy based on motivational interviewing (MI), used by health practitioners (family physicians and nurses) in a primary care setting and aimed at patients over 65 years old with a chronic disease who are being treated by polypharmacy and who have poor medication adherence, can achieve better results than the usual approach based on an informative model of providing education and advice. Study Design: Cluster-RCT (2 arm, 16 health centers, stratified by professional) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Spain Setting: Primary care clinic (health center) Inclusion criteria: >65, chronic disease, polypharmacy (≥5 medicines, or ≥12 daily doses for a period of ≥6 months), high probability for non-adherence (Haynes-Sackett yes, and inconsistent answers to at least one of the four Morisky-Green Qs). Exclusion criteria: serious psychiatric and neurological diseases, difficulties coping with basic daily activities (Barthel Index below 60), those who had cognitive impairment (Pfeiffer's test), those admitted to hospital at least twice in last year, patients under carer's supervision. Number of participants randomized: 32 (16 & 16) Health professionals, 70 vs 84 patients Number of participants included in analysis: 66 vs 81 (but included in analysis 70 vs 84) Age: 75.6 ± 5.9 vs 76.1 ± 5.8 Gender: female: 49 (70%) vs 57 (67.9%) Ethnicity: Not specified Number of medications: medication consumption: 8.7 ± 2.5 vs 9.0 ± 3.1 Frailty/functional impairment: Not specified, <60 Barthel index ADLs excluded Cognitive impairment: Cognitive impairment excluded Co-morbidities: Mean ± SD: chronic diseases: 4.9 ± 2.1 vs 5.1 ± 2.6
Interventions	Group 1: *Motivational interviewing (MI):* Intervention health professionals attended an additional 20 hour workshop taught by family doctor who is expert in field. Intervention professionals focused on motivational interviewing. The strategies of EMot are based on a collaborative, evocative style and respect for autonomy of the patient. The practice of EMot is based on 4 basic principles grouped under the acronym RULE: R (resist) resist the redirect reflex, U (understand) understand and explore the motivations of the patient himself, L (listen) listen empathically, and E (empower) empower the patient, favouring hope and optimism.

	Group 2: *Usual care.* Control patients received routine clinical attention based on transmission of info and persuasive advice Co-Intervention: Before intervention, health care providers in both groups attended a 15h workshop on patient safety and medication adherence. Intervention: 1) initial assessment of medication status, 2) detection of critical incidents and possible medication errors, 3) providing information, 4) developing customized action plan, 5) proposal for implementation. Provider: Physician or Nurse (Trained health professionals - 16 physicians and 11 nurses) Where: Patients home or health center When & how often: V0 baseline in health care setting (15m), V1 at 15-20 days at home (45-60m), V2 at 3 months in health care setting (15m), V3 at 6 months at home (45-60m) Intervention personalised: yes
Outcomes	Timing of outcome assessment: Baseline and 6 months *Medication adherence (objective)*: *Pill count.* Number of tablets presumably consumed/Number of tablets that should be consumed x 100. Adherent if average adherence >80% and <110%. Other (objective): *Average medication errors* according to group. Errors including sub-therapeutic dose, omission of administration, deteriorated drug, duplicate therapy, higher doses and other
Notes	Trial registration: NCT01291966 Consumer involvement: Not specified Funding source: Supported by Spanish Society of Family and Community Medicine and Andalusian Society of Family and Community Medicine research grant, and the Ministry of Health of the Government of Andalusia, Spain. Drop-out: 5 (3 vs 2) health professionals didn't recruit any participants, 2 patients withdrew, 4 lost to follow up (Perula de Torres paper says 5 lost to follow-up) Language translation: Yes - Perula de Torress paper translated to English Exact ICC value not reported. Paper states that "ICC in cRCT in primary care generally less than 0.05". Thus 0.05 was used to recalculate sample sizes, 57 intervention vs 67 control.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Blinded randomization. 32 professionals assigned randomly and stratified by type of professional
Allocation concealment (selection bias)	Unclear risk	Allocation based on clusters and was stratified by profession (nurse or physician). Unclear if/how allocation was concealed.

Blinding of participants and personnel (performance bias)	High risk	Not possible to mask the intervention, either to patients or providers
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear if assessors blinded. The final results were evaluated by a methodology expert of the investigation, which remained at all times blind to the status of patients.
Incomplete outcome data (attrition bias)	Unclear risk	Unclear who is in final results, states ITT.
Selective reporting (reporting bias)	Unclear risk	Unclear how they assessed medication adherence at baseline (i.e. how did they do pill count). Medication adherence mean only at baseline.
Other bias	High risk	Sample size calculation: 78 per group not reached <u>Recruitment bias (selective recruitment of cluster participants):</u> High risk. Participants recruited by consecutive sampling. "Time between the training program and patient recruitment and intervention was about two weeks" thus health professionals were aware of randomization during participant recruitment stage.

Morales Suarez-Vurela 2009

Methods	<u>Aim of study</u>: To assess the utility of the pillbox, individualized dispensing system and Practical dosing, to improve therapeutic compliance in polymedicated patients with diminution of mobility capacity. <u>Study Design</u>: RCT (open label, unit of allocation: individual) <u>Number of arms/groups</u>: 2
Participants	<u>Description</u>: Both patient/consumer and carer <u>Geographic location</u>: Spain <u>Setting</u>: Community (home) <u>Inclusion criteria</u>: ineffective management of medications due to >70 years & >3 prescribed medications and limited mobility. <u>Exclusion criteria</u>: cognitive impairment (Pfeiffer test less than 3 if he can read and write and less than 4 if he can not read or write) mentally incapacitated patients, hospitalised patients at start of study. <u>Number of participants randomized</u>: 182 (89 vs 93) <u>Number of participants included in analysis</u>: 182 (89 vs 93) <u>Age</u>: Mean (CI), Min-Max = 77.08 (76.224-77.936), 61 to 93 vs 77.39 (76.646-78.134), 20 to 70 <u>Gender</u>: Female: 64 (71.9%) vs 64 (68.8%) <u>Ethnicity</u>: Not specified <u>Number of medications</u>: (type unclear) Mean (CI), Min to Max: 8.35 (7,323-9,377), 3 to 60 vs 7,83 (7,403-8,257) 3 to 18, Number of medications/day = 9.22 (8.701-9.739) 0 to 23 vs 10.60 (9.946-11.254), 3 to 22

	<u>Frailty/functional impairment</u>: Not reported <u>Cognitive impairment</u>: Cognitive impairment excluded <u>Co-morbidities</u>: no total comorbidity score
Interventions	<u>Group 1</u>: *Practidose Pill-box:* a reusable pillbox, plastic container with seven compartments (7 days of week). Name of patient written on the outside of the container and also had treatment control sheet (medication list/chart). Only contains solid dose forms - this fact is rectified by introducing a cardboard pictogram of a jar of syrup, spoon, etc. in the corresponding space, at the time of administration which reminds the patient that he/she should also take this medication. It is not clear who filled the pill-box as the intervention is not well described. <u>Group 2</u>: Not specified - presumably *usual care* without pillbox <u>Co-Intervention</u>: N/A <u>Provider</u>: Nurse (district link nurse) and Pill-box <u>Where</u>: Unclear <u>When & how often</u>: In person baseline & 2 months, phone call at 14 days <u>Intervention personalised</u>: No (aside from individual medications in the box)
Outcomes	<u>Timing of outcome assessment</u>: Baseline & 2 months *<u>Medication adherence (subjective)</u>: Morisky-Green Medication Compliance:* nurse administered survey. Unclear how results are reported - appears to be reported as % patients who are compliant, but it is not defined)
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Not specified Drop-out: Nil Language translation: Yes - translated to English *Further information required:* more detail on randomization, allocation, recruitment and adherence measure (email correspondence - unsuccessful)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The selection of patients was made by assignment randomized by blocks". It appears these were blocks of 10 (5 intervention and 5 control for each nurse. But it is unclear how generated
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and	High risk	All patients aware of allocation, unblinded

personnel (performance bias)		
Blinding of outcome assessment (detection bias)	High risk	Unblinded - appears nurses administered intervention and follow-up on their own patients
Incomplete outcome data (attrition bias)	Low risk	No attrition specified
Selective reporting (reporting bias)	High risk	Multivariate analyses not reported in table - unclear what was done. Morisky-Green individual questions not reported, unclear how adherence summarised (suspect answer no to all questions)
Other bias	Low risk	Sample size of 83 in each group

Murray 1993

Methods	Aim of study: To determine the effect of unit-of-use packaging on medication compliance among elderly outpatients treated with complex medication regimens. Study Design: RCT (unit of allocation: individual) Number of arms/groups: 3
Participants	Description: patient/consumer Geographic location: USA Setting: primary care clinic (Geriatric outreach centers located in urban public housing units for the elderly and disabled (people living independently) Inclusion criteria: ≥60 years, ≥3 medications Exclusion criteria: medications pharmacologic and pharmacokinetic properties considered unfeasible for twice-daily regimen, nursing home. Number of participants randomized: 36 Number of participants included in analysis: 31 (Control 1: 12, Control 2: 10, Intervention: 9) Age: Mean (range) = C1: 71.3 (64-81), C2: 72.5 (60-87), I: 72.9 (63-81) Gender: Female: C1: 9 (75%), C2: 8 (80%), I: 6 (67%) Ethnicity: Black (not white): C1: 8 (75%), C2: 9 (90%), I: 6 (67%) Number of medications: type not specified: Mean ± SD: C1: 4.8 ± 2.2, C2: 3.8 ± 1.1, I: 5.1 ± 2.1 Frailty/functional impairment: Medical outcomes Study General Health Survey: Physical function mean ± SD = C1 52.8 ± 34.0, C2 43.3 ± 29.6, I: 37.9 ± 31.7 Cognitive impairment: Mean ± SD MMSE: C1: 27.2 ± 2.2, C2: 28.5 ± 1.0, I: 27.7 ± 1.8 Co-morbidities: Not specified
Interventions	Group 1 (intervention): *Unit-of-use medication packaging & regimen simplification*: medications in unit-of-use packages with twice daily dosing intervals (morning and evening). Medications in translucent plastic cups with translucent plastic snap-on lids. Yellow label for AM, blue label for PM.

	Group 2 (control 1): *usual care:* medications in conventional packaging and no change to dosing interval Group 3 (control 2): *regimen simplification:* medications in conventional packaging but dosing intervals made twice daily (morning and night) using two clear plastic zip lock bags. Co-Intervention: All medications packaged individually by study pharmacist and dispensed monthly (33 days supply) Provider: Pharmacist Where: Ambulatory clinic/Home When & how often: Monthly (medications resupplied monthly) Intervention personalised: No
Outcomes	Timing of outcome assessment: 6 months (assessed monthly) *Medication adherence (objective)*: *Pill count:* percentage compliant (note overadherence expressed as underadherence e.g. 90% not 110%). Scale 0-100. *Adverse clinical health outcomes (subjective):* Asked: "Have you had any side effects, ill effects, or any other problems caused by medications you have taken? (yes/no)"
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: The Health Foundation of Greater Indianapolis Drop-out: 4 withdrew, 1 lost to follow-up

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	No blinding of pharmacist who delivered the intervention and collected outcome data
Blinding of outcome assessment (detection bias)	High risk	No blinding of pharmacist who delivered the intervention and collected outcome data
Incomplete outcome data (attrition bias)	High risk	5 people missing (16%), 3 from intervention group (25%). 1 NH, 3 returned to prior regimen, 1 disliked unit-of-use packaging.
Selective reporting (reporting bias)	High risk	Compliance measured in 4 ways, subjective not reported at follow-up, results in abstract not matching main paper

Other bias	Unclear risk	No power calculation. Small sample size in each group. Groups not particularly well matched (e.g. mean number of drugs). Pill counts occurred in the pharmacy - patients may not have returned all meds, and this be more of an issue with unit-of-use packaging (a bag for empty containers was provided, but it is possible that containers were discarded and % containers returned was not reported).

Muth 2016

Methods	Aim of study: To test the feasibility of an intervention and cluster RCT study design, for an intervention designed to improve medication appropriateness and adherence in elderly patients with multimorbidity Study Design: Cluster-RCT (20 GP practices, unit of allocation: practice) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Germany Setting: Primary care clinic (GP practices) Inclusion criteria: *GP*: provision of primary care within German statutory health insurance system, and health care assistant could access Internet. *Patients*: ≥65 years, ≥3 chronic conditions, ≥5 chronic prescriptions, ≥1 practice visit in past quarter, ability to fill in questionnaire and participate in telephone interviews Exclusion criteria: *patients*: MMSE<26, life expectancy ≤6 months, alcohol and drug abuse (based on GP assessment) Number of participants randomized: 100 Number of participants included in analysis: 100 ITT (94 as per abstract) Age: mean ± SD 75.8 ± 6.7 vs 75.2 ± 5.88 Gender: female: 28 (56%) vs 24 (48%) Ethnicity: Not specified Number of medications: chronic prescriptions: 9.5 ± 2.67 vs 8.7 ± 2.66 Frailty/functional impairment: Falls: 7 (14%) vs 6 (12%), 94% Intervention and 92% Control were 'fending for themselves', which presumably means they were independently functioning Cognitive impairment: Excluded MMSE <26, MMSE data not reported Co-morbidities: Mean ± SD Schafer et al count of chronic diseases: 8.4 ± 2.52 vs 7.0 ± 2.62, Charlson score: 4.5 ± 2.64 vs 4.5 ± 2.46
Interventions	Group 1: *Prioritising Multimedication in Multimorbidity in general practices (PRIMUMpilot):* Intervention group received brown bag review and a checklist-based pre consultation interview with patient & health care assistant to detect potential medication issues and non-adherence, then a computer-assisted medication review carried out by GP and GP-patient consultation. Group 2: *Usual care* (not described)

	Co-Intervention: Both groups of GPs received practice guidelines for older patients Provider: GP with assistance from Healthcare Assistants Where: GP Clinic When & how often: once at baseline Intervention personalised: Yes - tailored to individual medications
Outcomes	Timing of outcome assessment: Baseline (0 weeks) and 12 weeks *Medication adherence (subjective)*: *Morisky* adherence: validated questionnaire, four items resulting in sum scores of 0-4 with low scores indicated good adherence. *Medication adherence (subjective)*: *Medication Adherence Rating Scale (MARS)*, validated questionnaire, five items resulting in sum score 5-25, with high scores indicating good adherence *Medication adherence (subjective)*: Discrepancy between medicines patients reported actually taking (at patient interview) and medicines prescribed (reported by GP). Three domains: drug score, dose score and regimen score. Scores outside of 0.8-1.2 considered deviant. Unsure if validated. *Health-related quality of life (subjective):* EQ-5d *Adverse clinical health outcomes (subjective):* Number of days in hospital
Notes	Trial registration: ISRCTN99691973 Consumer involvement: Not specified Funding source: German Federal Ministry of Education and Research, grant no. 01GK0702 Drop-out: 1 hospitalised, 7 lost to follow-up (5 & 2) ICC for adherence reported as 0.000, thus no need to recalculate results.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocation sequence generated by an external researcher using the random number generator of Microsoft Excel.
Allocation concealment (selection bias)	Low risk	Treatment allocation was concealed to practices and patients until data collection at baseline had been completed
Blinding of participants and personnel (performance bias)	High risk	Not blinded - participants could not be blinded
Blinding of outcome assessment (detection bias)	High risk	Not blinded - adherence assessment not blinded
Incomplete outcome data (attrition bias)	High risk	Significant amount of missing data for adherence measures, and reasons not adequately explained

Selective reporting (reporting bias)	Low risk	All outcomes reported as per methods
Other bias	Low risk	Aim for 100 patients (50:50), 10 GPs, 5 patients per cluster. <u>Recruitment bias (selective recruitment of cluster participants):</u> low risk, treatment allocation was concealed to practices and patients until data collection at baseline (and thus recruitment) had been completed.

Nascimento 2016

Methods	<u>Aim of study</u>: To evaluate the improvement on diabetes self-care (including adherence) after an individualised pharmacotherapy management service (home medication review and therapeutic education) in elderly patients <u>Study Design</u>: RCT (unit of allocation: individual) <u>Number of arms/groups</u>: 2
Participants	<u>Description</u>: Both patient/consumer and carer <u>Geographic location</u>: Portugal <u>Setting</u>: Diabetic Care Clinic & patients home <u>Inclusion criteria</u>: T2DM, ≥65years, HbA1c≥7.5%. <u>Exclusion criteria</u>: (unclear) cancer, cognitive impairment or other conditions that could "hinder communication" unless they could submit a caregiver <u>Number of participants randomized</u>: 90 <u>Number of participants included in analysis</u>: 87 (44 & 43) <u>Age</u>: mean ± SD: 74.2 ± 5.4 vs 72.3 ± 4.5 <u>Gender</u>: Female: 43.2% vs 41.9% <u>Ethnicity</u>: Not specified <u>Number of medications</u>: type not specified: 6.86 ± 3.32 vs 5.84 ± 2.76 <u>Frailty/functional impairment</u>: Not specified <u>Cognitive impairment</u>: Cognitive impairment needed carer <u>Co-morbidities:</u> no total score given
Interventions	<u>Group 1</u>: *Pharmacotherapy management service for T2DM elderly patients:* individualized pharmacotherapy management service at home, including analysis of necessity, safety and effectiveness of medications taken. Also received individualized therapeutic education on diabetes care especially pharmacotherapy. Unclear whether med review and education was limited to diabetes medications only, or all medications. <u>Group 2</u>: *Usual care:* Standard medical care consultation (no details) <u>Co-Intervention</u>: N/A <u>Provider</u>: Not specified - ?pharmacist <u>Where</u>: Home <u>When & how often</u>: Once at baseline (no details) <u>Intervention personalised</u>: Yes - individual medication review

Outcomes	Timing of outcome assessment: Baseline and six months *Medication adherence (subjective)*: *Medida de Adesao aos Traamentos (ref 68)*, a validated Portuguese/Spanish measure based on Morisky Green Test, Average level of adherence to drug therapy - seven questions, on scale 0-6, 6 being highest adherence *Condition specific outcomes (objective):* Fasting Blood glucose in mg/dl and Glycosylated Haemoglobin (HbA1c)
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Partly funded by DGS Drop-out: 3 lost to follow-up *Unpublished data:* Mean medications: Control = 5.84 +/- 2.76, Intervention = 6.86 +/- 3.32, Adherence assessed for all medications, not just diabetes medications, adherence measured using a Spanish tool that is based on Morisky.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not explicitly reported, but the way it is described it raises suspicion that it could have been alternating allocation, hence not random ("were randomised into a control and an intervention group, for a consecutive sampling")
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Clinical data accessed by an Independent clinical laboratory - unsure if blinded
Incomplete outcome data (attrition bias)	Low risk	90 randomized, 87 completed. No reasons given. but attrition small
Selective reporting (reporting bias)	Unclear risk	methods unclear, method of assessing adherence mentioned at end near conclusion
Other bias	Unclear risk	Methodology is very brief, making assessment of rigour and bias very difficult. Adherence assessment and analysis methodology is unclear.

Naunton 2003

Methods	Aim of study: To evaluate pharmacist-conducted post-discharge follow-up at home of high-risk elderly patients on various outcomes (including adherence). Study Design: RCT (unit of allocation: individual)

	<u>Number of arms/groups</u>: 2
Participants	<u>Description</u>: Both patient/consumer and carer <u>Geographic location</u>: Australia <u>Setting</u>: Home (post discharge) <u>Inclusion criteria</u>: ≥60 years, ≥2 chronic medical conditions requiring medication (≥1 of HF, IHD, COPD or DM), ≥4 prescribed regular medications. <u>Exclusion criteria</u>: lived in domiciliary care facility or beyond greater Hobart area, were to be visited at home by a community nurse within 5 days of discharge, had terminal malignancy or were unable to provide informed consent. <u>Number of participants randomized</u>: 136 <u>Number of participants included in analysis</u>: 121 (57 & 64), (unclear as number of participants alive at 90 days: 54 vs 59) <u>Age</u>: Median (range): 74 (65-90) vs 77 (60-91) <u>Gender</u>: Female: 56% vs 69% <u>Ethnicity</u>: Not specified <u>Number of medications</u>: Regular medications on discharge: Median (range): 8 (3-15) vs 8 (3-16) <u>Frailty/functional impairment</u>: Nursing assistance at home: 28% vs 21% <u>Cognitive impairment</u>: Not specified <u>Co-morbidities</u>: Chronic medical conditions: median (range) = 5 (2-9) vs 5 (2-13)
Interventions	<u>Group 1</u>: *Pharmacist post-discharge home visit*: Five days after discharge, patients visited at home by study pharmacists. Objective of visit was to educate, answer any queries, optimise medication management (e.g. Dosette or Webster if necessary), improve compliance, detect DRPs and improve liaison with community-based health services. Brief letter composed in the patient's home was given to them to present to the doctor. Study pharmacist also called GP and community pharmacy to inform of study. <u>Group 2</u>: *Usual care* (no specific post-discharge follow-up for this group) <u>Co-Intervention</u>: 89% in both groups were seen by hospital pharmacist prior to discharge <u>Provider</u>: Pharmacist <u>Where</u>: Home <u>When & how often</u>: Once, 5 days after discharge <u>Intervention personalised</u>: Yes - based on adherence assessment at home visit, specific strategies were offered such as compliance aids, carer assistance, community nursing, etc
Outcomes	<u>Timing of outcome assessment</u>: 90 days post discharge *<u>Medication adherence (subjective)</u>: Self-reported missing doses*: Compliance defined as 'never miss medication'. Non-compliance therefore any self-reported missed doses (from 'rarely' to 'once a day') Self-reported 'never' forget to take their medication. 1 question "How often would you say you miss taking your pills?", with 7

	response options from never to once a day. Presented as dichotomous variable adherent or not adherent. ?Not validated *Satisfaction with intervention (Subjective): satisfaction survey -* intervention group only *Adverse clinical health outcomes (Objective): Deaths:* % patients who died within 90 days of discharge. Retrospective medical record review and contact with family, and/or GP *Adverse clinical health outcomes (Objective): Unplanned hospital readmissions:* % patients with 1 or more unplanned readmission within 90 days of discharge (patients asked and retrospective medical records checked)
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Abbott Australasia Pharmacy Research Grant, through SHPA Drop-out: 2 withdrew (1I, 1C), 13 lost to follow-up (3C died, 3I & 2C uncontactable, 2I & 1C admitted to nursing home, 2I intensive nursing care)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised by the study pharmacist using a computer-generated list of random numbers.
Allocation concealment (selection bias)	Low risk	Randomisation occurred after discharge from hospital and collection of baseline data
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	High risk	Not blinded post-randomisation
Incomplete outcome data (attrition bias)	Low risk	Good breakdown of excluded patients
Selective reporting (reporting bias)	Low risk	As described in methods
Other bias	Low risk	None apparent

Nazareth 2001

Methods	Aim of study: To evaluate the effectiveness of a co-ordinated hospital and community pharmacy discharge care plan for elderly patients (75+) on ≥4 medications discharged from hospital. Study Design: RCT (4 hospitals, individual block randomisation) Number of arms/groups: 2
Participants	Description: Both patient/consumer and carer Geographic location: UK Setting: Hospital discharge (hospital and patient's home)

	Inclusion criteria: 75+ years, ≥4 medications, discharged home from elderly care wards (3 acute general and 1 long-stay hospital) to a catchment area of the 4 participating hospitals. Exclusion criteria: couldn't speak English, or too ill (no definition). Number of participants randomized: 362 (181 & 181) Number of participants included in analysis: 6 months: 306 (149 vs 157), Interviewed: 132 vs 135 Age: mean ± SD: 84 ± 5.2 vs 84 ±5.4 Gender: Female: 62% vs 66% Ethnicity: 97% white, not reported for individual groups but not significantly different Number of medications: oral prescribed medications at discharge: Mean 6, SD 2 overall (not reported individual groups, but not significantly different) Frailty/functional impairment: Not specified Cognitive impairment: MMSE≤ 15 (n=39) excluded from interview process Co-morbidities: Mean 3 chronic medical conditions (not reported individual groups, but not sig diff)
Interventions	Group 1: *Coordinated hospital & community pharmacy discharge*: Hospital pharmacist pre-discharge intervention: assessment of medication, rationalization of drug treatment, assessment of patients' ability to manage their medication, provision of information on current drugs and liaison with carers and community professionals (pharmacy, GP etc where appropriate). Written discharge plan given to patient, community pharmacist and GP. Community pharmacist intervention: Home visit at day 7-14 to check for discrepancies between what patient is taking vs those prescribed on discharge, assessment of patient knowledge ad adherence, patient counselling, removal of excess medications, and additional visits prn. Group 2: *Usual care:* Standard procedures. Discharge letter to GP. Pharmacists did not provide review of discharge medications or community follow-up. (Unclear what services the hospital pharmacy did provide - presumably some discharge counselling). Co-Intervention: N/A Provider: Pharmacist (hospital and community) Where: Discharge & Home When & how often: Pre-discharge in hospital and at home 7-14 days after discharge Intervention personalised: Yes (mostly standardised, but intervention tailored to address individual patient's medication management problems).
Outcomes	Timing of outcome assessment: Baseline and six months *Medication adherence (Subjective)*: *Self-reported adherence -* obtained through prescription medicine interview. adherence to prescribed drugs in the previous week. Validated self-report semi-structured interview (adherence score is out of 1, with 1 being 'total/highest' adherence). Mean (SD) out of 1.

	Knowledge about medicines (subjective): self-reported medication knowledge - Prescription medicine interview - patient's knowledge of prescribed drugs. Validated self-report semi-structured interview (knowledge score is out of 1, with 1 being 'total/highest' knowledge). Mean (SD) out of 1. *Satisfaction with intervention (subjective):* Validated client satisfaction questionnaire. Each item scored 1 to 4, mean score per item calculated *Adverse clinical health outcomes (objective): Service usage:* Hospital readmission, deaths, outpatient department attendance and GP attendance. Data from hospital data and GP surveys
Notes	Trial registration: ISRCTN66700837 Consumer involvement: Not specified Funding source: National Health Service Research and Development programme on the primary/secondary care interface Drop-out: 32 vs 24 died Fidelity: Discharge plans were 'misplaced' for 36/181 patients, and 52/181 patients did not receive the home visit

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	After consent, independently randomized by health authority's central community pharmacy office using computer-generated random numbers. Block randomization, stratified by trial centre.
Allocation concealment (selection bias)	Low risk	Randomisation done by an independent group after consent obtained
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Low risk	Research assistant remained blinded to allocation or patient
Incomplete outcome data (attrition bias)	High risk	High loss to follow-up - only 44% answered 6 month adherence.
Selective reporting (reporting bias)	Low risk	as per methods
Other bias	High risk	Poor fidelity of the intervention: Discharge plans were 'misplaced' for 36/181 patients, and 52/181 patients did not receive the home visit. Sample size "195 patients were required in each group" not reached.

Olesen 2014

Methods	Aim of study: This paper: To investigate the impact of pharmaceutical care on medication adherence, hospitalisation and the mortality of home living elderly (65+) patients prescribed polypharmacy. But the overall study aim also included a 3rd arm designed to assess the impact of an electronic reminder device on adherence. Study Design: RCT (2 arm results from 3 arm RCT, individual allocation) Number of arms/groups: 3 (2 discussed)
Participants	Description: patient/consumer Geographic location: Denmark Setting: Patients home (community) Inclusion criteria: ≥65 years, ≥5 current prescription drugs taken without assistance. Exclusion criteria: residence in a nursing home, terminal illness, cognitive disorders such as dementia, medication supervised by healthcare providers, immigration to Denmark after January 2005, and severe motor impairment. Patients hospitalised for more than 7 days during the study were excluded before the final adherence evaluation. Number of participants randomized: 630 (315, 315) Number of participants included in analysis: 517 (253 & 264) Age: Median (IQR, range): 74 (70-80, 65-94) vs 74 (70-80, 65-91) Gender: female: 133 (53%) vs 134 (51%) Ethnicity: Not specified (recent immigrants excluded) Number of medications: oral prescription medications: Median (IQR, range): 7 (5-8, 1-16) vs 7 (5-8, 3-18) *Note: only meds taken throughout the 12 month study period were included in the adherence assessment* Frailty/functional impairment: Not specified Cognitive impairment: Cognitive impairment such as dementia excluded Co-morbidities: Not specified
Interventions	Group 1: *Pharmaceutical Care:* Pharmacist home visit to deliver patient education, motivation, and regimen simplification. There was also a medication review to identify DRPs, but this was a minor component. The pharmacist examined medicines list with regard to possible side effects, interactions, and administration, then tried to make the regime less complex, informed the patients meanwhile about the drugs, listened to questions concerning the drug, handed over information leaflets, and motivated adherence. Phone call at 3, 6 & 9 months to inquire about patients' condition and changes in the medicine, uncover problems and answer questions. Group 2: Usual care - no intervention (not described) Co-Intervention: All groups had regular nurse home visits to collect data for medication counts. Provider: Pharmacist Where: Home & telephone When & how often: Home at baseline, phone call at 3, 6 & 9 months

	Intervention personalised: Yes - personalised based on medication, but broad intervention the same.
Outcomes	Timing of outcome assessment: 12 months (adherence), 24 months (health outcomes) *Medication adherence (objective)*: *Pill count* of oral prescription drugs. Nurse visited patients at baseline, 6 months and 12 months to photograph pills which were counted later by a 'counter pen' (combination of a marker and a digital camera). Adherence rate (%) per drug calculated as mean adherence rate during 1 year. <80% pills taken as prescribed = non-adherence (>100% pill taken was regarded as 100%, i.e. adherent) *Adverse clinical health outcomes (objective):* Unplanned hospital admissions to medical departments obtained from Danish e-Health Portal. *Adverse clinical health outcomes (objective):* Mortality data obtained from hospital e-journal (electronic hospital record that automatically records information on all deceased patients)
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Supported by the Danish Ministry of Health and the Association of Danish Pharmacies. Drop-out: excluded prior to intervention: 31 & 31 (hospitalised or medications administered), withdrew 15 & 5 (lack of interest), lost to follow up 16 & 15 (outside region, no adherence count, died) Fidelity: Poor - adherence only measured for 48% of medications. No data provided regarding whether pharmacists delivered the intervention exactly as intended, nor whether phone follow-ups all occurred. *Further information required:* hospitalisation, mortality and adherence data for third group (email correspondence - successful, but did not collect hospitalisation or mortality data, and adherence was measured by a different method - see Harbig 2012)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	945 envelopes prepared with each containing a study inclusion code. Patients selected an envelope at first home visit - inadequate details provided re randomisation method.
Allocation concealment (selection bias)	Unclear risk	At first home visit by a project nurse, patients were asked to select one envelope. Unclear if opaque envelopes, or order, or if nurse had knowledge.
Blinding of participants and personnel (performance bias)	High risk	Impossible to conceal the identity of patients in the pharmaceutical care group

Blinding of outcome assessment (detection bias)	High risk	Doesn't specify any blinding - project nurse photographed pills to be counted later by a counter pen.
Incomplete outcome data (attrition bias)	High risk	only able to assess adherence for 48% of medications, not sufficient detail as to why hospitalised patients were excluded
Selective reporting (reporting bias)	High risk	Three arm study - but only describes two arms. Outcomes mostly per methods, although additional adherence calculations were conducted that weren't specified in methods (e.g. within group comparisons). Harbig paper describes third arm adherence by a different method.
Other bias	Low risk	None noted - adherence was very high in the control group leaving little room for improvement

Pandey 2017

Methods	Aim of study: To assess the impact of text message reminders on adherence to medications and exercise in patients recently discharged from the hospital after a myocardial infarction (MI). Study Design: RCT (pilot single centre, individual allocation) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Canada Setting: Hospital discharge to community Inclusion criteria: ≥18, discharged from hospital after MI in preceding 2 weeks and enrolled in a structured cardiac rehabilitation program. Patients receiving treatment with medications from all four of the following classes: antiplatelets, BB, ACEI/A2RA and statins. Exclusion criteria: patients taking medications in dosing regimens > once daily, no mobile phone, unable to read and write in English or provide informed consent, or those who were incarcerated. Number of participants randomized: 34 Number of participants included in analysis: 33 (17 & 16) Age: 64.6 ± 11.5 vs 62.1 ± 11.0; Subgroup >65: 7 (41%) vs 8 (50%). Gender: 11 (65%) vs 2 (12%), not reported for subgroup Ethnicity: Not specified Number of medications: cardiac (post-MI) prescription medication: 10.1 ± 4.5 vs 8.0 ± 5.2; not reported for older subgroup Frailty/functional impairment: Not specified Cognitive impairment: Dementia: 3 (18%) vs 2 (13%) Co-morbidities: no total co-morbidity score
Interventions	Group 1: *Text message reminder*: Once daily text message at the time they preferred to take their medications. Text messages simply indicated that patients should remember to take their medications and contained no identifiable information such as medication names or classes. e.g. "Please remember to take your morning medications now" Group 2: Usual care (no text message)

	Co-Intervention: All participants received outpatient cardiac rehab program for 3 months and follow-up assessment at 12 months Provider: Automated (Set up by cardiac rehab nurses, then automated to send daily) Where: Via text message When & how often: Daily for 12 months Intervention personalised: Not really - standard wording "Please remember to take your morning medications now", time of day was modified for patient
Outcomes	Timing of outcome assessment: 12 months *Medication adherence (subjective)*: *Self-reported adherence:* Participants asked to use a logbook to record name and timing of medications taken on a daily basis. Logbooks were collected monthly. Absolute medication adherence calculated as percentage of total prescribed doses that were actually taken each month. 12 months adherence calculated as the mean of each of the 12 monthly measurements. Adherence outcome is % of days covered
Notes	Trial registration: NCT02783287 Consumer involvement: Not specified Funding source: Unclear: Brigham and Women's Hospital, and University of Waterloo listed under sponsors and collaborators Drop-out: 1 control withdrew

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a web-based random number generator in a 1:1 ratio.
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Patients and their health care providers were aware of the arm to which they had been randomized.
Blinding of outcome assessment (detection bias)	High risk	Open-label trial, no mention of blinding
Incomplete outcome data (attrition bias)	Unclear risk	1 withdrew only - but may be relevant given low patient numbers, especially in older people subgroup
Selective reporting (reporting bias)	Low risk	As described in methods
Other bias	Unclear risk	Persistence with the 4 post-MI medications not reported. Typically this is well below 100%, plus some medications may be stopped due to ADRs, etc. It is

		unlikely that no medications were stopped for any patients over 12 months. It is unclear how this was accounted for in the study.

Pereles 1996

Methods	Aim of study: To determine the effect of an inpatient self-medication program (SMP) on the ability to self-medicate, patient medication knowledge, compliance, and patient morale. Study Design: RCT (2 inpatient geriatric units, individual allocation) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Canada Setting: Hospital (prior to discharge from inpatient geriatric units) Inclusion criteria: discharge home (community living), patient responsible for administration of own medication, MMSE ≥20, ability to give informed consent, medically stable condition Number of participants randomized: 107 (51 & 56) Number of participants included in analysis: Unclear (107 for baseline, 74 for follow-up) Age: mean SD 80 ± 7 vs 80 ± 7 Gender: female: 37 (73%) vs 48 (86%) Ethnicity: Not specified Number of medications: medications/day: Inpatient: 4.8 ± 3 vs 4.7 ±2; Discharge: 4.7 ± 3 vs 5.1 ± 4 Frailty/functional impairment: Not specified Cognitive impairment: MMSE <20 excluded, MMSE 26 ± 3 Co-morbidities: Not specified
Interventions	Group 1: *Inpatient self-medication program*: Three stage program in which patient is given increasing responsibility for admin of his/her medications. 1. Patient is counselled by pharmacist and patient requests medications from nurses at appropriate times. 2. Patient is given 24 hour supply of medications to self-administer. Advances to next stage if no errors after 3-5 days. 3. Patient is given several days supply of medication. Average duration of program = 21.6 days (SD 19). Group 2: *Usual care* - medications administered by nursing staff Co-Intervention: 72 hours before discharge, both groups received pharmacist assessment of knowledge and functional ability to manage medicines and pre-discharge medication education from a pharmacist both groups had a 20 minute counselling session with a pharmacist. Provider: Pharmacist & Nurse Where: Inpatient geriatric unit (subacute, average LOS = 40 days) When & how often: Prior to discharge, continuously for an average of 21.6 days Intervention personalised: Yes - To some extent, e.g. 41% intervention patients discharged with a Dosette (and 34% control patients)

| Outcomes | Timing of outcome assessment: Discharge and 40 days post discharge
Medication adherence (objective): *Pill count:* Patients discharged with 40 days worth of medication, pill count conducted in home at 40 days. Proportion of medication errors (?assumed missed doses but not explained) of the total doses administered
Medication taking ability (objective): Assessed differently for each group: intervention = 2 or less errors on stage 2 of SMP considered able to self-medicate at discharge. Control = Pharmacist assessment at time of discharge counselling with input from other team members. YES/NO - self-medicating at discharge (note: there could be reasons other than failing the SMP that might explain why they were not self-medicating at discharge, such as patient preference)
Knowledge about medicines (objective): "short medication knowledge questionnaire" = Patients asked to name and describe appearance and purpose of their medication, describe their regimen and any potential side effects or drug interactions. % correct responses in each knowledge category |
| Notes | Trial registration: N/A
Consumer involvement: Not specified
Funding source: Not specified
Drop-out: 1 refusal, 32 lost to follow-up (19C, 14I) (5 death, 2 lost to follow-up, 21 RACF, 4 other)
Fidelity: 33 did not complete study protocol |

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Not blinded (unable to blind)
Blinding of outcome assessment (detection bias)	High risk	Medication ability not blinded (groups assessed differently) unclear if adherence was blinded
Incomplete outcome data (attrition bias)	High risk	33 did not complete study, and they were older, lower MMSE and had longer hospital stays
Selective reporting (reporting bias)	Low risk	Reported as per methods
Other bias	Unclear risk	Power analysis "suggested 48 patients in each group would be required", loss to follow-up meant didn't

		maintain required sample size. 33 did not complete study protocol - poor fidelity

Rich 1996

Methods	Aim of study: To evaluate the effect of a multidisciplinary treatment strategy on compliance rates for patients hospitalised with congestive heart failure Study Design: RCT (sub-study of larger RCT (Rich 1995), unit of allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: Hospital, discharge and post-discharge in the home Inclusion criteria: Aged 70+, admitted to hospital with CHF, at last one risk-factor for early readmission. Exclusion criteria: Severe dementia (inability to assist with self-care) or other serious psychiatric illness, limited life-expectancy (3 months), discharge to RACF living outside catchment area. Number of participants randomized: Unclear Number of participants included in analysis: 156 (80 & 76) Age: mean ± SD 80.5 ± 5.7 vs 78.4 ± 6.1 Gender: female 74% vs 59% Ethnicity: Caucasian: 40% vs 29% Number of medications: medications at discharge: 5.2 ± 2.4 vs 5.2 ± 2.5 Frailty/functional impairment: ADL: 5.7 ± 1.1 vs 5.7 ± 0.8 Cognitive impairment: severe dementia excluded Co-morbidities: no total co-morbidity score
Interventions	Group 1: *Multidisciplinary intervention for elderly people with CHF:* Education from study nurse about CHF and its management using a 15 page teaching guide prepared by the study team. Patients seen daily by a study nurse throughout the remainder of their hospital stay, and the importance of compliance with both medications and diet was emphasised repeatedly. Also visited by dietician and social service representative (who assisted in arranging appropriate post-discharge care). Shortly before discharge, geriatric cardiologist reviewed medications and made recommendations to primary physician regarding simplification and consolidation. Following discharge, all patients seen by hospital's home care department, and contacted regularly by study nurse. Group 2: *Usual care:* Conventional medical care + standard hospital services, including dietary teaching and pre discharge medication instructions. Co-Intervention: N/A Provider: Nurse (+ input from dietician, and geriatric cardiologist) Where: Hospital & home When & how often: During hospital, reinforced daily. Duration post-discharge unclear Intervention personalised: Yes

Outcomes	Timing of outcome assessment: 30 ± 2 days after discharge *Medication adherence (objective)*: *Pill count:* performed for all current medications, presented dichotomously as compliant (≥80%) or non-compliant *Adverse clinical health outcomes (objective): Hospital readmissions:* Number of people readmitted to hospital within 30 days of discharge
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: National Heart, Lung and Blood Institute grant Drop-out: Unclear

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocated based on terminal digit of a computer-generated sequence of random numbers (i.e. even or odd)
Allocation concealment (selection bias)	Low risk	Neither patient nor investigators were aware of treatment assignment until after randomization.
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Low risk	Pill count by experienced clinical pharmacist or trained pharmacy assistant blinded to treatment assignment
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up reported, ITT
Selective reporting (reporting bias)	Low risk	Reported as per methods, except for additional measure of adherence (>80%)
Other bias	Unclear risk	Unclear whether adherence assessment was for all medications or only cardiac medications which were the focus of this study

Saez de la Fuente 2011

Methods	Aim of study: To evaluate the utility of a pharmacotherapeutic information program at hospital discharge in polymedicated patients and the profile of modifications in the treatment of the patient at 30-50 days of hospital discharge Study Design: RCT (unit of allocation: individual) Number of arms/groups: 2
Participants	Description: Both patient/consumer and carer Geographic location: Spain Setting: Hospital discharge Inclusion criteria: using prescription medications for 3 or more months and ≥4 active ingredients at discharge.

	Exclusion criteria: transfer to geriatric residence, dementia and/or psychiatric illness incapacitated in the absence of a caregiver responsible for the medication at the time of the interview, and have Barthel index <20. Number of participants randomized: 59 (29 & 30) Number of participants included in analysis: 50 (26 & 24) (but methods says ITT) Age: median (range): 73 (28-93) vs 75 (14-96) Gender: Female n(%): 10 (34.5%) vs 11 (36.7%) Ethnicity: Not specified Number of medications: median (IQR): active ingredients/patient at discharge: 8.3 (7.4-9.3) vs 7.6 (6.5-8.7); Pharmaceutical forms/patient: 7.9 (7.1-8.8) vs 7.1 (6.0-8.1) Frailty/functional impairment: Barthel Index: Median (IQR) 100 (85-100) vs 100 (65-100) Cognitive impairment: Dementia/psychiatric illness: 8 (26.7%) vs 8 (26.7%) Co-morbidities: Not specified
Interventions	Group 1: *Pharmacotherapeutic discharge information program:* Verbal and written information about their treatment at hospital discharge - unclear who provided information, suspect pharmacist (as pharmacist conducted interview). Format and content unclear. Group 2: *Usual care* - no discharge information provided Co-Intervention: N/A Provider: Unclear - ?pharmacist Where: Discharge from hospital When & how often: Once, pre-discharge Intervention personalised: Yes (info provided presumably tailored to individual medication regimen)
Outcomes	Timing of outcome assessment: Discharge and 30-50days (mean 42.1, SD 9.6 days) *Medication adherence (subjective)*: *Morisky-Green Medication Compliance:* 4 questions: 1) Do you ever forget to take the medications, yes or no? 2) Take the medicines at the indicated time, yes or no? 3) When you feel better, stop taking the medication Yes or no? 4) If you ever feel sick the medications stop take them yes or no? ==> To consider good adherence, the response of all questions must be adequate (no, yes, no, no) *Adverse clinical health outcomes (objective): Deaths:* Number of deaths during follow-up *Adverse clinical health outcomes (subjective): ED and hospital admissions:* Telephone questionnaire - Number of ED or hospital readmissions during follow-up
Notes	Trial registration: Not specified Consumer involvement: Funding source: Not specified Drop-out: 9 lost to follow up (3 died, 5 in hospital, 1 moved) Note: Caregiver at discharge: 15 (57.7%) vs 17 (70.8%) Language translation: Yes - translated to English

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	At the time of discharge, patients were distributed randomly in 2 groups, by a block method with a 1: 1 ratio between both groups
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Patients not blinded, unclear about personnel
Blinding of outcome assessment (detection bias)	Unclear risk	Pharmacist was interviewer. At the time of the interview telephone, the interviewer was unaware of the treatment of the patient, as well as the previous result of adherence to discharge.
Incomplete outcome data (attrition bias)	Unclear risk	Minimal drop-out, unclear why those in hospital weren't counted as readmissions
Selective reporting (reporting bias)	Low risk	Appears per protocol
Other bias	Low risk	None apparent

Shimp 2012

Methods	<u>Aim of study</u>: To evaluate a patient-centered employer-based medication therapy management (MTM) program. <u>Study Design</u>: RCT (unit of allocation: individual) <u>Number of arms/groups</u>: 2
Participants	<u>Description</u>: patient/consumer <u>Geographic location</u>: USA <u>Setting</u>: Community (University) <u>Inclusion criteria</u>: University of Michigan beneficiaries (employees, retirees and their dependents), taking ≥7 prescription medications. Patients with a University of Michigan primary care provider were preferentially invited. <u>Number of participants randomized</u>: 133 (Intervention), "a similar number who consented but not invited formed control" <u>Number of participants included in analysis</u>: 128 (intervention) <u>Age</u>: Mean age 70 years (Intervention) <u>Gender</u>: 55% Female (Intervention) <u>Ethnicity</u>: Not specified <u>Number of medications</u>: prescription medications: 9.2 ± 3.2 (intervention) <u>Frailty/functional impairment</u>: Not specified <u>Cognitive impairment</u>: Not specified <u>Co-morbidities</u>: 3 ± 1.4 medical conditions (intervention)
Interventions	<u>Group 1</u>: *Focus on Medicines (FOM) Medication therapy management (MTM):* Two face-to-face meetings with University of

	Michigan clinical pharmacists. First visit was comprehensive review of all medications. Patients with DM, HT, dyslipidaemia, asthma, arthritis, chronic pain and OP were asked disease-specific questions. Patient questions were answered. Second visit patient and pharmacist discussed the recommendations and a medication action plan (MAP). This detailed DRPs, recommended action and person responsible. Group 2: *No intervention* Co-Intervention: N/A Provider: Pharmacist Where: Unclear - University or home? When & how often: Twice, unsure of timing Intervention personalised: Yes - patient-centered medication action plan
Outcomes	Timing of outcome assessment: Baseline (1 yr prestudy) and Final (1 yr poststudy) *Medication adherence (objective)*: *Medication possession ratio:* MPR defined as sum of all days of medication supply received during the 1 year pre study and 1 year post study periods, divided by the total number of days supply needed during 365 days. MPR calculated for top 8 drug classes for chronic conditions.
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: University of Michigan Drop-out: 5 withdrew *Further information required:* raw data on MRPs (author correspondence successful, but no further data was available, authors said "results showed no significant change")

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not specified, and those who agreed to participate compared with similar number of individuals meeting selection criteria but not invited to participate (control group)
Allocation concealment (selection bias)	High risk	not specified - patients randomly selected by study team?
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	High risk	Not blinded
Incomplete outcome data (attrition bias)	High risk	No details on attrition of control group etc. Would assume some people would change jobs

Selective reporting (reporting bias)	High risk	Adherence outcomes, both BMQ and Treatment Satisfaction Questionnaire for Medication, not included despite being a main outcome and listed in methods
Other bias	Unclear risk	Funded by university of Michigan, preference given to people with primary practitioner who worked at university of Michigan

Shively 2013

Methods	Aim of study: To determine the efficacy of a patient activation (Heart PACT) intervention compared with usual care on activation, self-care management, hospitalizations, and emergency department visits in patients at high risk of readmission/hospitalization for HF. Study Design: RCT (repeated measure design, unit of allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: Veterans Affairs Healthcare System (single site) Inclusion criteria: document clinical HF stage C, incident hospitalization or ED visit for HF treatment within previous 12 months, ≥18 years, live in San Diego county, read & speak English, telephone access, has a primary care provider. Exclusion criteria: inability to provide written consent, acute medical problems within previous month, or considered by investigators to be medically unstable, enrolled in speciality HF program or telehealth or had long term follow-up by cardiology after hospital admission, severe medical problems, life expectancy <1 year, acute substance abuse, psychiatric problems or homelessness. Number of participants randomized: 84 (43 vs 41) Number of participants included in analysis: 6 months: 68 (34 vs 34) Age: Grouped: mean ± SD 66.1 ± 10.76, range: 42-89 (Intervention: 63.4 ± 9.10, Control: 68.9 ± 11.73) Gender: 1 Female (1.2%) (0 vs 1) Ethnicity: White: 76.7% vs 78.0% (other races not extracted) Number of medications: Author reported all >4 medications (unpublished) Frailty/functional impairment: Not specified Cognitive impairment: Not specified Co-morbidities: 71% reported ≥3 co-morbidities
Interventions	Group 1: *Patient activation (Heart PACT):* 6 month activation/Heart PACT program developed to enhance self-management. Intervention used activation theory and was tailored to each participant's activation level. At each meeting/telephone call, goals and progress toward attaining these were discussed (Figure 2). Also received a self-management tool kit (BP cuff, weight scale, pedometer, HF self-management DVD, and educational booklet).

	Group 2: *Usual care* - general medical care and any HF-specific clinical care from primary care provider. Received self-management toolkit after final assessment (6 months) Co-Intervention: 2 hour baseline outcome assessment Provider: Nurse (advanced practice nurse) Where: Telephone & F2F. Unclear location - assume at clinic When & how often: 6 sessions over six months Intervention personalised: Yes - personalised based on activation level
Outcomes	Timing of outcome assessment: Baseline and six months *Medication adherence (subjective)*: *Self-reported medication adherence:* Medication adherence (as part of MOS specific adherence scale). "Took medications as prescribed (on time without skipping dose) in the past 4 weeks". Responses from 0 to 5, transformed to a 0-100 scale. *Adverse clinical health outcomes (subjective): Self-reported hospitalizations:* Patients asked to report any hospitalizations, ED visits, and other unscheduled visits including reason for visit and treatment. Results reported as mean (SD)
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Department of Veteran Affairs, Veterans Health administration, Health Services Research and Development Service, project 04-252 Drop-out: No details provided *Unpublished data:* author reported that participants were on >4 medications, most had minimum of 12 medications and 3 comorbid conditions.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A stratified block randomization approach, based on baseline activation, was used to ensure patients were equally distributed. No other details regarding randomization
Allocation concealment (selection bias)	Unclear risk	Randomly assigned after baseline assessment - unclear who allocated or if concealed
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not clear if outcome assessors were blinded
Incomplete outcome data (attrition bias)	Unclear risk	Missing completely at random (MCAR) analysis completed but not reported. Attrition rate 19%

Selective reporting (reporting bias)	Low risk	As per methods
Other bias	Unclear risk	Participants received $10 at baseline and 3 months, $20 at 6 months

Taylor 2003

Methods	Aim of study: To determine the effect of pharmaceutical care on the prevention, detection and resolution of drug-related problems in high-risk patients in a rural community. Study Design: RCT (3 clinics, unit of allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: primary care clinic (Family medicine clinics - rural) Inclusion criteria: adults (18+) at high risk for medication related adverse events (presence of 3 or more risk factors: $\geq$5 medications, $\geq$12 doses/day, $\geq$4 medication changes in previous year, $\geq$3 concurrent diseases, history of non-compliance, presence of drugs requiring therapeutic monitoring) attending a participating clinic. Exclusion criteria: significant cognitive impairment, history of missed office visits, scheduling conflicts, life expectancy <1yr. Number of participants randomized: 81 Number of participants included in analysis: 69 (33 & 36) Age: 64.4 $\pm$ 13.7 vs 66.7 $\pm$ 12.3 (p=0.467) Gender: Female: 63.6% vs 72.2% Ethnicity: White: 60.6% vs 61.1% Number of medications: type not specified, 6.3 $\pm$ 2.2 vs 5.7 $\pm$ 1.7 Frailty/functional impairment: Not specified Cognitive impairment: significant cognitive impairment excluded Co-morbidities: $\geq$3 concurrent diseases was inclusion criteria
Interventions	Group 1: *Outpatient pharmaceutical care:* Standard medical care + pharmaceutical care. Pharmaceutical care (~20mins) occurred with a pharmacist, before seeing physician at regularly scheduled office visits. Pharmacists evaluated indication, effectiveness, dosage, correctness and practicality of directions, drug-drug interactions, drug-disease interactions, therapeutic duplication, duration of treatment, untreated indications, and expense. Pharmacist reviewed medical record, conducted a chart review and examined medication history to determine compliance with and complications of medications and provided comprehensive individualized patient education that included a brief review of the disease, important lifestyle modifications and basic drug information. Therapeutic recommendations were communicated to physicians through discussions and progress notes. Group 2: *Usual care:* Standard medical care (assume no pharmaceutical care during clinic visits) Co-Intervention: Both groups received baseline and follow-up interview with pharmacist. Information collected included

	compliance, presence of medication misadventures, and medication knowledge. Provider: Pharmacist Where: Medical clinic When & how often: Continuous for 1 year at scheduled clinic visits Intervention personalised: Yes
Outcomes	Timing of outcome assessment: Baseline and 12 months *Medication adherence (subjective)*: *Self-reported compliance: percentage* of patients with medication compliance scores of 80-100%. Calculated by asking the patient the number of medication doses missed during the past week or month and dividing the estimated number of doses taken by the total number of doses prescribed. *Knowledge about medicines (objective):* Self-reports used to assess medication knowledge during each pharmacist-patient encounter. A knowledge score was determined by dividing the number of medications for which a patient reported the correct name, purpose, dose and frequency by the total number of medications and multiplying by 100. *Satisfaction with intervention (subjective):* Patient satisfaction with pharmacy-related services, survey. *Health-related quality of life (subjective):* Sf-36 health survey. *Adverse clinical health outcomes (objective): ED & hospital visits:* Number of emergency department visits and hospitalizations for each patient during preceding year - medical record audit *Condition specific outcomes (objective): Clinical markers of disease:* Number of people reaching goal level of BP$\leq$140/90, DM:HbA1c$\leq$7.5%, INR 2-3 and Lipids LDL concentrations *Other (subjective):* Patients with at least one medication misadventure
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: ASHP Research and Education Foundation Drop-out: 3 intervention refused, 6 lost to follow-up (3 & 3), 3 died (2 &1)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly assigned to a control group or an intervention group, no details on randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Not specified, order of consent/allocation unclear
Blinding of participants and personnel (performance bias)	High risk	Not blinded due to nature of intervention

Blinding of outcome assessment (detection bias)	High risk	No mention of blinding, may have impacted reporting of outcomes
Incomplete outcome data (attrition bias)	Unclear risk	12 (14.8%) lost to follow-up, no mention if characteristics similar
Selective reporting (reporting bias)	Low risk	reported as per methods
Other bias	Low risk	None apparent

Truelove 2015

Methods	Aim of study: To determine whether fixed dose combinations of generic drugs ('polypills') would promote use of optimal preventative drugs Study Design: RCT Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Australia Setting: Primary care clinic (General practices or Aboriginal Medical services) Inclusion criteria: established CVD (MI, stroke, or PVD = secondary prevention group) or a 5-year CVD risk of ≥15% using Framingham-based calculation (=primary prevention group), Enrolling Dr had to be satisfied that each medication was clearly indicated and no contraindication. Exclusion criteria: Contraindication to any component of polypill, responsible clinician feels change to current therapy will place patient at risk. Number of participants randomized: 623 (311 & 312) Number of participants included in analysis: 609 (304 & 305), Subgroup of more than 8 meds: 202 Age: More than 8 meds subgroup = 66.4 years ± 11.4 years Gender: 41.6% Female Ethnicity: Not specified Number of medications: > 8 prescription medications subgroup Frailty/functional impairment: Not specified Cognitive impairment: Not specified Co-morbidities: Not specified
Interventions	Group 1: *Polypill*: All previous CV medications stopped and started on a Polypill (Version 1 aspirin 75mg, simvastatin 40mg, lisinopril 10mg, atenolol 50mg, Version 2 aspirin 75mg, simvastatin 40mg, lisinopril 10mg, HCT 12.5mg). Group 2: Same medications but no polypill, i.e. usual care Co-Intervention: N/A N/A - Doctors given complete treatment autonomy after randomization. Both polypill and usual medications dispensed from designated pharmacies with same out of pocket costs. Provider: GP prescribed Where: General practice or aboriginal medical centre When & how often: Continuous unless stopped by GP or patient

	Intervention personalised: Not really - two versions of polypill. Otherwise no personalisation
Outcomes	Timing of outcome assessment: Baseline, 1 month, then at 6 monthly intervals for 18 months *Medication adherence (subjective)*: *self-reported use* of combination treatment (≥2 BP-lowering medications an antiplatelet and a statin). Patient must have reported taking each component medication on at least four of the seven preceding days. This captures combined effect of changes by health care provider and patient adherence
Notes	Trial registration: ACTRN126080005833347 Consumer involvement: Not specified Funding source: NHMRC of Australia Fidelity: 62.4% still taking polypill at end of study (suggesting there had been many GP/patient changes during study) Drop-out: 6 refused (3 & 3), 2 died (1 & 1), 6 missing/unable to contact (3 & 3)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central, computer-based randomisation service. Stratified by study center, indication and prescription of all appropriate therapies at baseline (yes vs no)
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Unable to blind, designed as an open trial
Blinding of outcome assessment (detection bias)	High risk	Blinded endpoints but, adherence was self-reported so unable to blind this outcome
Incomplete outcome data (attrition bias)	High risk	97.7% and 97.8% completed, but only 62.4% taking polypill at end of study
Selective reporting (reporting bias)	Low risk	as per methods
Other bias	Unclear risk	Trial study sample size calculation 1000, only 623 recruited due to insufficient resources. Only 62.4% taking polypill at end may indicate poor fidelity

Vinluan 2015

Methods	Aim of study: To evaluate the effect of pharmacist discharge counselling on patient adherence to heart failure (HF) therapy among an elderly US population and assess hospital readmission rates. Study Design: RCT Number of arms/groups: 2

Participants	Description: patient/consumer Geographic location: USA Setting: Hospital Discharge Inclusion criteria: ≥65 years admitted with a new diagnosis of HF or already had diagnosis and were readmitted with HF exacerbation, prescribed ≥5 medications at discharge. Exclusion criteria: Living in long-term facility, hearing or cognitive impairment, could not communicate in English, did not manage their own medications, lacked a telephone, or were unable to give informed consent. Number of participants randomized: 16 (7 & 9) Number of participants included in analysis: Adherence: 2 & 2, Hospitalisation: 7 & 9 Age: 74 ± 5.9 vs 71 ± 6.9 Gender: Female 86% vs 78% Ethnicity: Not specified Number of medications: chronic/regular medications; 8.1 ± 2.9 vs 8.3 ± 2.2 Frailty/functional impairment: Not specified Cognitive impairment: Cognitive impairment excluded Co-morbidities: total number not specified
Interventions	Group 1: *Pharmaceutical discharge HF counselling*: Individual inpatient counselling by a pharmacist and telephone call follow-up with review of current medications and HF counselling after discharge at day 3, 30, 60 and 90. Group 2: *Usual care:* Regular care by nurses (including discharge counselling using generated d/c med list and HF handout) Co-Intervention: Pharmacist performed a comprehensive review of inpatient HF medication regimen for all patients to ensure appropriate therapy was initiated, reviewed drug interactions, drug-disease interactions and duplicate therapy. Provider: Pharmacist Where: Hospital and telephone When & how often: Hospital at baseline, telephone day 3, 30, 60 and 90. Intervention personalised: Yes
Outcomes	Timing of outcome assessment: 90 days post discharge *Medication adherence (objective)*: *Prescription refill history* from community pharmacy, percentage of participants adherent *Adverse clinical health outcomes (subjective): Rehospitalisation:* Patient asked number of hospital admissions within 90 days after hospital discharge. Number of deaths also collected (source?)
Notes	Trial registration: N/A Consumer involvement: not specified Funding source: Nil funding Drop-out: Details not specified, but for adherence 14 drop out (7 & 7)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomization was performed using envelopes created by an outside affiliate with an assigned number inside
Allocation concealment (selection bias)	Low risk	Sealed envelopes only opened in front of patient and pharmacist once patient agreed to participate
Blinding of participants and personnel (performance bias)	High risk	Unable to blind, unclear if this would impact outcomes
Blinding of outcome assessment (detection bias)	Unclear risk	Self-reported patient outcomes, unclear if blinded or not for pharmacist and refill history
Incomplete outcome data (attrition bias)	High risk	Massive attrition - unable to reach by phone. Also said 7 & 7 lost to follow-up, but still reported 2 & 2 (should be 0 & 2)?
Selective reporting (reporting bias)	High risk	Stated rehospitalization data obtained from patients during phone calls. However they have data for all participants? Also unclear how they got deaths data
Other bias	Low risk	None apparent

Volume 2001

Methods	Aim of study: To describe changes in patients' adherence to therapy regimens, patients' expectations of the care they receive from their pharmacist, patients' satisfaction with pharmacy services and patients' HRQOL after the provision of pharmaceutical care. Study Design: Cluster-RCT (16 pharmacies, cluster unit of allocation: pharmacy) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Canada Setting: Community pharmacy Inclusion criteria: coverage of medications under Alberta Health & Wellness senior drug benefit plan (age≥65yrs), ≥3 medications according to dispensing records, able to complete telephone interviews, residing in Alberta for 12 of 15 study months, agree to get prescriptions from study pharmacy (Kassam 2001). Exclusion criteria: communication and language barriers, terminal disease, unable to provide informed consent Number of participants randomized: 16 pharmacies (8 vs 8), 363 pts (159 vs 204) Number of participants included in analysis: 292 completed Age: 73.89 ± 6.09 vs 73.18 ± 6.11 Gender: Female: 63.5% vs 69.6% Ethnicity: Not specified

	Number of medications: Prescription: 4.67 ± 2.82 vs 3.90 ± 2.49. Non-prescription: 0.63 ± 0.92 vs 0.73 ± 1.17 Frailty/functional impairment: Not specified Cognitive impairment: Not specified Co-morbidities: Not specified
Interventions	Group 1: *Pharmaceutical care research and education project (PREP)*: Comprehensive Pharmaceutical Care. Treatment pharmacists (enrolled in an intensive education program) used the Pharmacist's Management of Drug Related Problems (PMDRP) instrument to summarize the information collected during patient interview, and SOAP (subjective, objective, assessment and plan) record to document actions and follow-ups. Group 2: *Usual care*. Control pharmacists not told which patients had or had not agreed to participate. Co-Intervention: N/A Provider: Pharmacists (community) Where: Community pharmacies When & how often: One interview with frequent follow-up Intervention personalised: Yes - based on interview and required pharmaceutical care
Outcomes	Timing of outcome assessment: Baseline and 12-13 months *Medication adherence (subjective)*: *Morisky self-reported adherence:* Adherence to medication regimens assessed using a four item self-report Morisky (validated) measure. Summing numeric values for each answer, provides a summary adherence score ranging from 0-4, with lower scores indicating better adherence. *Satisfaction with intervention (subjective):* Patient satisfaction with pharmacy services using 34-item instrument based on work by MacKeidan and Larson and Johnson et al. Using 7 point Likert scale with 1 indicating highest satisfaction. General satisfaction extracted only. *Health-related quality of life (subjective):* SF-36 health survey, validated
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Alberta Ministry of Health, Alberta Pharmaceutical Association, University of Alberta Central Research Fund, Merck Frosst Canada, Hoechst Marion Roussel, Alberta Health-Health Services Research Innovation Fund, drug references for the pharmacists were provided by Bristol-Myers Squibb Drop-out: Unclear: 5 treatment and 7 control pharmacies supplied patient data. 3 treatment and 1 control never recruited patients. ICC not reported, number of participants in intervention and control groups at follow-up unclear. Authors contacted for more information - no response.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Pharmacies paired based on Statistics Canada median income for the first three digits of pharmacy's postal code. The study statistician did not know the identity of the pharmacies and he randomly assigned pharmacies to treatment or control within the pair. One pair were very closely located, thus assigned to same treatment/control to minimise contamination. Unclear why groups still balanced (8 & 8)
Allocation concealment (selection bias)	Unclear risk	Statistician didn't know identity of pharmacies, but steps taken to minimize contamination and match characteristics
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind patients to intervention. Control pharmacists were not told which patients had or had not agreed to participate.
Blinding of outcome assessment (detection bias)	Unclear risk	Telephone survey by Population Research Lab at the University - unclear if blinded
Incomplete outcome data (attrition bias)	High risk	Only patients with data at all three time points were included in the analysis, T1 = 363, T2 = 292
Selective reporting (reporting bias)	Low risk	Appears to be presented as per methods
Other bias	Unclear risk	"We intended that each pharmacy would identify enough to produce sample of 50 participants" - not reached, sample size based on HRQoL Recruitment bias (selective recruitment of cluster participants): high risk, patient recruitment occurred after allocation of clusters resulting in potential for recruitment bias. "it is possible that pharmacists selected patients whom they believed would benefit from the intervention or who had a more positive attitude toward pharmaceutical care".

Willeboordse 2017

Methods	Aim of study: To investigate the effectiveness of clinical medication reviews (CMR) on quality of life and geriatric problems in comparison with usual care in older patients with geriatric problems in general practice Study Design: Cluster-RCT (22 General practices, cluster unit of allocation: GP practice) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Netherlands

	Setting: primary care clinic (General practice clinics) Inclusion criteria: PRACTICE: inclusion = all GP practices members of Academic Network of GPs. Practice not performing CMRs on a regular basis and would not start doing if randomized to control. PARTICIPANTS: Inclusion = ≥65, newly presented with a geriatric problem in general practice and used ≥1 prescribed drug chronically (≥3months). Geriatric problems identified by screening electronic records and by screening questionnaire. Geriatric problems included mobility, dizziness, fear of falling, urinary incontinence and cognitive impairment. Patients were included if they scored ≥5 on the VAS scales (range 1–10) of the geriatric problems or reported ≥1 fall in the preceding 6 months. Exclusion criteria: PARTICIPANTS: recorded dementia diagnosis, GP excluded patients who had recent CMR or deemed unable to participate. Number of participants randomized: 518 (275 & 243) Number of participants included in analysis: T0 = 270 vs 239, T2 = 215 vs 211, (unpublished adherence results for 208 vs 198) Age: 77.8 ± 7.7 vs 77.8 ± 8.0 Gender: female: 177 (64.4%) vs 159 (65.4) Ethnicity: Born Dutch or other European: 91.7% vs 93.6% Number of medications: number of drugs reported by patient: 6.1 ± 3.1 vs 5.6 ± 3.2 Frailty/functional impairment: Mobility problems (≥5 VAS) = 57.9% vs 62.6% Cognitive impairment: Cognitive problems (≥5 VAS) = 25.5 vs 26.9%, Diagnosed dementia excluded Co-morbidities: Chronic diseases: 2.77 ± 1.76 vs 3.23 ± 2.19
Interventions	Group 1: *Optimised clinical medication reviews (Opti-Med):* 1) Preparation: info from EMRs, pharmacy and screening questionnaire collected including drug use, medication history, potential DRPs, medical problems, recent lab results and non-lab measurements. 2) Clinical medication review: expert team of GP/nursing home physician and community pharmacist performed review using adapted systematic tool to reduce inappropriate prescribing (STRIP) method. 3)Pharmacotherapeutic treatment plan (PTP): PTP sent to patient's GP, 4) Implementation of PTP: patients invited for consultation with GP in which the PTP was discussed and determined together with the patient Group 2: *Usual care.* Expert team also performed CMR analyses but GPs and patients did not receive the results. Co-Intervention: N/A Provider: Independent expert team (doctor and pharmacist) & Patients GP Where: Primary care clinic When & how often: Once - baseline Intervention personalised: Yes
Outcomes	Timing of outcome assessment: Baseline and six months

	Medication adherence (subjective): *Self-reported adherence problems* assessed in the screening and follow-up questionnaire *Satisfaction with intervention (subjective): Medication Satisfaction Questionnaire*: assessed on a 7-point Likert scale. A 1 point change on the MSQ score was considered clinically meaningful *Health-related quality of life:* SF-12 and EQ-5D-3L *Adverse clinical health outcomes (objective): Drug related Problems*: Number of DRPs per patient - using the DOCUMENT checklist. Assessed by expert team at baseline and by one researcher at follow-up.
Notes	Trial registration: NTR4264 Consumer involvement: Not specified Funding source: Dutch Organisation for Health Research and Development Drop-out: 9 excluded prior to intervention (5 & 4), 51 withdrew (33 & 18), 42 lost to follow up (27 & 15) Fidelity: 274 of 275 received CMR, 247 discussed with patient *Unpublished data*: Adherence worsened or persisted: 65 vs 54, Adherence improved or remained the same: 143 vs 144 ICC value: 0.08, thus this was used to recalculate sample sizes, 57 intervention vs 67 control.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization of practices performed by statistician blinded to characteristics of practices using a computer generated list of random numbers
Allocation concealment (selection bias)	High risk	Randomisation done at practice level before patients recruited - could have influenced recruitment of patients
Blinding of participants and personnel (performance bias)	High risk	No blinding, but blinding to treatment allocation not possible due to nature of the intervention
Blinding of outcome assessment (detection bias)	Unclear risk	Subjective outcomes unblinded, unclear if researcher blinded
Incomplete outcome data (attrition bias)	High risk	Higher drop out & loss to follow up in intervention group: 51 withdrew (33 & 18), 42 lost to follow up (27 & 15)
Selective reporting (reporting bias)	Unclear risk	Raw data not reported
Other bias	Unclear risk	Sample size 500 patients, not maintained during follow-up. Based on EQ-5D. 274 of 275 received CMR, 247 discussed with patient

		Recruitment bias (selective recruitment of cluster participants): high risk, randomisation was carried out before patients were recruited, thus potential for selective recruitment based on practice knowledge of being intervention or control group

Williams 2012

Methods	Aim of study: To test the feasibility and impact of a multifactorial Medication Self-Management Intervention (MESMI) to improve blood pressure control and medication adherence in adults with co-existing diabetes and CKD disease. Study Design: RCT (single hospital, unit of allocation: individual) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: Australia Setting: Outpatient clinic Inclusion criteria: ≥18 years, comprehended English, mentally competent (AMT), Type 1 or 2 diabetes and CKD (modified diet in renal disease eGFR >15 or diabetic kidney disease) and systolic hypertension ≥130mmHg. Exclusion criteria: >50km from city centre. Number of participants randomized: 80 (39 vs 41) Number of participants included in analysis: 75 (36 vs 39), adherence 74 (35 vs 39) as per author correspondence Age: 68 ± 8.3 vs 66 ± 10.8 Gender: Female: 17 (42.6%) vs 26 (63.4%) Ethnicity: Australia born: 14 (35.9%) vs 15 (36.6%) Number of medications: Prescribed medications (excluding insulin and OTC) 7.6 ± 2.6 vs 7.2 ± 3.3 Frailty/functional impairment: Not specified Cognitive impairment: AMT: 10 (10-11) vs 11 (11-10), cognitive impairment excluded Co-morbidities: Other long term illnesses: 7.7 ± 2.5 vs 8.2 ± 2.5
Interventions	Group 1: *Medication Self-Management Intervention (MESMI)*: Multifactorial intervention consisting of self-monitoring of BP, individualised medication review, 20min DVD, and fortnightly motivational interviewing follow-up telephone contact for 12 weeks to support BP control and optimal medication self-management. Patients taught how to take BP correctly, and recorded BP daily for 3 months. Medication review involved drawing up a medication chart (generic name, indication, dose, targets). DVD had 3 sections: how BP affects body, benefits & safety of prescribed medications, tips to help take medications as prescribed. Motivational interviewing: open-ended questions used to prompt discussion about the participant's well-being, BP and medications. Group 2: *Usual care:* Standard outpatient care Co-Intervention: N/A Provider: Nurse (renal specialist, doctorial qualification and motivational training)

	<u>Where</u>: Home & Telephone <u>When & how often</u>: Home intervention, then 12 weeks of support and follow-up phone calls <u>Intervention personalised</u>: Yes
Outcomes	<u>Timing of outcome assessment</u>: 9 months post intervention (12 months post enrolment) *<u>Medication adherence (objective)</u>*: *Pill count:* Percentage medication adherence to all long-term prescribed medications measured by pill counts. Insulin and OTC (vitamins) not included in pill count. *Condition specific outcomes (objective): Change in BP (checked by research assistant), HbA1c, eGFR, Creatine*
Notes	Trial registration: ACTRN12607000044426 Consumer involvement: Not specified Funding source: Australian Research Council grant (LP0774989), Sigma Theta Tau International Small grant, Nurses Memorial Centre Australian legion of Ex-servicemen and women scholarship, and Mona Menzies Nurses Board of Victoria Grant. Drop-out: 1 withdrew, 3 died, 1 lost to follow-up Fidelity: Accuracy of pill count confounded by participants unable to recall when they started their new prescription. Only 30 participants saved their medication boxes to enable a full pill count to be performed. Unpublished data: authors contacted regarding number of people included in adherence follow-up, total people included in calculation was 35 vs 39

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized by off-site statistician, stratified block randomisation
Allocation concealment (selection bias)	Low risk	Following recruitment, participants were allocated code numbers prior to enrolment and being randomized by an off-site statistician.
Blinding of participants and personnel (performance bias)	High risk	Participants could not be blinded and were asked not to disclose group allocation to research assistant
Blinding of outcome assessment (detection bias)	Low risk	Research assistant blinded to group assignment
Incomplete outcome data (attrition bias)	High risk	Pill count not possible for most (only 30 saved all pill boxes enabling complete count)

Selective reporting (reporting bias)	High risk	Sample size calculated as 108 participants - did not reach target sample size and modified inclusion criteria to try to increase recruitment
Other bias	Unclear risk	Accuracy of pill count confounded by participants unable to recall when they started their new prescription. Only 30 participants saved their medication boxes to enable a full pill count to be performed. Sample size calculated as 108 participants - did not reach target sample size

Winland-Brown 2000

Methods	Aim of study: To investigate the effect of three medication management approaches on medication adherence. To examine the relationship between medication adherence and the utilization of health care resources, including number of physician office visits, hospitalizations, and home health visits. Study Design: RCT (unit of allocation: individual) Number of arms/groups: 3
Participants	Description: patient/consumer Geographic location: USA Setting: Independent living facility Inclusion criteria: capable of following simple directions, had a medication mismanagement episode, and had a hospitalization for medication non-adherence or an illness in which therapeutic accuracy was necessary for its management Exclusion criteria: Not specified Number of participants randomized: 61 (16, 24, 21) Number of participants included in analysis: 61 (16, 24, 21) Age: mean: 87 years, range 70-100 Gender: 35 F, 26 M Ethnicity: Primarily Jewish Number of medications: Type not specified, range: 3-15 Frailty/functional impairment: Not specified Cognitive impairment: 17.5% had dementia Co-morbidities: Total number not specified
Interventions	Group 1: *Pre-poured pill box:* medication management pack, no voice-activation Group 2: *Automated voice activated dispenser:* voice-activated message that audibly reminded and automatically dispensed individual doses of the medication to the participant Group 3: *Usual care:* self-administration of own medications Co-Intervention: Nurses visited patients each week to refill medication packs and address any questions or concerns (unclear if control group also visited) Provider: Nurse filled medication packs Where: Independent living facility (patient homes) When & how often: Weekly for 6 months Intervention personalised: No

Outcomes	Timing of outcome assessment: Baseline (for health care utilisation) and 6 months *Medication adherence (Objective)*: *Pill count*: Average number of missed doses via pill count *Adverse clinical health outcomes (objective): Healthcare utilisation:* Medical records examined for number of physician visits, hospital admissions, home visits and transition to a higher level of care. *Condition specific outcomes (objective): Biochemical markers of adherence*: Measured by the impact on medical diagnosis. Hypertensive group defined as adherent if sustained normotensive, cardiac adherent by INR 2.0 to 3.0, antipsychotic adherent by stable blood levels and mood stabilization, diabetes by stable blood glucose and periodic HbA1c <9%
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Not specified Drop-out: Nil specified *Further information required:* biomedical markers of adherence as per protocol (author correspondence - successful, no further results available)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Clients "were randomly assigned to one of two medication management programs" (details unclear) and "clients of similar age, gender, and cognition were assigned to a control group" (not randomised)
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind participants
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of blinding, unclear if nurses who refilled pack each week also conducted adherence assessment
Incomplete outcome data (attrition bias)	Low risk	No attrition mentioned
Selective reporting (reporting bias)	High risk	Missing data on impact on the medical diagnoses
Other bias	Unclear risk	Groups unbalanced; G2 all had been prolonged hospitalisation compared to 7/16 in G1 and none in usual care group. Also, half of the G2 participants had 2hrs home health services/day compared to none in the G1 and usual care groups.

Wood 1992

Methods	Aim of study: To determine the effects of an inpatient self-administration of medication programme on compliance post discharge among elderly patients Study Design: Cluster-RCT (Two wards intervention, Two wards control, 1 int & 1 con per hospital) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: UK Setting: Hospital inpatient (pre-discharge) from rehabilitation wards Inclusion criteria: rehabilitating with the ultimate aim of discharge to their own home to live alone. Exclusion criteria: Nil mentioned Number of participants randomized: 33 (18 & 15) Number of participants included in analysis: 22 (11 & 11) Age: 85.4 ± 6.0 vs 84.8 ± 5.8 Gender: M:F = 1:8 (88.8% F) vs 1:6.5 (86.7%) Ethnicity: Not specified Number of medications: Number of dose taking events per day: 8.1 ± 5.0 vs 6.17 ± 5.0 Frailty/functional impairment: Not specified Cognitive impairment: Abbreviated mental test score: 9.1 vs 9.4 Co-morbidities: Not specified
Interventions	Group 1: *Inpatient self-administration*: Three distinct phases: Phase 1: medicine containers labelled as for discharge, drugs handed to patient at appropriate times and full supervision of medication selection & ingestion. After 7 days, or earlier if appropriate, patient moved to phase 2. Phase 2: patient required to request medication at appropriate times. After seven error-free days, patient moves on. Phase 3: patient becomes totally responsible for his/her own medication. Medicines stored in locked cupboard. Compliance checked by tablet count. Group 2: *Usual care*: discharge medicines issued by nursing staff immediately prior to discharge. Co-Intervention: N/A Provider: Care team - including pharmacist & nurse Where: Hospital inpatient (pre-discharge) When & how often: Up to 3 weeks, inpatient Intervention personalised: Yes - moved through phases only if able to self-administer medications
Outcomes	Timing of outcome assessment: 2 weeks and 3 months post discharge *Medication adherence (Objective)*: *Pill count:* Average percentage of non-compliance calculated by pill count. No errors made, few errors (1-15% noncompliance) and many errors (>15%)
Notes	Trial registration: N/A Consumer involvement: Not specified Funding source: Not specified

	Drop-out: 8 lost to follow-up (4 & 4), plus 3 intervention could not be analysed

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Wards allocated - randomisation method not stated
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Not blinded. blinding was not possible for the type of intervention provided unless the researcher was not involved in the provision of intervention, unclear if this had any impact on the outcome
Blinding of outcome assessment (detection bias)	Unclear risk	Not specified if home visit staff were blinded
Incomplete outcome data (attrition bias)	High risk	4 lost to follow-up from both groups, 3 intervention patients excluded because they had received new medications but transferred to original containers = potentially unbalanced analysis
Selective reporting (reporting bias)	Unclear risk	Additional data in results that aren't specified in methods (e.g. errors sufficient to be detrimental to health)
Other bias	Low risk	Recruitment bias (selective recruitment of cluster participants): low risk, recruitment occurred after allocation but all patients on the ward were included in the study (no exclusions), thus limited risk of recruitment bias.

Wu 2006

Methods	Aim of study: To investigate the effects of compliance and periodic telephone counselling by a pharmacist on mortality in patients receiving polypharmacy Study Design: RCT (unit of allocation: individual) Number of arms/groups: 2
Participants	Description: Both patient/consumer and carer Geographic location: China Setting: Specialist medical clinic at a hospital Inclusion criteria: Non-compliant (pharmacist assessed medical clinic records), ≥5 drugs on ≥2 consecutive visits to the clinic Exclusion criteria: non-Cantonese dialects or a different language, or had conditions that prevented effective communication (deaf, mute,

	dementia, psychological disorders), patients living in nursing homes with supervised treatment. Number of participants randomized: 442 (219 & 223) Number of participants included in analysis: 442 (219 & 223) (but 43 died by follow-up) Age: 71.2 ± 9.4 vs 70.5 ± 11.1 Gender: Female 51% vs 52% Ethnicity: Not specified - all spoke Cantonese Number of medications: drugs for chronic illnesses: 6.0 ± 1.3 vs 5.9 ± 1.2 Frailty/functional impairment: Not specified Cognitive impairment: Dementia excluded Co-morbidities: Not specified	
Interventions	Group 1: *Telephone counselling by a pharmacist*: Patients received a 10-15 minute telephone call from pharmacist at midpoint between clinic visits (6-8 calls over 2 yrs). Pharmacist asked about patient's treatment regimens, clarified any misconceptions, explained side effects, reminded of next clinic appointment, reinforced importance of compliance. Group 2: *Usual care:* No telephone intervention Co-Intervention: All patients received 10-15 minute education talk by pharmacist during screening. Pharmacist determined compliance using structured questionnaire Provider: Pharmacist Where: Telephone to home When & how often: 6-8 telephone calls for 2 years Intervention personalised: Yes	
Outcomes	Timing of outcome assessment: Screening or Enrolment and 2 years *Medication adherence (subjective)*: Patient asked if they had missed any doses, changed their regimens in terms of doses, frequency and timing, or had drugs left over. Compliant 80-120%. This information was checked against dispensing information. *Adverse clinical health outcomes (objective): All-cause mortality* *Adverse clinical health outcomes (objective): Hospitalisations:* Rate of admission to hospital, number of emergency room visits and hospital stay in two years before and after screening	
Notes	Trial registration: SRCTN48076318 Consumer involvement: Not specified Funding source: Hong Kong Government Health Care and Promotion Fund and MSD international grant. Drop-out: 25 & 38 died No ICC reported - unable to contact authors due to age of study. Thus unit of analysis error considered.	

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Pharmacist blinded to randomisation codes, which were computer generated by statistician and sealed in envelopes labelled with consecutive numbers.
Allocation concealment (selection bias)	Low risk	Envelopes opened by clinic nurse in an ascending manner, and patients allocated
Blinding of participants and personnel (performance bias)	High risk	Blinding was not possible because the intervention was complex and caregivers were involved
Blinding of outcome assessment (detection bias)	High risk	Blinding not possible, could have had a blinded research review outcomes
Incomplete outcome data (attrition bias)	Unclear risk	ITT, no loss to follow-up. But 60 defaulters before randomisation, of which 31 died
Selective reporting (reporting bias)	Low risk	Baseline reports as compliant/non-compliant, follow-up reports who remains compliant/non-compliant (number can be computed). Otherwise as per methods
Other bias	Unclear risk	Sample size 1067 to account for non-compliance and achieve significant reduction in mortality - not reached

Young 2016

Methods	Aim of study: To evaluate the effects of the patient activation intervention on self-management (SM) adherence, hospital readmission, ED visit rates at 30 days, 3 & 6 months. Study Design: RCT (Block randomisation of 4-6) Number of arms/groups: 2
Participants	Description: patient/consumer Geographic location: USA Setting: Two rural critical access hospitals Inclusion criteria: ≥21 years, HF as one of discharge diagnoses, 3) New York Heart Association class II to IV or class I symptoms and ≥1 HF related hospitalisation/ED visit in past year, discharged to home, passed mini-cognitive screen, understood English, had access to a phone. Exclusion criteria: scheduled procedures/surgeries, depressive symptoms (score ≥3 on Patient Health Questionnaire-2), liver cirrhosis, renal failure, end stage and/or terminal illness that affected their abilities to perform SM behaviours. Number of participants randomized: 105 (54 & 51) Number of participants included in analysis: 100 (51 vs 49) Age: 68.7 ± 11.8 vs 71.8 ± 12.6 Gender: Female: 52.9% vs 75.5% Ethnicity: Caucasian: 94.1% vs 95.9 Number of medications: Medications per day (type unknown) 16.4 ± 10.0 vs 15.9 ± 7.4 Frailty/functional impairment: Not specified

	Cognitive impairment: Had to pass mini-cognitive assessment to be included Co-morbidities: total comorbidities 7.8 ± 2.5 vs 8.0 ± 2.7
Interventions	Group 1: *Patient AcTivated Care at Home Model (PATCH)*: Usual care + 12 weeks of PATCH intervention. The intervention comprised of two phases in which the in-hospital discharge education session was followed by 12 weeks of post-discharge education sessions delivered by telephone. Patients received SM toolkit (calendar for weight and salt, scales, electronic pill organizer reminder alarm). Each intervention session lasted 45-50 minutes. Booster sessions for subjects struggling at home. Group 2: *Usual care* (the standard discharge teaching for HF and scheduled follow-up doctor appointments). Co-Intervention: N/A Provider: Unclear - nurse? Where: Phase 1: In hospital, Phase 2: post discharge via telephone When & how often: Post-discharge phone calls twice a week for first 2 weeks, then weekly 3-6 weeks, then every second week 7-12) Intervention personalised: Yes - tailored based on activation level, pre-set goals and specific SM needs, booster sessions given to those struggling with SM
Outcomes	Timing of outcome assessment: Hospital discharge and 6 months (180 days) *Medication adherence (subjective)*: *Self-reported adherence:* Number of days when any medication doses were missed in past 7 days, Grouped as 0 or ≥1 days (dichotomous) *Adverse clinical health outcomes (objective): All cause readmissions and ED visits* - self-report and primary care provider report
Notes	Trial registration: NCT01964053. Consumer involvement: Not specified Funding source: National Institutes Nursing Research of the National Institutes of Health Drop-out: 3 intervention withdrew prior to intervention, 2 control withdrew/lost to follow-up

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Project statistician used an on-line pseudo-random number generator to create an allocation schedule, random ordering of block sizes 4 and 6 was used to maintain even accrual throughout the study.
Allocation concealment (selection bias)	Low risk	Group assignments placed in sealed envelope and opened sequentially as patients were enrolled
Blinding of participants and	High risk	Blinding of subject and intervention is impossible

personnel (performance bias)		
Blinding of outcome assessment (detection bias)	Unclear risk	Data collector was blinded to treatment assignment. Unclear if this blinding was completely possible as the subjects were aware of their treatment group and may have told assessor
Incomplete outcome data (attrition bias)	Low risk	Minimal attrition, sample calculations allowed for 15% but it was much less
Selective reporting (reporting bias)	Low risk	As per methods
Other bias	Low risk	None apparent, sample size 96

Footnotes

Characteristics of excluded studies

Adams 2015

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (authors didn't collect number of medications)

Ahmad 2011

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Al-Asseri 2001

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Al-Khadra 2014

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Allen 1986

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Allen 2011

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Altavela 2008

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Alvarez 2001

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Antoniades 2012

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Antonicelli 2008

| **Reason for exclusion** | EXCLUDE Outcome = not medication adherence or medication taking ability |

Artinian 2003

| **Reason for exclusion** | EXCLUDE Medications = unable to determine if > 4 medications (no response from author) |

Ascione 1984

| **Reason for exclusion** | EXCLUDE Medications < 4 regular medications or group mean ≤4 (intervention and outcome only at CV medications, average 2) |

Bailey 2012

| **Reason for exclusion** | EXCLUDE Participants mean age ≤65 years |

Barker 2012

| **Reason for exclusion** | EXCLUDE Outcome = not medication adherence or medication taking ability |

Basger 2015

| **Reason for exclusion** | EXCLUDE Outcome = not medication adherence or medication taking ability |

Basheti 2016

| **Reason for exclusion** | EXCLUDE Participants mean age ≤65 years |

Bennett 2003

| **Reason for exclusion** | EXCLUDE Participants mean age ≤65 years |

Bhattacharya, 2016

| **Reason for exclusion** | EXCLUDE Outcome = follow-up too short (3 weeks) |

Biese 2011

| **Reason for exclusion** | EXCLUDE Medications < 4 regular medications or group mean ≤4 (conference paper for 2014 paper) |

Biese 2014

| **Reason for exclusion** | EXCLUDE Medications < 4 regular medications or group mean ≤4 |

Bilotta 2011

| **Reason for exclusion** | EXCLUDE study design not RCT, cluster RCT or quasi RCT |

Birtwhistle 2004

| **Reason for exclusion** | EXCLUDE Participants mean age ≤65 years |

Blenkinsopp 2000

| **Reason for exclusion** | EXCLUDE Medications < 4 regular medications or group mean ≤4 (antihypertensives only) |

Bogner 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Bolas 2004

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Bolton 2004

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Boult 2013

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Branda 2013

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Braun 2009

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Bronson 1986

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Bryant 2011

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Bryson 2008

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Burrelle 1986

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Calvert 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Cedilnik 2016

Reason for exclusion	EXCLUDE Intervention = not directed at consumer or their carer (directed at GP)

Chan 2012

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Chan 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Chau 2012

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Chen 2016

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Choudhry 2008

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Chow 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Clarkesmith 2013

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Clemson 2004

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Clifford 2006

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Coleman 1999

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Coombes 2018

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (only looking at adherence to medications for secondary prevention of stroke - between 1 and 3 medications/person)

Costa 2008

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Cotterell 1992

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Coull 2004

Reason for exclusion	EXCLUDE Medications = = unable to determine if > 4 medications (no contact with authors)

Criswell 2010

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Crotty 2005

Reason for exclusion	EXCLUDE Setting = participants not living in community or discharged from hospital to community

Crowley 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

D'Agostino 2006

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Damush 2011

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Day 1992

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Day 1998

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

de Lusignan 2001

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Denneboom 2007

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Denneboom 2008

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Dickson 2011

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Doucette 2009

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Doughty 2002

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Doyon 2009

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Drenth-van 2013

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Dunn 1995

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Duong 1996

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Eggink 2010

Reason for exclusion	EXCLUDE Outcome = follow-up too short (adherence 23 days)

Eikelenboom 2016

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Elliott 2008

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (new medicines only)

Elliott 2012

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Ellis 2000

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Enguidanos 2012

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Epstein 1990

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Esposito 1995

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean≤4 (assumed given low MCI scores)

Evans 2010

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Fabacher 1994

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Fan 2012

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Farmer 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Fernandes 2012

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (intervention targeting hypertension only)

Fernando 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Fernley 1983

Reason for exclusion	EXCLUDE Outcome = follow-up too short (adherence 7-10 days)

Figar 2006

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Fikri-Benbrahim 2013

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Fikri-Benbrahim 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Fincher 2009

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Finley 2003

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Fischer 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Fortney 2007

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Fortney 2011

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Fortney 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Frennet 2011

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Frey 2001

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Friedman 1996

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Fugazzaro 2016

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT (non-randomised as per 2018 paper)

Fulmer 1999

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (capped maximum 4 medications per person, hence average <4)

Gabriel 1977

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Garcao 2002

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Garcia 2017

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Garza 2016

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Gellis 2014

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Gialamas 2009

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (authors didn't collect number of medication)

Gould 2011

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Grant 2003

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Green 2008

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (adherence to antihypertensives only)

Grice 2014

Reason for exclusion	EXCLUDE Setting = participants not living in community or discharged from hospital to community

Gujral 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Gums 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Gwadry-Sridhar 2005

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Han 2010

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Hansen 2009

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Haramiova 2017

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (protocol only, blood pressure lowering medication only)

Harari 2008

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Hawe 1990

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Hayes 1998

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Hedegaard 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Heisler 2010

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Heisler 2011

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability (conference abstract for 2012 paper)

Heisler 2012

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Heisler 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Hesselink 2004

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Ho 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Hohmann 2014

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Holdford 2013

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Hsieh 2008

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (TB meds only)

Hugtenburg 2012

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Hunter 1996

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Insel 2016

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (adherence to 1 medicine only)

ISRCTN12752680

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication-taking ability. Note: secondary outcomes were changed 17/07/17, adherence was previously listed but no longer included in the study protocol.

ISRCTN18285541

Reason for exclusion	EXCLUDE Medications - unable to determine if eligible as study never completed. "Investigators decided to close the clinical trial because the rate of inclusion of patients was being so slow that it was impossible to reach the necessary number in a reasonable time". Dr José Luis González Guerrero (joselglezg@gmail.com)

Jager 2017

Reason for exclusion	EXCLUDE Intervention = not directed at consumer or their carer (GP is participant)

Jahangard-Rafsanjani 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Jarab 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Jarab 2012a

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Jensen 2003

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Jerant 2003

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (authors didn't collect number of medications)

Jiang 2007

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Johnson-Warrington 2016

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (COPD only)

Johnston 2000

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (no response from authors)

Junling 2015

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Kalichman 2011

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Karagiannis 2016

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (diabetic medications only)

Kaukab 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Kaur 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Kavin 2010

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Kelly 1990

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Keyserling 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Khonsari 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Khunti 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Kim 2014

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (adherence to BP medications only)

Kim 2015

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Kim 2015a

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Kimball 2010

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Koberlein-Neu 2016

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Kogos 2004

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Kono 2004

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Kotowycz 2010

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Kozuki 2006

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Kraemer 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Krass 2007

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Kripalani 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Kripalani 2012a

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Krishnamurthi 2014

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (TB medications only)

Krishnaswami 1981

Reason for exclusion	EXCLUDE Participants mean age ≤65 years or more than 20% aged 65 years

Kutzleb 2006

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Lam 2011

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (antihypertensives only)

Lam 2017

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Lampela, ACTRN12616001411437

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Lange 2010

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Laramee 2003

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (authors didn't collect information)

Leiva-Fernandez 2014

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (COPD only)

Lenaghan 2007

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Levine 1979

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Levy 2004

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Li 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Li 2013

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (no response from authors)

Lin 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Lluch-Canut 2006

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Lowe 1995

Reason for exclusion	EXCLUDE Outcome = follow-up too short (adherence measured at 10 days)

Lowe 2000

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Lu 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Luttik 2014

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (total unknown, adherence for individual medication classes only)

Ma 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

MacDonald 1977

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Mackenzie 2013

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (no response from authors)

Maduka 2013

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Magid 2011

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Maislos 2004

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Malet-Larrea 2016

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Maly 1999

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Margolius 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Marin 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Marquez Contreras 2009

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Martin 1982

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (total not provided, low medication regimen complexity)

Martin 2011

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Martinez 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Matsuyama 1993

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Mazzuca 1986

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

McCarthy 2013

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

McCarthy 2017

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

McGeoch 2006

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Mehos 2000

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Mehuys 2008

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Mehuys 2011

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Meredith 2002

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Miller 1988

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Miller 2008

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Mitchell 2014

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Moczygemba 2012

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Moreno 2016

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Morisky 1990

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Morrison 2016

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Mullan 2009

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Muniz 2010

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Murray 2007

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

NCT00838344

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (diabetic medication only)

NCT02140619

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (persistence to statin or antiplatelet only)

NCT02490423

Reason for exclusion	EXCLUDE Participants mean age ≤65 years (mean age 63.2 as per investigator, Dr Horne)

NCT02905474

Reason for exclusion	EXCLUDE Participants mean age ≤65 years (mean age 57 as per author email)

Nesari 2010

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Newman 2016

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Nishita 2013

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Noureldin 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Obreli-Neto 2011

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Ogedegbe 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Oliveira-Filho 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Ostbring 2014

Reason for exclusion	EXCLUDE Outcome = follow-up too short (adherence measured 2 weeks after intervention)

Ostovaneh 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Park 2011

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Parker 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Pearl 2003

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Peng 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Perl 2016

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Peters-Klimm 2010

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Phumipamorn 2008

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Pitner 2004

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Pladevall 2010

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Pladevall 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Plant 2015, ACTRN12609000554268

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Polack 2008

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Ponnusankar 2004

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Powers 2011

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (CVD adherence only, email sent to authors for actual number of medications but no response)

Pringle 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Pérez-Escamilla 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Ramaekers 2009

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (authors had no additional information)

Ramanath 2011

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Raynor 1993

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Richmond 2010

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Roden 1985

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Rose 2016

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Rothschild 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Rozenfeld 1999

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (adherence only to 1 or 2 CV medications)

Rubak 2011

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Rytter 2010

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Safren 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Salisbury 2016

Reason for exclusion	EXCLUDE Medications unable to determine if > 4 medications (authors only collected info on CVD medications)

Samtia 2013

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Sanchez 2012

Reason for exclusion	EXCLUDE Outcome = follow-up too short (adherence at 7 days only)

Sandler 1989

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Schneider 2008

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (adherence to lisinopril only)

Schou 2013

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Schou 2014

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability (conference abstract to 2013 paper)

Schwalm 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Schwartz 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Schwartz 2017

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Scott 2004

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Selak 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Shah 2013

Reason for exclusion	EXCLUDE Outcome = follow-up too short (adherence 7-14 days only)

Sherrard 2009

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Sherrard 2015

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Shuster 1998

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Sidel 1990

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Simkins 1986

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Simoni 2011

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Sit 2016

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (no response from authors)

Sledge 2006

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Smith 1997

Reason for exclusion	EXCLUDE Outcome = follow-up too short (adherence measured at 7-10days only)

Smith 2004

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Smith 2007

Reason for exclusion	EXCLUDE Medications unable to determine if > 4 medications (no information available from authors)

Soloman 1998

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (no response from authors)

Sookaneknun 2004

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Soong 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Souter 2017

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (no response from authors)

Stange 2013

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Stanhope 2013

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Strobach 2000

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Stromberg 2005

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Sweeney 1989

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Tai 2014

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Touchette, 2012

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Tu 1999

Reason for exclusion	EXCLUDE Setting = participants not living in community or discharged from hospital to community

Vaillant-Roussel 2016

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Varma 1999

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (authors did not collect this information)

Verbeek 2016

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Via-Sosa 2013

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Villani 2014

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (no response from authors)

Vinks 2009

Reason for exclusion	EXCLUDE study design not RCT, cluster RCT or quasi RCT

Vivian 2002

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Vollmer 2014

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Wakefield 2011

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Wakefield 2012

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Wandless 1981

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4

Wang 2013

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Wild 2016

Reason for exclusion	EXCLUDE Participants mean age≤65 years

Williams 2004

Reason for exclusion	EXCLUDE Medications < 4 regular medications or group mean ≤4 (adherence to diabetic medication only)

Williford 1995

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Yu 2012

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Zermansky 2002

Reason for exclusion	EXCLUDE Outcome = not medication adherence or medication taking ability

Zhao 2004

Reason for exclusion	EXCLUDE Participants mean age ≤65 years

Zhao 2015

Reason for exclusion	EXCLUDE Medications = unable to determine if > 4 medications (authors did not have information regarding number of medications)

Footnotes

Characteristics of studies awaiting classification

ACTRN12606000247572

Methods	RCT
Participants	(i) Australian veteran or war widow(er)s living in the community aged 39 to 97 years; (ii) receiving more than five medicines every day; or (iii) having three or more concurrent medical conditions. Participation restricted to veterans who are willing to use just one local medical officer (LMO) and one community pharmacy for the duration of the trial and whose LMO and community pharmacy are willing to participate. Excluded if already using a DAA, residing in an aged care facility or participating in other studies with similar aims.
Interventions	The intervention involved the veteran's Local Medical Officer (LMO) prescribing a DAA in which the veteran's pharmacy packed and dispensed the veteran's medication for the 12 months of the intervention phase.
Outcomes	Change in GP rated severity of illness, <u>change in adherence</u> and number of medications found in the home
Notes	ACTRN12606000247572 First enrolment Dec 2000. No protocol or results published. Investigators unable to be contacted.

Andrews, NCT03162848

Methods	Pilot RCT
Participants	5o years or older, heart failure diagnosis, prescribed diuretics, self-administering medications, able to open an electronic cap, able to speak, hear and understand English, not hospitalised, no cognitive impairment
Interventions	The SystemCHANGE™ intervention utilizes the Socioecological Model and Plan-Do-Check Act model as its framework and focuses on changing the individual's environment to change behaviour using small experiments with feedback. At initial home visit, the PI will work with the participant to identify important people for medication-taking, routines, and cycles of routines. Possible solutions to incorporate medication-taking into routines will be identified by the participant and PI and the participant will start implementing these solutions. Medication adherence will continuously be monitored using medication event monitoring systems. At one month, the participant will be sent a report on medication-taking and a phone call will occur with the PI to discuss if solutions improved medication adherence or if other solutions need to be implemented. At month two, the intervention will end but participants are urged to continue to use solutions long term.
Outcomes	Acceptability and feasibility using open ended questionnaire, systems thinking using questionnaire, Kansus City Cardiomyopathy questionnaire, <u>Medication adherence using medication event monitoring systems</u>
Notes	NCT03162848 No protocol or results published. Estimated study completion date July 2018. Number of medications unclear. Investigator contacted for more information - no response. Investigator contacted: Angela Andrews, University of Missouri, Kansas City.

Demers 2014

Methods	Pilot RCT
Participants	Patients with heart failure
Interventions	Multi-component intervention to enhance HF care after discharge, with or without the support of a CP for the patient. The 3-month intervention included: (a) a talking scale, (b) a diuretic decision support tool, (c) literacy sensitive HF home based education sessions and (d) a HF specific hospital discharge summary sent immediately to the primary care physician.
Outcomes	Self-care was assessed using the SCHFI for the patient and CP; HF knowledge explored with the Knowledge Assessment questionnaire; CP burden measured with the modified Oberst scale; <u>medication adherence with the Medication Possession Ratio</u>.
Notes	Conference abstract only

	Patient enrolment started in October 2012 with last follow up visit planned for July 2014. Full results plan to submit January 2019. Age and number of medications unknown (mean age of first 85 patients recruited was 76years). Investigator contacted: Dr Catherine Demers. Hamilton Health Sciences, Canada

Flink 2016

Methods	RCT
Participants	18 years or older with COPD or congestive heart failure admitted at a short-term medical ward and who are living in their private home. Exclusion: diagnosis of dementia, need an interpreter to communicate in Swedish
Interventions	Included patients transition to home will be bridged through a telephone-call from a patient activation coach two days post-discharge. The patients will thereafter get motivational interviewing sessions by the same patient activation coach with the goal that the patients are motivated to the knowledge, skills and confidence needed to manage the four main activity areas: 1) medication management; 2) adhere to care plan/ follow-up visits according to the discharge plan; 3) recognize indications (symptoms/signs) that the condition is worsening and how to respond; and 4) contact and manage relations/encounters with health care providers. Patients in control group will receive standard care, i.e. discharge and follow-up as in normal procedures.
Outcomes	Re-hospitalization, healthcare usage, medication adherence (Morisky), patient activation, health-related quality of life, basic psychological needs, depression
Notes	NCT02823795 Protocol published 2016. Estimated study completion date September 2018. Age and Number of medications unclear - Author contacted for more information - awaiting data.

Kristeller, NCT02047448

Methods	RCT
Participants	18 years and older, admitted to hospital with heart failure or COPD, anticipated eventual discharge to home, agreeable to participate in monthly counselling sessions. Exclusion: cognitive impairment, non-English speaking, anticipated discharge to a long-term care or skilled nursing facility, permanent long-term care facility resident, surgical patient, hospice patient, patients who die within 30 days of initial hospitalisation.
Interventions	The hospital pharmacist will meet with the patient and complete medication reconciliation, assess the patient's understanding of the medications, and identify medication-related problems. The hospital pharmacist will complete a pharmacist discharge care plan and a

	copy will be sent to the participating community pharmacist. The patients will be scheduled for the first meeting with their community pharmacist within 1 week of hospital discharge. The community pharmacist will interview the patient about their general health and any current symptoms of heart failure or COPD, identify any additional medication-related problems, follow-up on any issues as described in the pharmacist discharge care plan, and provide patient education. The patients will then meet with their community pharmacist for counselling and patient education at monthly intervals for 6 months following hospital discharge.
Outcomes	<u>Medication adherence</u> (proportion of days covered calculation), medication related problems, patient satisfaction, hospital readmissions or ED visits
Notes	NCT02047448 No results published - unclear age and number of medications Contacted investigator, A/Prof Judith Kristeller, Wilkes University - no response

Ostbring 2018

Methods	RCT
Participants	18 years or older, admitted for angiography, verified coronary artery disease, planned for follow up at the outpatient clinic, Swedish speaking. Exclusion: cognitive impairment or any other condition making interview or phone calls impossible, non-participation in the standard follow-up, prior participation in this study (pilot).
Interventions	Medication review and Motivational Interviewing (MI) for patients with Coronary Heart Disease (CHD). Clinical pharmacists competent in MI and cardiology will conduct medication interviews and medication reviews at the outpatient clinic. The intervention will continue during 9 months, with interviews and reviews as needed. Follow-up of results will take place 16 months after inclusion (corresponding to 4 months after the end of intervention).
Outcomes	Cholesterol levels, percentage of patients adherent to individual medications (cholesterol, ACE inhibitors, acetylsalicylic acid, PSY-12 antagonist and betablocker), blood pressure, quality of life, hospital readmissions and emergency department visits
Notes	NCT02102503 Protocol published 2018. Extension of earlier pilot study (Ostbring 2014) which was excluded due to short follow-up. Unclear if overall adherence measure will be provided. Age and number of medications unavailable (but pilot study met eligibility). Publication anticipated 2019.

Pakpour, NCT02842840

Methods	RCT
Participants	Participants aged >65years and able to give informed consent. Exclusion: recurrent stroke, diagnosis of subarachnoid haemorrhage,

	significant impairments precluding participation, another condition likely to impact participation (e.g. life-threatening condition), expected discharge to hospital/nursing home setting.
Interventions	Combined patient and family based intervention involving behavioural treatment and series of educational/motivational interventions.
Outcomes	<u>Patient-reported medication adherence rating scale</u>, changes in blood pressure, changes in intention to medication adherence, changes in action plan, changes in coping plan, changes in quality of life, changes in perceived behavioural control to medication adherence, changes in self-monitoring to medication adherence, changes in illness perceptions (Brief Illness Perception Questionnaire).
Notes	NCT02842840 Number of medications unknown - older stroke cohort likely mean >4.

Reilly 2016

Methods	Pilot RCT
Participants	60 in patients with Congestive Heart Failure
Interventions	Multicomponent health education intervention that combines a) an interactive computer-based CHF education video viewed during hospital stay and geared toward helping patients understand CHF and its management, b) Educational weekly mailings to reinforce the Kognito video, and c) 4 weekly post-discharge phone counselling using motivational interviewing techniques
Outcomes	The outcomes assessed 1 month post-discharge were knowledge using the Atlanta HF Knowledge Score, HF- specific quality of life using the Minnesota Living with Heart Failure questionnaire (HF-specific), general quality of life using the SF-36 physical component score, diet adherence using sodium intake estimated from 24-h dietary recall, and <u>medication adherence using the Morisky Medication Adherence Scale</u>. Medication adherence improved more in the control arm after 1 month (0.05 [1.13] vs. 1.13 [2.32]). However, in this small pilot study (n = 30 in each group), no outcome reached statistical significance.
Notes	Conference abstract published 2016. No full paper. Age and number of medications unknown - author believes >65years and >4medications. Author contact: Dr Natarajan Sundar.

Footnotes

Characteristics of ongoing studies

Ahmad, NTR1194

Study name	Effect of medication review and counselling of community pharmacist of patients discharged from the hospital on medication safety and compliance.

Methods	RCT
Participants	Patients older than 60 years; using 5 or more prescription-only chronically used drugs when admitted to the hospital, discharged from the departments of cardiovascular disease, lung disease or internal medicine. Exclusion: discharged to nursing home, too confused to participate, terminally ill or unable to communicate in Dutch.
Interventions	A systematic medication review by community pharmacists. Pharmacy technicians will counsel patients at home at baseline and at 1, 3, 6, 9 and 12 months, using cognitive behaviour therapy according to the theory of planned behaviour.
Outcomes	Occurrence of drug related problems, attitudes to drugs, <u>persistence of drug adherence</u>, quality of life, re-hospitalisation related to medicines and cost-adherence
Starting date	Start date: Feb 2008, Closing date: June 2009
Contact information	Investigator: Dr Jacqueline Hugtenburg, VU University Medical Center, Amsterdam (email: jg.hugtenburg@vumc.nl)
Notes	NTR1194 Protocol published 2010, Baseline (qualitative) published 2012 Investigator contacted for follow-up adherence data - no response

Al-Ganmi, ACTRN12616000910404

Study name	The Effectiveness of Motivational Interviewing (MINT) and Text Message Reminders on Medication Adherence among Patients with Heart Disease.
Methods	Sequential mixed methods with a nested pilot Randomised Controlled Trial (RCT). This pilot RCT will test the effectiveness of a multifaceted intervention, comprising motivational interviewing (MINT) plus text message reminders, to influence the adherence of patients to their cardiac medications. The RCT will compare the effect of a multifaceted intervention with current standard care to enhance medication adherence outcomes. The control group will receive the standard usual care cardiac rehabilitation program and they will complete the baseline and follow-up questionnaires.
Participants	18 years or older, established diagnosis of cardiac disease and referred to cardiac rehabilitation, ≥1 cardio-protective medication, must have primary responsibility for taking their medications, be able to speak, read and understand English, own a mobile phone (able to receive and reply to phone/text messages), willing to give written and oral consent and ≥1 medication non-adherence factor.
Interventions	Patients identified as non-adherent based on the result of exploratory phases (phase one and two) will be invited to participate in the pilot randomised controlled trial (RCT) phase. Participants in the intervention group will receive usual care plus behavioural counselling about medication adherence using motivational interviewing (MINT) techniques and text message reminders (TM). Each patient will receive approximately 30-40 minutes of a single

	MINT counselling session by the researcher following recruitment. The MINT counselling will be delivered by the researcher who is a registered nurse. TM will be sent to participants: one text message daily for two weeks, then on alternate days for two weeks and then on a weekly basis for the next 6 months.
Outcomes	Self-reported medication adherence rate - assessed by Medication Adherence Questionnaire (MAQ)
Starting date	first enrolment: 1/09/2016, last data collection: 03/07/17
Contact information	Dr Ali Al-Ganmi, University of Technology Sydney/Faculty of Health (email: ali.h.al-ganmi@student.uts.edu.au)
Notes	ACTRN12616000910404 Trial not completed due to lack of participants within inclusion criteria. Manuscript currently under review (January 2019). Unpublished details provided by authors: 120 participants = 82 (68.3%) aged 65years or older, 66 (55%) used 4 or more medications

Bernal, ACTRN12611000452998

Study name	Medication Reviews ReDirected (MedReDi): Acute Coronary Syndrome as an Indication for Home Medicine Review, a Randomised Controlled Trial
Methods	Randomized controlled trial to compare the directed home medicines review service to usual care following acute coronary syndromes
Participants	All patients aged 18 to 80 years and with a working diagnosis of acute coronary syndrome, who are admitted to two public, acute care hospitals, will be screened for enrolment into the trial. Exclusion criteria will include: not being discharged home, documented cognitive decline, non-Medicare eligibility, and presence of a terminal malignancy.
Interventions	Patients randomized to receive the intervention will be offered usual post-discharge care and a directed home medicines review at two months post-discharge (i.e. acute coronary syndrome as a referral trigger). The pharmacist review should occur at or near two months post-discharge. Accredited pharmacists completing the reviews will be given additional training and a brief assessment quiz on evidence-based management of acute coronary syndrome (ACS) and how to include this into an ACS-specific home medicine review.
Outcomes	The primary outcome will be the proportion of patients who are adherent to a complete, guideline-based medication regimen (using medication possession ratio assessed by dispensing records). Secondary outcomes will include hospital readmission rates, length of hospital stays, changes in quality of life, smoking cessation rates, cardiac rehabilitation completion rates, and mortality
Starting date	First enrolment 25/04/2012
Contact information	Dr Daniel Bernal, formally of University of Tasmania (Email: ddbernal@utas.edu.au)

Notes	ACTRN12611000452998 Protocol published 2012: https://www.ncbi.nlm.nih.gov/pubmed/22463733 Dr Bernal confirmed participant mean age>65years and mean number of medications >4. Intending to publish results soon.

Hogg, NCT01534559

Study name	Pharmacist-led Medicines Management Outpatient Service (MMC)
Methods	Randomized controlled trial in outpatient medicines management clinic
Participants	Inclusion: >18years admitted to hospital and meeting at least one of: ≥5 medications, ≥3 changes to medication in hospital, past history of medication related problems or patient referred to medicines management clinic service by hospital doctor or pharmacist due to concerns about ability to manage medicines. Exclusion: discharged to residential/nursing homes, palliative care patients, unable to give informed consent (e.g. Alzheimer's), unable to use telephone at home.
Interventions	Medicines management clinic within an outpatient setting as well as follow-up telephone calls from a clinical pharmacist (extension of the ongoing integrated medicines management programme (IMMP)).
Outcomes	Time to readmission to hospital, number of readmissions, number of GP consultations/home visits, number of accident and emergency visits, medication appropriateness index, health-related quality of life, medication adherence assessments (using medication adherence report scale and beliefs about medicines questionnaire), cost utility analysis
Starting date	Study start date Nov 2014, final data collection Dec 2017
Contact information	Anita Hogg, Northern Health and Social Care Trust, Northern Ireland (email: anita.hogg@northerntrust.hscni.net)
Notes	NCT01534559 Anita Hogg confirmed participant mean age >65 years and mean number of medications >4 Manuscripts currently being drafted

Parker, NCT02424786

Study name	Non-adherence and Polypharmacy in Elderly Patients With Chronic Renal Failure: Predictors and an Intervention
Methods	Randomized controlled trial
Participants	Patients >65years in dialysis treatment or with CKD stage 5.
Interventions	Medication lists from the patients randomized in the intervention group will be evaluated by the research physician with the help of STOPP/START criteria.

	Feedback of this screening will be given to the team responsible for patient treatment.
Outcomes	Medication non-adherence - measured by Morisky medication adherence scale and visual adherence scale. Secondary outcomes: improvement of polypharmacy, associations between beliefs about medication/anxiety/depression with adherence & QOL, predictors for non-adherence, risk factors for non-adherence, changes in number of inappropriate medications
Starting date	Start date May 2015, Study completion September 2017
Contact information	Krystina Parker, University Hospital Akershus
Notes	NCT02424786 Krystina Parker confirmed: 180 patients, mean number of medications 11.1 (range 4-19) Currently preparing two manuscripts.

Simmons, NCT02979353

Study name	A Randomized Controlled Trial to Deprescribe for Older Patients With Polypharmacy Transferred From the Hospital to Skilled Nursing Facilities (Shed-Meds)
Methods	Randomized Controlled Trial - one hospital and 14 area skilled nursing facilities
Participants	Inclusion criteria: 50 years or older, hospitalised, Medicare-eligible, discharged to a post-acute care facility, >5 medications, speaks English, primary home residence within one of 9 surrounding counties. Exclusion: long-term care, life expectancy <6 months, enrolled in a clinical drug trial, stage IV cancer, incarcerated, homeless or unable to provide consent (and no surrogate).
Interventions	Participants assigned to the intervention group will receive a clinical review of their prescribed medications by a research clinician (Pharmacist, Physician, and/or Nurse Practitioner) followed by a patient interview to assess their willingness to discontinue or reduce some of their medicines based on the clinical recommendations of the team. Hospital and out-patient providers also will be part of the deprescribing decision process. Deprescribing actions will be initiated in the hospital prior to discharge and continue through the skilled nursing facility stay.
Outcomes	Changes in total number of medications, change in functional health status, change in drug burden index, change in medication adherence (using adherence to refills and medication scale)
Starting date	Study start date March 2017, Completion Date April 2021
Contact information	Dr Sandra Simmons, Vanderbilt University Medical Center (email:sandra.simmons@vanderbilt.edu)
Notes	NCT02979353 Pilot study published - didn't assess adherence Full study ongoing

Footnotes

Additional tables

1 Primary outcome - medication-taking ability

Study	Measure of medication-taking ability	Outcome
Begley 1997	Objective measure: 5 task dexterity test (e.g. opening child resistant closure)	Not reported
Cargill 1992	Objective measure: Behaviour score /100 for congruency between supply of medications on hand and prescribed medications (/40), verbalising correct regimen (/30), maintaining each prescribed med (/20), appropriate use of OTC (/10). Points deducted for sequestering old scripts, inappropriate use of alternative medications, or mixing medications together.	Mean read from graph: Control: 74, Group 2: 84, Group 3: 86.
Lingler 2016	Objective measure: Medication Management Instrument for Deficiencies in the Elderly (MedMaIDE). MedMaIDE uses interview and observation to assess ability to self-administer medications using three areas: knowledge of medications, how to take medications, and how to procure medications. Each medication is reviewed during administration. Scores 0-13, max total deficiency score is 13.	Unpublished results: intervention 0.595 ± 0.725 vs control 0.297 ± 0.777
Manning 2007	Subjective measure: Self-reported safety, Since discharge, how many mistakes have you made taking your medications (score 0-4)?	mean $\pm$ SD: intervention 0.78 ± 0.4187 (n=72) vs control 0.79 ± 0.4113 (n=57)
Pereles 1996	Objective measure: Assessed differently for each group: intervention = pharmacist assessment with input from other team members, primarily based on having made 2 or less errors on stage 2 of the inpatient self-medication program were considered able to self-medicate at discharge. Control = Pharmacist assessment with input from other team members at time of discharge counselling. YES/NO - self-medicating at discharge (note: there could be reasons other than failing the SMP that might explain why they were not self-medicating at discharge, such as patient preference)	n(%): intervention 39 (76.5%) vs control 39 (69.6%)

Footnotes

2 Primary outcome - adherence (studies not included in meta-analyses)

Study	Measure of adherence	Outcome
Al-Rashed 2002	Objective measure: Percentage compliance using home medicines stocks and refill prescriptions between visit 1 & 2	Intervention: 70% (n=342 medications) vs control 15.8% (n=328 medications)

Blalock 2010	Subjective measure: Brief Medication Questionnaire (5-item regimen screen that assesses how medication is used)	Not reported
Bond 2007	Subjective measure: Extended Medication Adherence Report Scale (MARS) questionnaire, 12 statements about medicine taking, scores range 12-60	Med(IQR): Intervention 59 (57-60) vs control 59 (57-60)
Cargill 1992	Objective measure: Pill count, percentage of pills taken compared to those prescribed	Mean scores: control: 74.5, intervention (Group 3): 76.2
Cohen 2011	Objective measure: Medication possession ratios	Not clearly reported
Hanlon 1996	Subjective measure: self-report proportion of medications for which the patient's response agreed with the directions for use on their action profile	Intervention 77.4% (n=86 people) vs 76.1% (n=83 people)
Holland 2007	Subjective measure: Medication Adherence Report Scale (MARS) scores from 5 (very poor adherence) to 25 (perfect adherence).	Mean (median): 23.74 (25), n=101 vs 23.55 (25), n=103
Krska 2001	Subjective measure: Pharmaceutical care issues including potential or actual compliance issues, number of baseline issues resolved at three months.	51 of 74 issues resolved (n=168) vs 21 of 69 issues resolved (n=164)
Lim 2004	Subjective measure: Self-reported, patients asked if they 'forgot to take medication as directed'. Then categorised as least compliant (compliant base, not at 2mth), not-compliant (not compliant at base or 2mth), compliant (compliant at 2mth)	Not clearly reported, unadjusted OR: 1.50 90% CI: 0.73-3.08
Marek 2013	Objective measure: Machine recorded or nurse pill count, average percentage of correct doses per month	Not reported for control group. MD2: 98.8 % (SD: 0.32), planner: 97.4% (SD: 5.19)
Pandey 2017	Subjective measure: Participants used a logbook to record name and timing of medications taken on a daily basis. Absolute medication adherence calculated as percentage of total prescribed doses that were actually taken each month. 12 months adherence calculated as the mean of each of the 12 monthly measurements. Adherence outcome is % of days covered	Intervention: 91% (n=9), Control: 73% (n=8)
Pereles 1996	Objective measure: Patients discharged with 40 days worth of medication, pill count conducted in home at 40 days. Number of medication errors as a proportion of the total doses administered	Not clearly reported. After controlling for age & MMSE, I: 0.045, C: 0.086, p < 0.001.

Shimp 2012	Objective measure: Medication possession ratios defined as sum of all days of medication supply received during year divided by the total numbers of days supply needed - calculated for top 8 drug classes for chronic conditions	Not reported - MRPs were very high for both groups (range 0.84-0.96) and no clinically meaningful changes were observed over time for either group. And fewer patients reported missed doses after the intervention
Taylor 2003	Subjective measure: Self-reported number of medication doses missed. Presented as % adherence.	Intervention mean 100 vs control mean 88.9 ± SD 6.3
Volume 2001	Subjective measure: Morisky adherence, scores 0-4, lower scores better adherence	mean SD: 0.56 ± 0.75 vs 0.47 ± 0.69, number of participants in each group unclear
Willeboordse 2017	Subjective measure: self-reported adherence problems	Persistence of adherence problems = OR: 0.83 (0.54 to 1.27), p=0.38. (unpublished = Adherence worsened or persisted: 65 vs 54, Adherence improved or remained the same: 143 vs 144)
Winland-Brown 2000	Objective measure: Pill count, average number of missed doses (unclear over what time period)	Group 1 = 15.1, Group 2 = 1.7, Control = 19.7

Footnotes

3 Secondary outcome - medication knowledge

Study	Measure of medication knowledge	Outcome
Al-Rashed 2002	Pharmacist delivered questionnaire, percent scores for correct answers (drug use, dose, dosage interval)	Drug use: 97.4 vs 69.5, Dosage interval 97.4 vs 86.0, Dose: 98.5 vs 91.5
Begley 1997	Patients asked about name, purpose, dose, dosage frequency and side effects. Accuracy compared to hospital discharge or GP instructions.	Group A 70%, Group B 68%, Group C 66% (control)
Bernsten 2001	Interview-based questionnaire calculating % correctness (looking at 4 areas: indication, number of dosage units taken per dose, number of doses per day and awareness of potential adverse effects). Higher scores = better knowledge	Change at 18mths: +3.19 ± 15.18 (n=704) vs +3.16 ± 16.19 (n=636)
Bond 2007	Patients were asked whether they "knew more about their medicines compared with a year ago" on five point Likert scale. Those that said agree/strongly agree.	Trial report: 73% vs 65%

Grymonpre 2001	Knows purpose of prescribed drugs, expressed per prescribed drug	304/327 (n=93) vs 335/373 (90%)
Hanlon 1996	Self-report knowledge of 'how they took each analysed medication and what the medication was for', proportion of correct responses	89.4% (n=86) vs 90.6% (n=83)
Khdour 2009	COPD knowledge questionnaire (validated)- effectiveness of education in helping persons with COPD. 16 T/F questions, correct response = 1, range 0-16, higher score = better knowledge	Median (IQR): 75.0 (32.0) vs 59.3 (33.0)
Lim 2004	Composite % Knowledge of dose (D), frequency (F) and indication (I), percentage correct.	Not reported
Manning 2007	Assessment of knowledge of indication, dosage frequency and special comments or cautions. 0 (for no correct responses) to 3 (all correct responses).	1.96 ± 0.7561 vs 1.66 ± 0.6851
Messerli 2016	Knowledge of medicines and daily use - phone questionnaire. 58 questions - included assessing knowledge	Not reported.
Nazareth 2001	Prescription medicine interview - patient's knowledge of prescribed drugs. Validated self-report semi-structured interview (knowledge score is out of 1, with 1 being 'total/highest' knowledge). Mean (SD) out of 1.	0.69 ± 0.35 (n=65) vs 0.68 ± 0.32 (n=68)
Pereles 1996	"short medication knowledge questionnaire" = Patients asked to name and describe appearance and purpose of their medication, describe their regimen and any potential side effects or drug interactions. % correct responses in each knowledge category	<u>Discharge</u>: Name: 69% vs 55%, Appearance: 77% vs 66%, Times: 80% vs 69%, Purpose: 77% vs 72%, Side effects: 6% vs 4%; <u>Follow-up</u>: Name: 77% vs 68%, Appearance: 85% vs 83%, Time: 87% vs 78%, Purpose: 84% vs 85%, Side effects: 5% vs 4%
Taylor 2003	Self-reports used to assess medication knowledge. Score determined by dividing the number of medications for which a patient reported the correct name, purpose, dose and frequency by the total number of medications and multiplying by 100.	mean ± SD: 92.6 ± 3.4 vs 42.9 ± 12.8

Footnotes

4 Secondary outcome - satisfaction

Study	Measure of satisfaction	Outcome (intervention vs usual care)

Bernsten 2001	Self-reported rating of services provided, satisfaction with services and general opinion of pharmaceutical care. Questionnaire administered by pharmacist. Results presented as percentage who agree/mainly agree	Rating of services 73.8% vs 64.6%; satisfaction: 93.9% vs >90%; general opinion 77% (intervention group only)
Bond 2007	Overall score on 15 positive and negative statements of most recent pharmacy visit (total score 15-75, higher scores better)	Median (IQR): 46 (40-55) vs 43 (38-49)
George 2016	User satisfaction regarding the use of the computer program questionnaire (USUCPQ): an 8 item measure based on 7 point Likert score (max score 56, higher scores better)	Total satisfaction: 45.33 ± 7.81 vs 44.68 ± 6.75
Hanlon 1996	Health Care Attitude Questionnaire: 3 questions on pharmacy-related health care satisfaction (directions received, explanation of SES, number/types of drugs), based on 5 point Likert scale (lower scores better).	Total score: 5.2 ± 1.5 vs 5.4 ± 1.7
Holland 2007	Satisfaction questionnaire, usefulness of community pharmacist visits	75 (64%) considered the visits to have been extremely or very useful
Lingler 2016	Acceptability of the intervention using a set of Likert scaled questions and eliciting open-ended comments	88% of caregivers reported intervention topics useful and relevant, 92% reported that the intervention was helpful for managing the patient's treatment plan
Lopez Cabezas 2006	Catalan Health Department satisfaction survey, asking participants about the care and information received and asking them to provide a global scoring (0-10)	8.9 ± 1.3 vs 8.8 ± 1.5
Manning 2007	Level of satisfaction using 5 point Likert scale (5 = highest), "How satisfied were you with the form you received from the nurse when she/he was talking to you about your medications?	4.24 ± 0.6986 vs 4.26 ± 0.8768
Naunton 2003	Survey of intervention group only	94% very satisfied, 84% stated information they were given 'helped a great deal'
Nazareth 2001	Validated client satisfaction questionnaire, each item scored 1 to 4, mean score per item calculated (higher = better)	3.4 ± 0.6 (n=62) vs 3.2 ± 0.6 (n=61)

Taylor 2003	Mean ± SD number of patients with pharmacy-related satisfaction (details unclear)	81.9 ± 4.8 vs 89.0 ± 6.2
Volume	Satisfaction with pharmacy services using 34-item instrument and 7 point Likert scale (lower scores = better). General satisfaction extracted.	1.53 ± 0.77 vs 1.62 ± 0.88
Willeboordse 2017	Medication satisfaction questionnaire assessed on a 7-point Likert scale	*B* (95% CI): 0.11 (-0.08 to 0.30), p=0.25

Footnotes

5 Secondary outcome - HRQoL

Study	Measure	Time point	Outcome
Bernsten 2001	SF-36	18 months	Change: GH: +0.28 vs -0.66, MH: -0.80 vs -1.34, PH: -0.95 vs-0.68
Bond 2007	SF-36	12 months	Med (IQR): GH: 52 (35-65) vs 50 (35-70), MH: 80 (64-88) vs 80 (64-88), PH: 60 (35-80) vs 65 (35-85)
	EQ-5D	12 months	Med (IQR): 0.73 (0.7-0.9) vs 0.73 (0.7-0.9)
Cohen 2011	VR-36 (Veterans SF-36)	6 months	Change: Med (IQR): MH: 0.48 (-3.37,4.32), C: 0.78 (-2.67, 4.23), PH: 1.65 (-5.21,1.31), C: -1.95 (-5.21, 1.31)
Hale 2016	MLHFQ	90 days	62.2 ± 20.6 vs 28.2 ± 22.3
Hanlon 1996	SF-36	12 months	Mean ± SD: GH: 37.4 ± 1.6 vs 35.2 ± 1.7, MH: 61.1 ± 1.8 vs 60.4 ± 1.8, PH: 44.1 ± 2.0 vs 42.2 ± 2.0
Holland 2007	EQ-5D, VAS	6 months	EQ5D: 0.58 ± 0.29 vs 0.52 ± 0.34, VAS: 58.2 ± 19.6 vs 58.6 ± 19.8
	MLHFQ		47.7 ± 26.3 vs 44.5 ± 27.9
Khdour 2009	SGRQ	12 months	Mean (CI): 61.8 (57.9, 65.6) vs 65.3 (61.0, 69.6)
Krska 2001	SF-36	3 months	No significant differences - values not reported
Lopez Cabezas 2006	EQ-5D (Spanish & Catalan)	12 months	Mean SD: 64 ± 15.4 vs 60.6 ± 17.8, Subgroup >70yrs: 63.8 ± 15.3 vs 58.4 ± 15.9
Marek 2013	SF-36	12 months	Mean (CI): MD.2 vs planner = PCS: 0.095 (-0.450, 0.640), MCS: 0.241 (-0.459, 0.940)
			Mean (CI): Planner vs Control = PCS: 1.390 (0.816, 1.963), MCS: 1.686 (0.949, 2.423)
Muth 2016	EQ-5D	12 weeks	Change: -0.6 ± 19.61 vs -1.0 ± 13.66

Taylor 2003	SF-36	12 months	Mean SD: GH:57.0 ± 19.6 vs 50.1 ± 15.9, MH: 73.1 ± 21.2 vs 72.3 ± 17.1 , PH: 68.6 ± 24.0 vs 56.1 ± 27.5
Volume 2001	SF-36	12-13 months	MCS: 56.14 ± 8.30 vs 54.55 ± 8.65, PCS: 36.87 ± 11.62 vs 38.39 ± 11.44
Willeboordse 2017	SF-12	6 months	Regression coefficients adjusted for baseline: PCS: -0.06 (-3.19 to 3.06), MCS: 0.16 (-2.89 to 3.22)
	EQ-5D-3L		Regression coefficients adjusted for baseline: utility: 0.02 (-0.02 to 0.05), VAS: 2.30 (-0.16 to 4.76)

Footnotes

GH: general health, MH: mental health, MCS: mental summary, PH: physical health, PCS: physical summary, MLHFQ: Minnesota Living with Heart Failure Questionnaire (21 items, coded 0-5, higher scores indicate adverse impact on life), SGRQ: St George's Respiratory Questionnaire (76 items, total score 100, higher = better), VAS: visual analogue scale

6 Secondary outcome - adverse clinical health outcomes

Study	Timepoint	ED/Hospital admissions	Mortality	Adverse drug reactions	GP visits
Al-Rashed 2002	3mths	Total hospital visits (not number of people hospitalised): 8 (n=43) v 28 (n=40)			Total unplanned visits: 43 (n=43) vs 59 (n=40)
Bernsten 2001	18mths	Self-reported, 35.6% vs 40.4%, n-values unclear			
Chrischilles 2014	3mths			Self-reported, 100/802 (12.9%) vs 33/273 (12.2%)	
Cossette 2015	30 days	ED visits, 18% (n=108) vs 20% (n=95)			
Haag 2016	30 days	ED or hospital readmission, 2/11 (18%) vs 1/11 (9%)			
Hale 2016	90 days	No. participants: ED: 3/11 (27%) vs 6/14 (43%), Hospitalization:			

		1/11 (9%) vs 7/14 (50%), Total No.: ED 4 vs 7, Hospital 2 vs 8			
Hanlon 1996	12mths			Self-reported, 30.2% (n=86) vs 40% (n=83)	
Holland 2007	6mths	Number of ED admission 134, n=148 vs 112, n=143	30/148 vs 24/143		
Khdour 2009	12mths	n= 71 & 72, ED: 40 vs 80, Hospital: 26 vs 64, Total hospital days: 164 vs 466			n=71 vs 72 Unscheduled: 28 vs 47
Lim 2004	2mths			Self-reported & assessed by physician, Residual ADRs from baseline: 4/13 vs 4/8	
Lipton 1994	6mths	Total days in hospital: 2.29±5.96, n=350 vs 2.02±5.83, n=356			
Lopez-Cabezas 2016	12mths	Patients with re-admission: 23/70 (32.9%) vs 31/64 (48.4%)	>70yrs subgroup, 7/53 (13.2%) vs 13/50 (26.0%)		
Marusic 2013	30 days	Readmission or ED: 20/80 (25%) vs 27/80 (33.8%)		?self-reported: 24/80 (30%) vs 30/80 (37.5%)	
Messerli 2016	28 weeks	Self-reported unplanned GP visit or Hospitalisation: total during study: 110 vs 99, n unclear, ?181 vs 191			*

Murray 1993	6mths			Self-reported side effects, ill effects or other problems with medication: C1: 2/12, C2: 2/10, Int: 1/9	
Muth 2016	12 weeks	Days in hospital: (T1+T2)-T0 = -0.4 ± 0.73 vs -0.2 ± 0.69, n = unclear			
Naunton 2003	90 days	1 or more unplanned readmission, 16/57 (28%) vs 29/64 (45%)	3/57 (5%) vs 5/64 (8%)		
Nazareth 2001	6mths	Readmissions: 38/136 (27.9%) vs 43/151 (28.4%), Outpatient department: 39/137 vs 40/151	22/137(16.1%) vs 19/151 (12.6%)		76/107 vs 82/116
Olesen 2014	24mths	Unplanned admissions: 77/253 (30%) vs 73/264 (28%)	19/253 (7.5%) vs 14/264 (5%)		
Rich 1996	90 days	Readmission: 18/80 (22.5%) vs 22/76 (28.9%)			
Saez de la Fuente 2011	50 days	Total readmissions: 5 (n=26) vs 7 (n=24); ED: 7 (n=26) vs 9 (n=24) - *(note percentages listed in paper don't match n values)*	2 (?n=26) vs 1 (?n=24)		
Shively 2013	6mths	HOSP: mean (SD): 0.21 (0.409) vs 0.32 (0.475), ED: 0.33 (0.478) vs 0.37 (0.489) n=39 vs 37			

Taylor 2003	12mths	Hospital: 2/33 vs 11/36, ED: 4/33 & 6/36			
Vinluan 2015	90days	Hospital admissions 2/7 vs 2/7	2/7 vs 0/7		
Willeboordse 2017	6mths			DRPs: Baseline: 4.4 ± 1.9 vs 3.7 ± 1.7. % solved: 20.2 (12.2 to 28.1)	
Winland-Brown 2000	6mths	Hospitalizations G1: 4/16, G2: 3/24, C: 12/21			Physician visits: G1: 1.5/mth, G2: 1/mth, C: 1/mth
Wu 2006	2yrs	Med(IQR), n=219 vs 223 ED visits: 0 (-1, 2) vs 0 (-1, 2), Hospital visits: 0 (-1, 2) vs 1 (-1, 2), Days in hospital: 0 (-4, 10) vs 3 (-2, 17.5)	25/219 vs 38/223		
Young 2016	180days	Hosp: 18/51 (35.3%) vs 20/49 (40.8%). ED visits: 12/51 (23.5%) vs 11/49 (22.4%)			

Footnotes

7 Secondary outcome - condition-specific outcomes

Study	Measure	Outcome
Blalock 2010	Falls (self-reported) in 12 months (ITT analysis)	≥1 fall: 53/93 vs 52/93
Bond 2007	Total score (/8) for reaching targets at 12 months (aspirin, lipid, BP, smoking, alcohol, physical activity, diet and BMI).	4.6 ± 1.2 vs 4.6 ± 1.1
Cohen 2011	Percentage achieving targets at 6 months (SBP<130, LDL<100, HbA1c<7%)	16% (n=50) vs 4.1% (n=49)

Lee 2006	Systolic and diastolic blood pressure (mmHg) and LDL-cholesterol (mg/dl) at 6 months post phase 1.	SBP: 124.4 ± 14.0 vs 133.3 ± 21.5, DBP: 67.5 ± 9.9 vs 68.6 ± 10.5, LDL: 87.5 ± 24.2 vs 88.4 ± 21.0
Nascimento 2016	Fasting blood glucose and HbA1c at 6 months	FBG: 117.3 ± 26.8 vs 142.2 ± 32.9 HbA1C: 7.7 ± 0.8 vs 7.99 ± 0.67
Taylor 2003	Number of people reaching goal level at 12 months (BP≤140/90, HbA1c≤7.5%, INR 2-3 and LDL)	BP: 22 (91.7%) vs 8 (27.6%) Diabetes: 13 (100%) vs 5 (26.7%) INR: 4 (100%) vs 1 (16.7%) LDL: 14 (77.8%) vs 1 (5.9%)
Williams 2012	Blood pressure, HbA1c, eGFR and creatinine levels at 12 months (9 months post intervention)	SBP: Mean (CI) -6.9 (-13.8 to 0.02) vs -3.0 (-8.4 to 2.4), HbA1c: Med (IQR): 7 (7-9) vs 8 (7-9), eGFR: Med (IQR): 48 (38-76) vs 46 (32-72) Creatinine: Med (IQR): 117 (82-144) vs 108 (89-171)

Footnotes

8 Secondary outcome - cost effectiveness

Study	Measure of costs	Outcome
Bernsten 2001	Direct costs of the study; including additional time spent by pharmacists, cost associated with contacts with other health professionals, cost of hospitalisation and drugs.	Average cost per patient (saving): Denmark: 1298.13 vs 1419.88 (+121.75) Germany: 2992.25 vs 3167.25 (+175.00) Northern Ireland: 735.22 vs 750.01 (+14.79) Sweden: 1266.76 vs 1250.34 (-16.42)
Bond 2007	Total NHS-related study costs: including cost of intervention and other treatment (e.g. medicines, hospital, other health consultations)	Median cost (IQR): 970.5 (667.0-1489.0) vs 835.2 (534.4-1396.3)
Lipton 1994	Medicare Part B Charges, and total hospital inpatient charges	Total charges: 2769±4789 vs 2598±3722 Inpatient charges: 5472±10904 vs 5263±11478

Lopez Cabezas 2006	Hospitalization costs, adding in intervention direct costs, delivered materials and time spent by the pharmacist	Average cost per patient: 997 vs 1575

Footnotes

9 Secondary outcome - other

Study	Measure	Outcome (Intervention vs usual care)
Chrischilles 2014	Mean (SD) number of medication management problems from a list of 8 problems: including questions on multiple prescribers, multiple pharmacies, mail-order prescriptions, confusion whether medication was taken, taking medication without knowing indication, problems affording medications, feeling that medications aren't working and feeling that medications aren't doing what they were intended to do.	1.4 ± 1.4 vs 1.6 ± 1.5
Lingler 2016	Medication deficiency checklist. A 15 item, investigator developed instrument, that uses caregiver interviews to assess for the presence of errors and problems (e.g. taking at the wrong time).	2.19 ± 1.52 vs 2.36 ± 1.51
Moral 2015	Average number of medication errors according to group. Errors including subtherapeutic dose, omission of admin, deteriorated drug, duplicate therapy, higher doses and other (As reported in Perula de Torres 2014 paper)	0.429 vs 1.145
Taylor 2013	Number of participants with at least one medication misadventures	2.8% (n=33) vs 3.0% (n=36)

Footnotes

References to studies

Included studies

Al-Rashed 2002

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Data and analyses

1 Interventions versus usual care

1.1 Primary Outcome: Adherence, grouped by types of interventions (dichotomous)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Primary Outcome: Adherence, grouped by types of interventions (dichotomous)	18		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 Educational interventions	2	182	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.33, 2.06]
1.1.2 Behavioural interventions	4	528	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.07, 1.38]
1.1.3 Mixed educational and behavioural interventions	12	3147	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.08, 1.37]
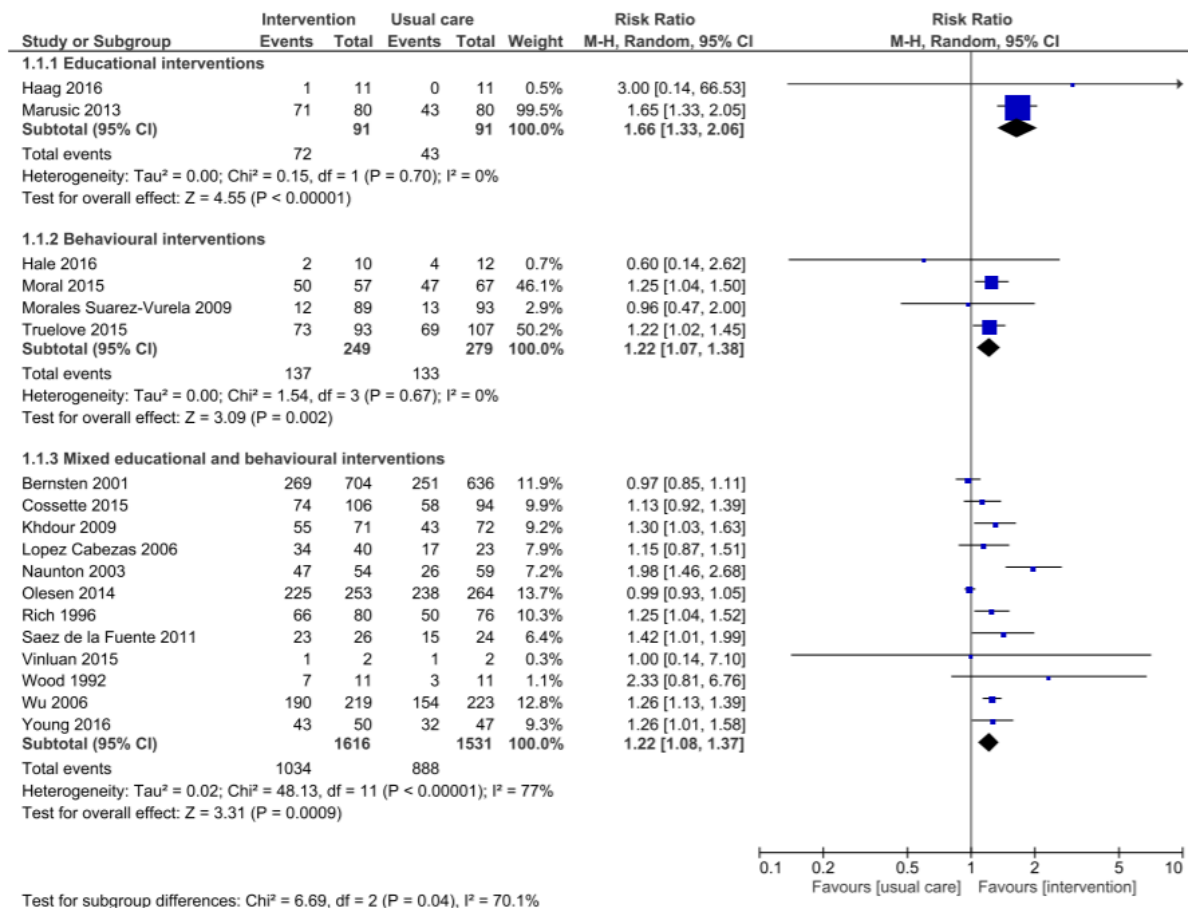
1.2 Primary Outcome: Adherence, grouped by types of interventions (continuous)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.2 Primary Outcome: Adherence, grouped by types of interventions (continuous)	13		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 Educational interventions	5	1165	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.12, 0.43]
1.2.2 Behavioural interventions	1	21	Std. Mean Difference (IV, Random, 95% CI)	1.90 [0.82, 2.97]
1.2.3 Mixed educational and behavioural interventions	7	1825	Std. Mean Difference (IV, Random, 95% CI)	0.48 [-0.08, 1.04]
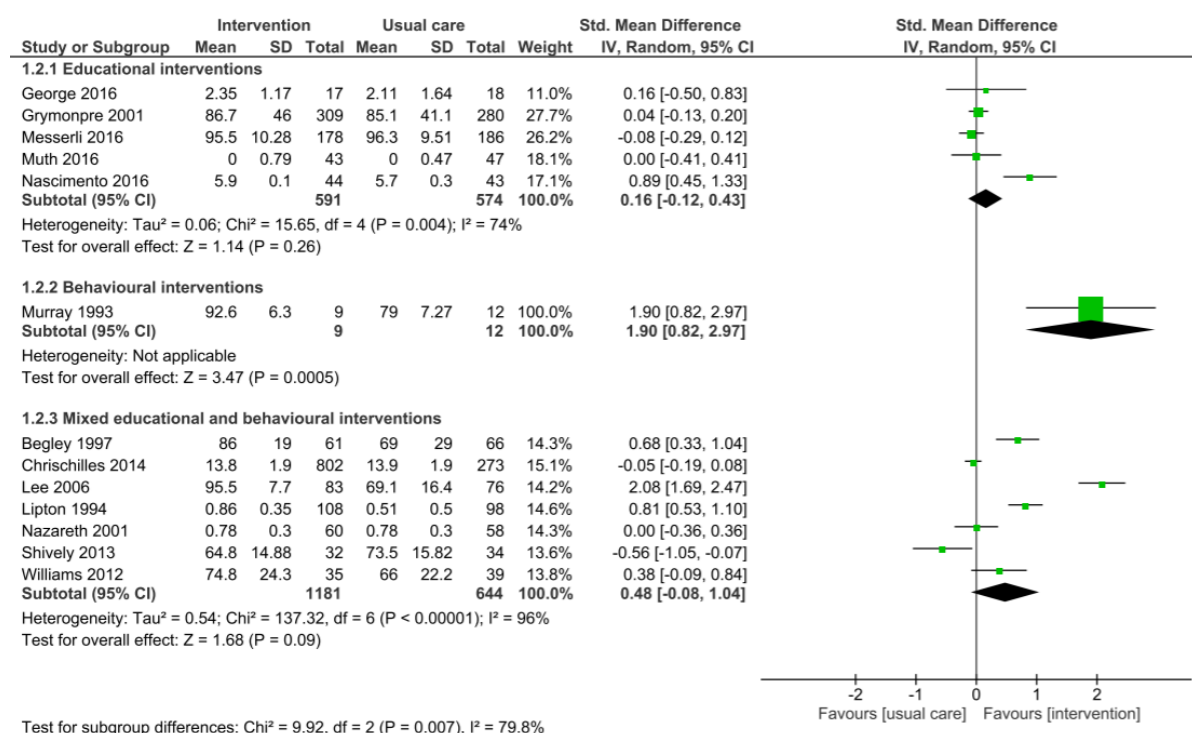
1.3 Primary Outcome: Adherence, mixed interventions, grouped by intervention duration (dichotomous)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.3 Primary Outcome: Adherence, mixed interventions, grouped by intervention duration (dichotomous)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.3.1 Short duration (≤3 months)	6	486	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.13, 1.74]
1.3.2 Long duration (>3 months)	5	2505	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.97, 1.27]
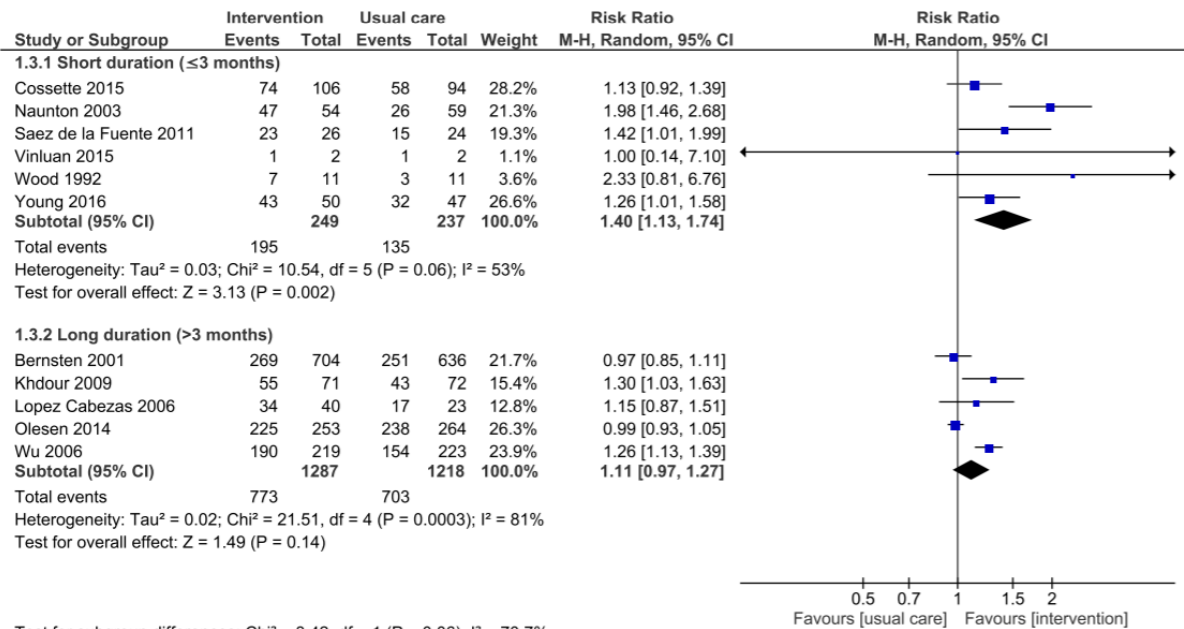
1.4 Primary Outcome: Adherence, mixed interventions, grouped by intervention duration (continuous)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.4 Primary Outcome: Adherence, mixed interventions, grouped by intervention duration (continuous)	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 Short duration (≤3 months)	3	398	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.52, 0.88]
1.4.2 Long duration (>3 months)	4	1427	Std. Mean Difference (IV, Random, 95% CI)	0.70 [-0.25, 1.65]
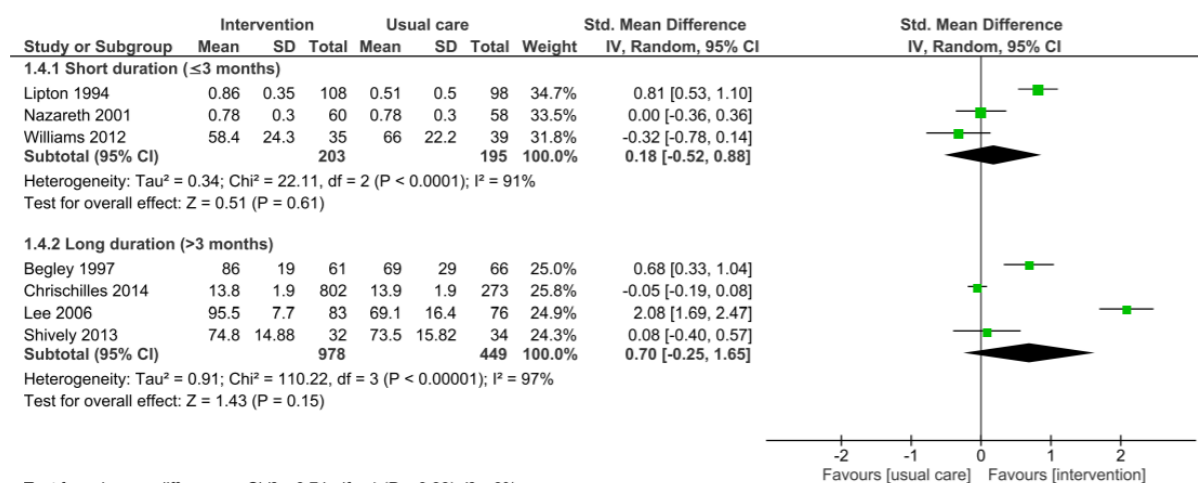
1.5 Primary Outcome: Adherence, mixed interventions, grouped by subjective or objective outcome measures (dichotomous)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.5 Primary Outcome: Adherence, mixed interventions, grouped by subjective or objective outcome measures (dichotomous)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5.1 Objective outcome measure	5	762	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.93, 1.38]
1.5.2 Subjective outcome measure	7	2385	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.09, 1.46]
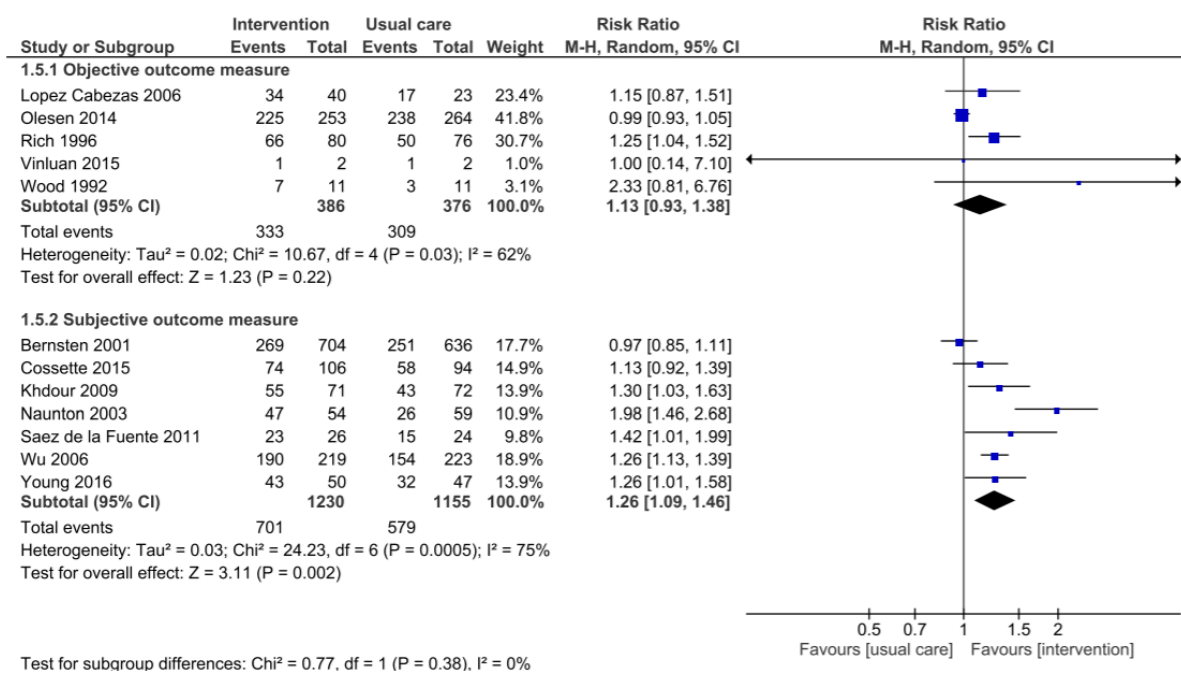
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1.6 Primary Outcome: Adherence, mixed interventions, grouped by subjective or objective outcome measure (continuous)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.6 Primary Outcome: Adherence, mixed interventions, grouped by subjective or objective outcome measure (continuous)	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.6.1 Objective outcome measure	3	360	Std. Mean Difference (IV, Random, 95% CI)	0.82 [-0.49, 2.13]
1.6.2 Subjective outcome measure	4	1465	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.23, 0.66]
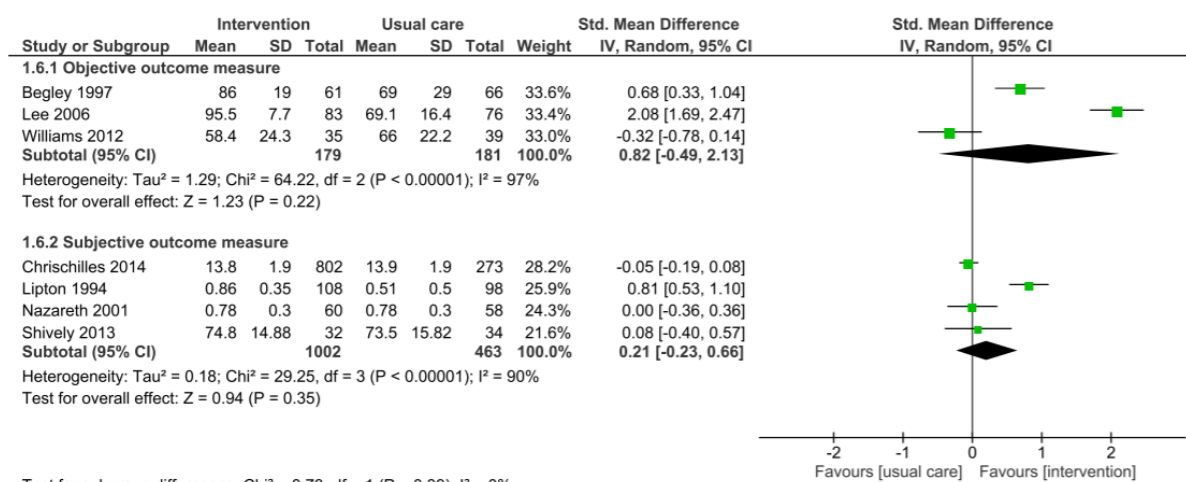
1.7 Primary Outcome: Adherence, mixed interventions, grouped by provider (dichotomous)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.7 Primary Outcome: Adherence, mixed interventions, grouped by provider (dichotomous)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7.1 Provider: Pharmacist	8	2672	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.04, 1.41]
1.7.2 Provider: Nurse	2	297	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.02, 1.38]
1.7.3 Provider: Two or more health professionals	2	178	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.88, 2.16]
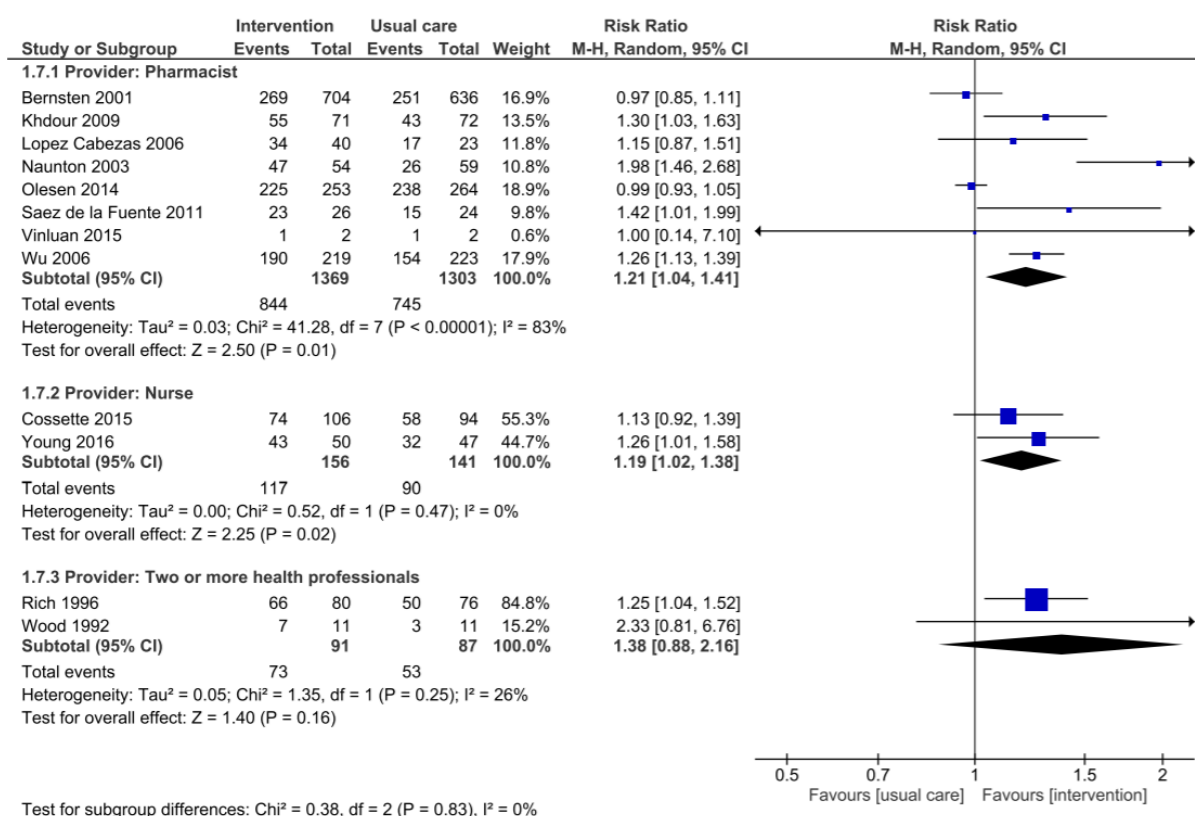
1.8 Primary Outcome: Adherence, mixed interventions, grouped by provider (continuous)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.8 Primary Outcome: Adherence, mixed interventions, grouped by provider (continuous)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8.1 Provider: Pharmacist	2	286	Std. Mean Difference (IV, Random, 95% CI)	1.38 [0.01, 2.75]
1.8.2 Provider: Nurse	2	140	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.53, 0.27]
1.8.3 Provider: Two or more health professionals	2	324	Std. Mean Difference (IV, Random, 95% CI)	0.42 [-0.38, 1.21]
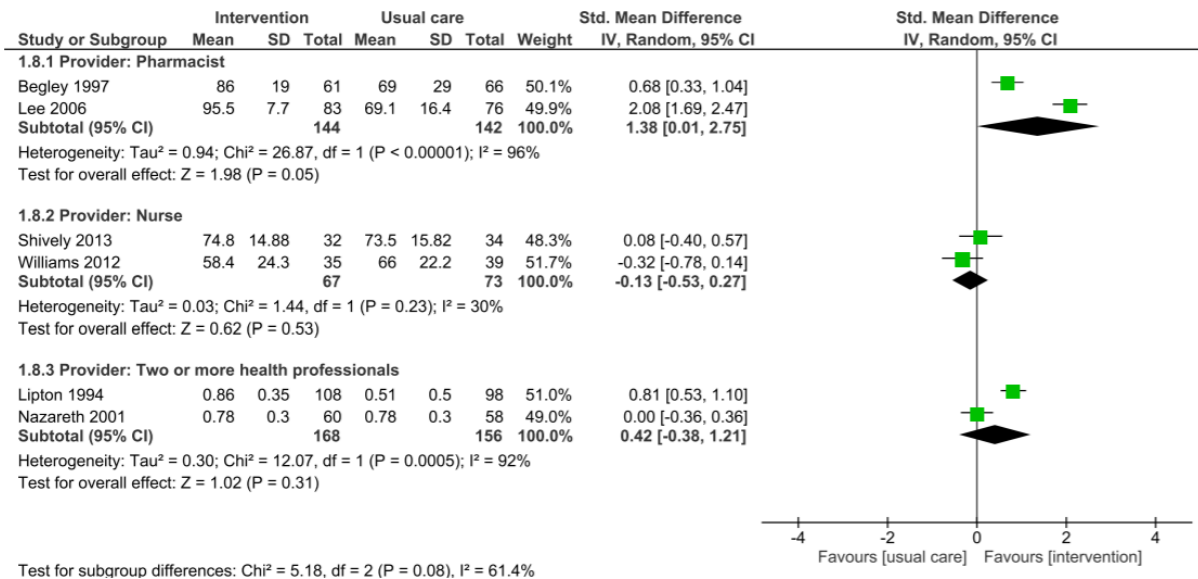
1.9 Secondary Outcome: ED/Hospital admissions, grouped by type of intervention (dichotomous)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.9 Secondary Outcome: ED/Hospital admissions, grouped by type of intervention (dichotomous)	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.9.1 Educational interventions	3	554	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.71, 1.48]
1.9.2 Behavioural interventions	2	70	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.08, 0.55]
1.9.3 Mixed educational and behavioural interventions	11	1827	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.90]
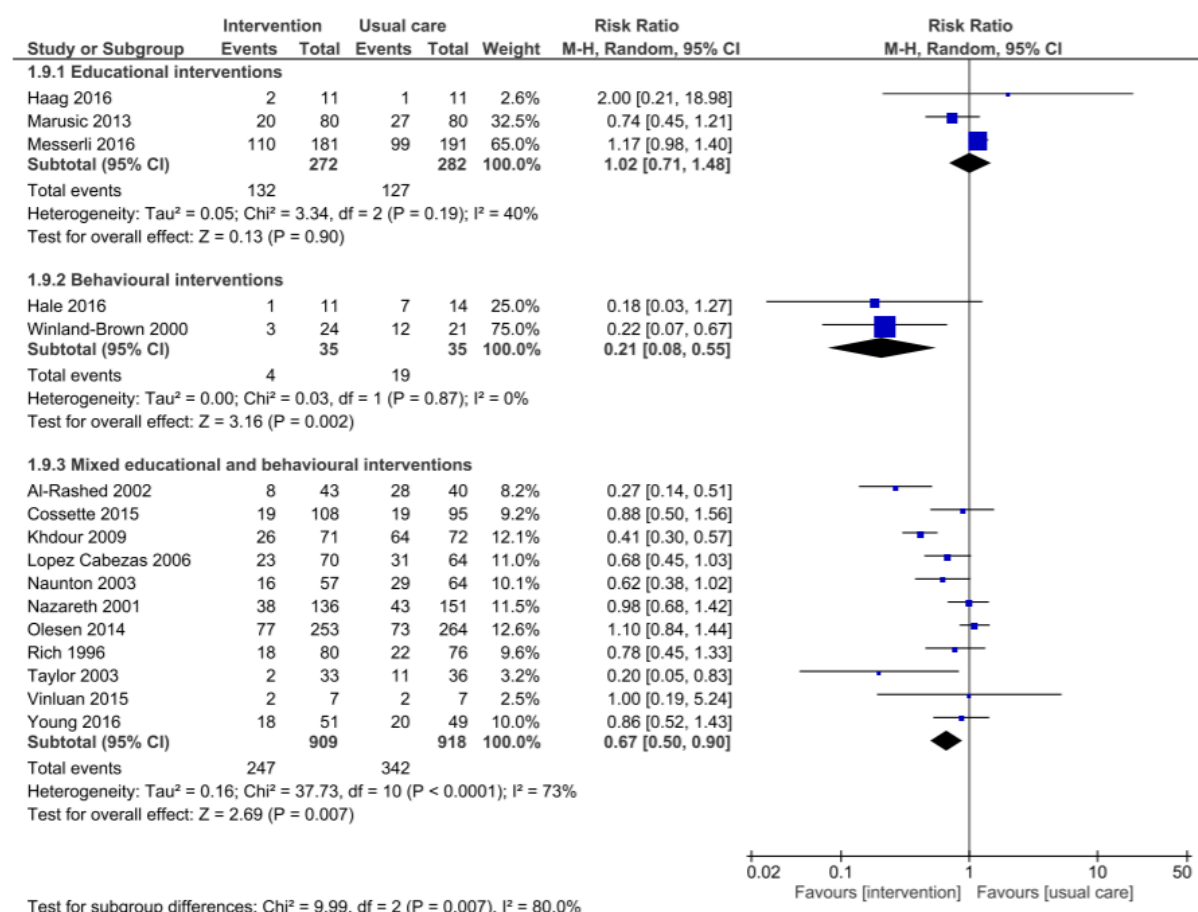
1.10 Secondary Outcome: Mortality, mixed interventions

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.10 Secondary Outcome: Mortality, mixed interventions	7	1776	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.70, 1.36]

	Intervention		Usual care			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Holland 2007	30	148	24	143	22.9%	1.21 [0.74, 1.96]	
Lopez Cabezas 2006	7	53	13	50	11.7%	0.51 [0.22, 1.17]	
Naunton 2003	3	57	5	64	5.1%	0.67 [0.17, 2.69]	
Nazareth 2001	22	137	19	151	19.4%	1.28 [0.72, 2.25]	
Olesen 2014	19	253	14	264	15.9%	1.42 [0.73, 2.76]	
Vinluan 2015	2	7	0	7	1.3%	5.00 [0.28, 88.53]	
Wu 2006	25	219	38	223	23.7%	0.67 [0.42, 1.07]	
Total (95% CI)		874		902	100.0%	0.97 [0.70, 1.36]	
Total events	108		113				

Heterogeneity: Tau² = 0.06; Chi² = 9.13, df = 6 (P = 0.17); I² = 34%
Test for overall effect: Z = 0.16 (P = 0.87)

2.5 **Chapter summary**

This review highlighted a lack of RCTs evaluating interventions for improving medication-taking ability, and large variations in the design and quality of those that were identified. As a result, we were unable to determine the effect of interventions on medication-taking ability.

This review identified 48 studies evaluating interventions for improving medication adherence, but there were large variations in the intervention design, duration, follow-up and risk of bias of included studies. Low quality evidence suggests that mixed interventions involving patient/carer education and/or medication review with one or more behavioural elements (e.g. regimen simplification, motivational interviewing, follow-up or dose administration aids) may improve the proportion of people who are adherent to their prescribed medication. Healthcare providers should consider a combination of educational and behavioural strategies, tailored to their patient's need, to optimise medication use.

Within mixed interventions for improving medication adherence, pharmacist-led interventions were more effective than those delivered by nurses or multi-disciplinary teams and each of the individual studies that had a significant impact on medication adherence were delivered at the hospital-community interface (e.g. in hospital, at discharge, post-discharge or at hospital outpatient clinics).

Only a few studies focussed on participants with cognitive impairment. Eighteen of the 50 included studies excluded participants with cognitive impairment and a further sixteen studies had no clear details regarding cognitive function of participants. Studies that did report cognitive function generally showed that participants had high mean/median cognitive function scores or that only a low percentage of participants had cognitive impairment. Only two studies specifically focussed on people with dementia, and their interventions (one educational and one mixed) were both targeted towards carers.

Given the ageing population and increasing rates of polypharmacy, and the lack of robust controlled trials conducted to date, there is a need for further well-designed RCTs to investigate the effects of interventions for improving medication-taking ability and medication adherence in older adults prescribed multiple medications. Priority should be given to trials using validated, objective measures of medication-taking ability and medication-adherence, that are adequately powered to detect clinically significant effects and that measure ADEs and cost-effectiveness. Targeted interventions for people with cognitive impairment are also warranted given the increasing number of older people with dementia.

3. CHAPTER THREE: Patterns of medication use in older people attending Australian memory clinics

3.1 <u>Preface</u>

Chapter one highlighted that there has been limited research regarding the appropriateness of medications used in people living with cognitive impairment. Clinical practice guidelines for dementia recommend a review of medication as part of diagnostic and management processes, but there has been limited international and no Australian research regarding patterns of medication use in the cognitive diagnostic setting, such as outpatient memory clinics. This knowledge is important to help determine the nature and extent of suboptimal prescribing and medication use in this setting and to guide the development of future interventions and practice-change to improve medication use. This chapter presents three published manuscripts describing cross-sectional and longitudinal analyses of medication use, and potential consequences associated with PIM use, in people attending nine memory clinics in Australia utilising data from the Prospective Research In MEmory clinics (PRIME) study.

3.2 <u>Chapter objective</u>

To explore the types and appropriateness of medications used by older people with dementia or MCI attending memory clinics.

3.3 <u>Publications</u>

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Ilomäki J, Elliott RA. *Potentially inappropriate medications and anticholinergic burden in older people attending memory clinics in Australia*. Drugs Aging. 2016. 33: 37-44.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Elliott RA. *Dietary supplement use in older people attending memory clinics in Australia*. J Nutr Health Aging. 2017. 21: 46-50.

Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Wolfe R, Connors MH, Elliott RA. *Potentially inappropriate medications, anticholinergic burden and mortality in people attending memory clinics*. J Alzheimers Dis. 2017. 60: 349-358.

3.4 <u>Appendices</u>

Appendix 2: Chapter Three – Monash University research ethics approval

Appendix 3: List of potentially inappropriate medications in cognitive impairment (PIMcogs)

CrossMark

SHORT COMMUNICATION

Potentially Inappropriate Medications and Anticholinergic Burden in Older People Attending Memory Clinics in Australia

Amanda J. Cross[1] · Johnson George[1] · Michael C. Woodward[2] · David Ames[3,4] ·
Henry Brodaty[5,6] · Jenni Ilomäki[1] · Rohan A. Elliott[1,7]

Abstract

Background   There has been limited research into potentially inappropriate medication (PIM) use and anticholinergic burden in patients attending memory clinics.

Objectives   The aim of this study was to explore the use of PIMs related to cognitive impairment (PIMcog), anticholinergic cognitive burden (ACB) and concomitant use of anticholinergic medications with cholinesterase inhibitors (ChEIs) in patients attending memory clinics.

Methods   Cross-sectional analysis of baseline data from the Prospective Research In MEmory clinics (PRIME) study was performed. Participants were community-dwelling patients who attended nine memory clinics and had a diagnosis of mild cognitive impairment or dementia. PIMcog were defined as any medication considered potentially inappropriate for patients with cognitive impairment according to the Beers or STOPP criteria. Clinically significant ACB was defined as total score of ≥ 3 on the ACB scale.

Results   A total of 964 patients, mean age 77.6 years, were included. PIMcog were used by 206 (21.4 %) patients. Anticholinergics and sedatives were the most common PIMcog. PIMcog use was associated with higher number of medications (adjusted OR 1.26; 95 % CI 1.19–1.33) and with not having completed secondary level education (adjusted OR 1.71; 95 % CI 1.01–2.89). One hundred and thirteen (11.7 %) patients had a clinically significant ACB score (≥ 3). ChEIs were used by 575 patients and 65 (11.3 %) of these had an ACB score ≥ 3. There was no statistically significant difference in ChEI use between patients with and without an ACB score ≥ 3.

Conclusion   PIMcog use, clinically significant anticholinergic burden, and concurrent use of anticholinergics with ChEIs were prevalent in patients attending memory clinics. Efforts are needed to improve prescribing for people with cognitive impairment.

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Key Points

One in five memory clinic patients used at least one medication considered potentially inappropriate in cognitive impairment.

One in ten memory clinic patients, including patients who used cholinesterase inhibitors, had a clinically significant anticholinergic cognitive burden.

Strategies to improve medication use in patients with cognitive impairment are needed.

△ Adis

1 Introduction

Inappropriate medication use is associated with increased risk of adverse drug events (ADEs) and healthcare costs [1–3]. Older people are more susceptible to ADEs than younger adults due to factors including altered pharmacokinetics and pharmacodynamics, comorbidities, polypharmacy and drug interactions [1, 4]. Older people with cognitive impairment also have increased susceptibility to cognitive adverse effects of medications [1, 4].

A number of criteria have been developed to identify potentially inappropriate medication (PIM) use in older people, including the Beers criteria [5] and the Screening Tool of Older Peoples' Prescriptions (STOPP) [6] criteria. There are no specific tools for identifying PIMs in patients with cognitive impairment. However, it is well recognised that certain classes of medications including barbiturates, benzodiazepines, anticholinergics, antispasmodics and muscle relaxants are associated with increased risk of adverse effects in people with cognitive impairment [5, 6]. Unless there is no suitable alternative, these medications should be avoided due to their adverse cognitive effects and association with delirium [5, 6].

Anticholinergic medications are commonly used in older people and can increase the risk of cognitive impairment, functional impairment and mortality [7, 8]. They may also antagonise the potential benefits of cholinesterase inhibitors (ChEIs) [9], which are one of only two classes of medications currently approved for management of Alzheimer's disease.

Several tools to assess anticholinergic burden are available. One of the most widely used and validated tools is the anticholinergic cognitive burden (ACB) scale [10, 11], which assigns a score for each medication (out of 3) based on the expected anticholinergic potency. Higher medication regimen ACB scores have been associated with worse cognitive and functional performance [12]. For every one point increase in ACB score, a decline in Mini Mental State Examination (MMSE) score of 0.33 points over 2 years and a 26 % increase in risk of death have been reported [7].

There has been limited research into PIM use and anticholinergic burden in patients attending memory clinics. A small 2003–2004 US study ($n = 100$) reported that 22 % of patients attending a memory clinic used a PIM, and 14 % used a ChEI together with an anticholinergic medication [13]. There are no data on PIM use in patients attending Australian memory clinics.

Memory clinics in Australia are ambulatory assessment services for people with suspected memory and related cognitive disorders [14]. Memory clinics involve an interdisciplinary healthcare team, including geriatricians, psychiatrists, neurologists, nurses and social workers [14].

Review of patient's medications is typically performed by a physician; pharmacists are not involved in memory clinics.

The aims of this study were to explore the use of PIMs related to cognitive impairment (PIMcog), anticholinergic burden and concomitant use of anticholinergic medications with cholinesterase inhibitors in patients with dementia or mild cognitive impairment (MCI) attending memory clinics in Australia.

2 Methods

2.1 Design, Setting and Participants

This was a cross-sectional analysis of baseline data from the Prospective Research In MEmory clinics (PRIME) study (National Institute of Health Clinical Trials registry number: NCT00297271). PRIME was a 3-year, multicentre, observational study designed to assess the management of patients with MCI and dementia who attended nine memory clinics affiliated with secondary or tertiary care hospitals across four of the eight states/territories of Australia. Patients were recruited at their initial assessment visit or a subsequent follow-up appointment between April 2005 and July 2008 (inclusive).

Patients were eligible for inclusion if they had been diagnosed with dementia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria [15] or MCI according to the Petersen criteria [16]. Participants had to be community dwelling with <40 h/week nursing care, be fluent in English, be able to provide written informed consent directly or through a legal guardian/proxy, and have a carer willing to provide consent. Further details of the PRIME study have been previously published [17].

2.2 Data Collection

Data were collected by clinic staff (physicians and nurses) and trained research nurses. Demographic and clinical data included age, weight, sex, level of education, living arrangements, cognitive impairment diagnosis, age at diagnosis, MMSE score [18] and clock drawing test score [19].

Diagnosis groups included Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, mixed Alzheimer's disease and vascular dementia, MCI and other.

2.3 Measures

Medication use: Medication data were collected via patient and carer interviews conducted at the clinic. Secondary

sources, including hospital/clinic records, patients' medication packages and medication lists, were examined if available. Current exposure to all medications, including prescription and non-prescription, regular and when required, was recorded at the time of recruitment. Medication names (brand and generic) were recorded; no information regarding strength or dose was collected, nor whether the medication was prescribed or purchased over the counter. Medications were coded using the Anatomical Therapeutic Chemical Classification System 2015 [20]. Polypharmacy was defined as five or more medications and hyperpolypharmacy as ten or more [21].

PIMcog use: PIMcog was defined as medication that was considered potentially inappropriate for use in older people with cognitive impairment according to the Beers 2012 criteria [5] or STOPP 2014 criteria [6]. Criteria unrelated to cognitive impairment were excluded. The PIMcog list consisted of 14 medication classes and 89 individual medications (electronic supplementary material, Appendix S1).

ACB score: The ACB scale assigns a score of zero for medications with no known anticholinergic activity, one for medication with possible anticholinergic properties (in vitro evidence of muscarinic receptor antagonism), two for medication with definite clinical anticholinergic properties and three for definite anticholinergic properties that may cause delirium [10, 22]. A score was given for each medication listed on the ACB 2012 scale [10, 23], and a total ACB score for each patient was calculated. A total score of three or more is considered to represent clinically significant anticholinergic burden [10].

2.4 Statistical Analyses

Descriptive statistics were used to describe the general demographics and features of medication use. Bivariate analyses, to compare characteristics of PIMcog users with nonusers, and patients with and without clinically significant ACB, were performed using Pearson's χ^2, Mann–Whitney U test and independent samples t tests. Multivariate logistic regression models using all variables from bivariate analyses were used to calculate adjusted odds ratios (ORs) with 95 % confidence intervals (CIs) to identify factors associated with PIMcog use.

Results are presented as means and standard deviations (SDs), medians and interquartile ranges (IQRs), numbers and percentages or adjusted ORs with 95 % CIs.

Data analysis was conducted using the Statistical Package for Social Sciences (SPSS, version 22.0; IBM Corp. Armonk, USA).

3 Results

3.1 Participant Characteristics

Of 967 patients included in the PRIME study, three were excluded from our analysis due to missing data, leaving 964 patients. Their mean (SD) age was 77.60 (7.4) years, 456 (47.3 %) were women, 121 (12.6 %) had not completed secondary level education and 121 (12.6 %) lived alone. The most common diagnoses were Alzheimer's disease ($n = 521$, 54.0 %) and MCI ($n = 185$, 19.2 %). The median (IQR) cognition scores for the population were MMSE 24/30 (20–27) ($n = 957$, missing data from seven patients) and clock drawing test 9/10 (5–10) ($n = 816$, missing data from 148 patients).

Most patients (98.2 %) used at least one medication. Polypharmacy was present in 642 (66.6 %) and hyperpolypharmacy in 170 (17.6 %) patients. The median (IQR) number of medications per patient was 6 (4–8), range 0–20. The most commonly used medications were cholinesterase inhibitors ($n = 576$), platelet aggregation inhibitors ($n = 460$), HMG CoA reductase inhibitors ($n = 372$), proton pump inhibitors ($n = 220$) and angiotensin-converting enzyme inhibitors ($n = 214$).

Polypharmacy was more prevalent in people diagnosed with dementia than those with MCI (68.3 vs 59.5 %, $p = 0.028$). There was no statistically significant difference in the median number of medications ($p = 0.139$) or prevalence of hyperpolypharmacy ($p = 0.376$) between the two groups.

3.2 PIMcog Use

Two hundred and six (21.4 %) patients were using at least one PIMcog; 47 (4.8 %) used two or more. The most common classes of PIMcog were anticholinergics and sedatives (Table 1). The most common individual PIMcogs were temazepam ($n = 47$), oxazepam ($n = 23$), prednisolone ($n = 22$), prochlorperazine ($n = 18$), ranitidine ($n = 16$) and oxybutynin ($n = 15$) (electronic supplementary material, Appendix S1).

In bivariate analysis, PIMcog users were older, more likely to be female, less educated, on more medications, diagnosed with cognitive impairment later in life and had higher MMSE scores than non-users (Table 2).

The multivariate logistic regression model, using variables from Table 2 (excluding polypharmacy/hyperpolypharmacy given their relationship to number of medicines) indicated lower education level (adjusted OR 1.71; 95 % CI 1.01–2.89) and higher number of medications (adjusted OR 1.26; 95 % CI 1.19–1.33) were independently associated with PIMcog use.

△ Adis

Table 1 Potentially inappropriate medications for people with cognitive impairment (PIMcog) by medication class

PIMcog class	Number
Anticholinergic	104
Antipsychotics	27
Tricyclic antidepressants	27
Antimuscarinics (urinary)	20
Antispasmodics	13
First-generation antihistamines	7
Other antidepressants (with anticholinergic properties)	7
Antiparkinson agents	3
Other antihistamines (with anticholinergic properties)	0
Skeletal muscle relaxants	0
Sedatives and hypnotics	103
Benzodiazepines (BZD)	95
Non-BZD hypnotics	7
Barbiturates	1
Other medications that can induce delirium	50
Systemic corticosteroids	26
Histamine-2 receptor antagonists	24
Total	257

3.3 Anticholinergic Burden

According to the ACB scale, 431 patients (44.7 %) were taking a medication with anticholinergic properties. One hundred and thirteen (11.7 %) had a clinically significant ACB score (ACB ≥3); of these, 74 (65.5 %) used one or more medications with an ACB score of three, while 39 (34.5 %) had an ACB ≥3 due to the additive effect of multiple medications with an ACB score of one or two. In both bivariate and multivariate analyses, only a higher number of medications was associated with total ACB ≥3 (adjusted OR 1.23; 95 % CI 1.15–1.30) (Table 3).

The most common ACB medications were frusemide ($n = 82$), atenolol ($n = 77$), warfarin ($n = 75$), digoxin ($n = 63$) and metoprolol ($n = 49$), which all have an ACB score of one. The most common medications with an ACB score of three were oxybutynin ($n = 15$) and amitriptyline ($n = 11$).

Overall, 234 (24.3 %) patients were either using a PIMcog or had a medication regimen ACB score of three or more.

Table 2 Characteristics of users of potentially inappropriate medications (PIMcog) compared with non-users

Characteristic	PIMcog users ($n = 206$) n (%), unless specified	PIMcog non-users ($n = 758$) n (%), unless specified	p value[a]	Adjusted odds ratio (95 % CI)[b]
Age [years], mean (SD)	79.0 (7.5)	77.2 (7.4)	0.002	1.02 (0.91–1.14)
Age at diagnosis [years], mean (SD)	77.6 (7.71)	75.8 (7.6)	0.002	1.02 (0.91–1.13)
Sex [female]	113 (54.8)	343 (45.2)	0.018	1.24 (0.79–1.93)
Weight [kg], mean (SD)	70.5 (14.6)	71.3 (13.5)	0.516	0.99 (0.98–1.01)
Living alone	24 (11.6)	97 (12.8)	0.748	0.67 (0.35–1.27)
Education less than secondary level	40 (19.4)	81 (10.7)	<0.001	1.71 (1.01–2.89)
Family history of dementia	66 (32.0)	280 (36.9)	0.223	0.78 (0.52–1.18)
Cognitive diagnosis			0.084	
MCI	42 (20.4)	143 (18.9)		
AD	98 (47.6)	423 (55.8)		0.74 (0.43–1.29)
Other dementias[c]	66 (32.0)	192 (25.3)		1.26 (0.70–2.26)
Total number of medications, median (IQR)	8 (6–11)	5 (3–7)	<0.001	1.26 (1.19–1.33)
Polypharmacy	183 (88.8)	459 (60.6)	<0.001	
Hyperpolypharmacy	78 (37.9)	92 (12.1)	<0.001	
MMSE score [/30], median (IQR)	24 (21–27)	23 (19–27)	0.028	1.01 (0.96–1.06)
Clock drawing score [/10], median (IQR)	9 (6–10)	8 (5–10)	0.140	1.01 (0.98–1.17)

AD Alzheimer's disease, *CI* confidence interval, *IQR* interquartile range, *MCI* mild cognitive impairment, *MMSE* Mini Mental State Examination, *PIMcog* potentially inappropriate medication for people with cognitive impairment, *SD* standard deviation

[a] Bivariate p values based on Pearson χ^2, Mann–Whitney U test and independent samples t test, as appropriate

[b] Odds ratio, 95 % CI based on multivariate logistic regression

[c] Other dementias: vascular dementia (VaD), Lewy body dementia (LBD) frontotemporal dementia (FD), mixed dementia and other

Table 3 Characteristics of participants with an ACB score ≥3 compared with those with an ACB score <3

Characteristic	ACB ≥3 (n = 113) n (%), unless specified	ACB <3 (n = 851) n (%), unless specified	p value[a]	Adjusted odds ratio (95 % CI)[b]
Age [years], mean (SD)	77.7 (7.5)	77.6 (7.4)	0.901	1.06 (0.94–1.20)
Age at diagnosis [years], mean (SD)	76.1 (7.5)	76.2 (7.7)	0.869	0.94 (0.83–1.06)
Sex [female]	60 (53.1)	396 (46.5)	0.225	1.29 (0.76–2.18)
Weight [kg], mean (SD)	72.6 (13.6)	70.9 (13.7)	0.275	1.01 (0.99–1.03)
Living alone	16 (14.2)	105 (12.3)	0.691	1.25 (0.60–2.57)
Education less than secondary level	19 (16.8)	102 (12.0)	0.192	0.79 (0.40–1.56)
Family history of dementia	33 (29.2)	313 (36.8)	0.141	0.78 (0.47–1.28)
Cognitive diagnosis			0.311	
MCI	20 (17.7)	165 (19.4)		
AD	56 (49.6)	465 (54.6)		1.21 (0.53–2.80)
Other dementias	37 (32.7)	221 (26.0)		1.49 (0.67–3.35)
Total number of medications, median (IQR)	8 (6–11)	5 (4–8)	<0.001	1.23 (1.15–1.31)
Polypharmacy	101 (89.4)	541 (63.6)	<0.001	
Hyperpolypharmacy	42 (37.2)	128 (15.0)	<0.001	
ChEI use	65 (57.5)	510 (59.9)	0.624	0.78 (0.42–1.42)
MMSE score [/30], median (IQR)	24 (19–27)	24 (20–27)	0.823	0.96 (0.91–1.02)
Clock drawing score [/10], median (IQR)	9 (5–9)	9 (5–10)	0.395	1.00 (0.91–1.11)

ACB anticholinergic cognitive burden, *AD* Alzheimer's disease, *ChEI* cholinesterase inhibitor, *CI* confidence interval, *IQR* interquartile range, *MCI* mild cognitive impairment, *MMSE* Mini Mental State Examination, *PIMcog* potentially inappropriate medication for people with cognitive impairment, *SD* standard deviation

[a] Bivariate *p* values based on Pearson χ^2, Mann–Whitney *U* test and independent samples *t* test, as appropriate

[b] Odds ratio, 95 % CI based on multivariate logistic regression

[c] Other dementias: vascular dementia (VaD), Lewy body dementia (LBD) frontotemporal dementia (FD), mixed dementia and other

3.4 Anticholinergic Use with ChEIs

Of the 575 patients using a ChEI, 258 (44.9 %) also used a medication with potential or actual anticholinergic cognitive effects and 65 (11.3 %) had an ACB score of three or more. Of the 65 patients with ACB ≥3, 41 (63 %) used a potent anticholinergic medication (ACB score of three), and 24 (37 %) had a significant ACB score due to the additive effect of multiple ACB medications.

There were no significant differences in ChEI use between those with ACB ≥3 and those with ACB <3 (adjusted OR 0.78; 95 % CI 0.42–1.42).

4 Discussion

Almost one in four patients attending Australian memory clinics used a PIMcog or had a clinically significant anticholinergic burden. As patients were recruited either at their initial assessment visit at the memory clinic or a subsequent follow-up appointment, the data reflects a combination of primary care prescribing and possible changes that resulted from memory clinic review.

The most prevalent PIMcog classes were anticholinergic and sedative medications. Sedatives should generally be avoided in patients with dementia as they are associated with prolonged sedation and long-lasting memory deficits [24]. Anticholinergic medications can impair psychomotor speed, reduce cognitive functioning and increase mortality [7, 22]. Clinically significant anticholinergic cognitive burden (ACB ≥3) was present in 11.7 % of patients. These results are consistent with other studies in community-dwelling patients with dementia, which reported that 15–22 % of patients used a medication considered inappropriate in people with cognitive impairment [13, 25, 26]. There has been limited study of ACB in people with dementia; however, studies in the general older population suggest that 5–28 % take potent anticholinergic medications or have clinically significant anticholinergic burden [7, 27, 28].

In our study, PIMcog use and anticholinergic burden were associated with taking a higher number of medications, a finding that is consistent with previous studies [25, 26]. PIMcog use was also associated with lower education. Past research suggests this may be due to lower educated patients playing a less active role in their health or the

confounding effect of polypharmacy, as lower education is also associated with polypharmacy [29].

More than one in ten patients prescribed a ChEI also had a clinically significant anticholinergic medication burden. This is generally consistent with previous studies [9, 13, 30]. Other studies that have used alternative anticholinergic burden tools have reported concomitant use of a ChEI and an anticholinergic in up to one-third of patients [8, 31]. The use of anticholinergic medication with a ChEI has been associated with a greater rate of cognitive and functional decline than using a ChEI alone [9].

Of particular interest is that more than one-third of patients with a clinically significant anticholinergic burden had the burden as a result of additive effects of multiple medications. This may suggest lack of awareness among prescribers regarding anticholinergic medications, or it may be a consequence of multiple prescribers who do not consider the 'whole' patient or who do not have access to a complete medication list. Past research on deprescribing [32] suggests that an educational intervention regarding anticholinergic prescribing in patients with cognitive impairment, including the potential additive cumulative effects of medications, may be beneficial.

Although it may be expected that PIMcog users and people with high ACB scores would have worse cognition, multivariate analyses found no association. This may indicate that some physicians deprescribed PIMcogs as cognitive function declined. 'Dementia severity' has been suggested as a common reason for deprescribing [33]. This relationship should be further explored in longitudinal studies.

Polypharmacy was present in two-thirds of participants and was associated with PIMcog use and anticholinergic burden. Polypharmacy is known to be associated with increased risk of hospital admissions, functional and cognitive impairment, falls and mortality [34–36]. These findings support the need for interventions that encourage deprescribing, especially of PIMcogs and anticholinergic medications, in patients attending memory clinics. Electronic decision support when prescribing/dispensing medications, to prompt healthcare professionals to identify PIMs and make risk–benefit assessments, may be beneficial. This intervention could be particularly valuable in identifying potential additive cumulative anticholinergic effects or interactions with ChEIs that prescribers may otherwise overlook. A computerized PIMs dashboard that flagged individuals with a PIM or high anticholinergic score has previously been found to be an efficient mechanism to rapidly screen medication regimens [37].

A recent systematic review identified prescriber barriers to deprescribing, including knowledge and skill deficits (e.g. assessing benefits and harms of therapy, and recognising adverse drug effects), lack of time, therapeutic inertia, fear of negative consequences, reluctance to stop medications prescribed by other physicians and patient resistance to change [38]. Lack of access to a complete medication history for patients attending memory clinics has also been identified as a barrier to identifying medication-related problems [39].

In general, studies suggest that interdisciplinary care involving physicians and pharmacists can improve appropriateness of prescribing [40, 41]. A small Australian study reported that placing a pharmacist in a specialist memory clinic improved the accuracy of medication histories and identification of medication-related problems [39]. The current study supports the need for comprehensive interdisciplinary medication reviews for patients with known cognitive impairment including those attending memory clinics.

Our study had some strengths and limitations. Strengths included the large sample size and inclusion of patients from nine memory clinics across four of the eight states/territories of Australia with a broad range of cognitive diagnoses. Most existing literature has only examined specific populations such as those with advanced dementia [42], those residing in residential aged care facilities [43], or those with a particular cognitive diagnosis [26, 30].

A limitation of our study was that lack of information on medication doses prevented us from taking dosage into consideration when estimating anticholinergic burden. This may have resulted in overestimation of potential anticholinergic burden in patients who were using low or 'when required' doses. A recognized limitation of explicit criteria such as Beers and STOPP is that they do not take individual patients' circumstances into consideration. Therefore, some medications identified as PIMcogs, including those identified by the ACB scale, may have been clinically appropriate for individual patients. For example, in some cases oral corticosteroids may have been an appropriate therapeutic choice despite the risk of adverse cognitive outcomes. As the PRIME study was not designed for the purpose of analysing appropriateness of medication use, information required to conduct implicit reviews of medication appropriateness (taking into consideration co-morbidities, contraindications, previous treatments, etc.) was not available. Another limitation is that these criteria were not developed to assess medication appropriateness in an Australian setting. However, criteria such as Beers and STOPP are widely used and internationally accepted measures of prescribing quality in population studies. Finally, our study included data that were collected between 2005 and 2008 and prescribing patterns may have changed since that time.

5 Conclusion

Nearly one in four patients with cognitive impairment attending memory clinics used a PIMcog or had a clinically significant anticholinergic burden. More than one in ten patients taking a ChEI also had a significant anticholinergic burden. Further research into interventions such as pharmacist medication review and targeted deprescribing is warranted to help reduce PIMcog use and improve health outcomes in this population.

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DIETARY SUPPLEMENT USE IN OLDER PEOPLE ATTENDING MEMORY CLINICS IN AUSTRALIA

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Abstract: *Background:* Dietary supplement use is common in older adults. There has been limited research in people attending memory clinics. *Objectives:* To explore the use of dietary supplements in older people attending Australian memory clinics. *Design:* Cross-sectional analysis of baseline data from the Prospective Research In MEmory clinics (PRIME) study. *Participants:* Community-dwelling older people who attended nine memory clinics and had a diagnosis of mild cognitive impairment (MCI) or dementia. *Measurements:* Dietary supplement was defined as a product that contains one or more: vitamin, mineral, herb or other botanical, amino acid or other dietary substance. Non-prescribed supplement was defined as a supplement that is not usually prescribed by a medical practitioner. Polypharmacy was defined as use of five or more medications. *Results:* 964 patients, mean age 77.6 years, were included. Dietary supplements were used by 550 (57.1%) patients; 353 (36.6%) used two or more. Non-prescribed supplements were used by 364 (36.8%) patients. Supplement use was associated with older age (OR: 1.12, 95% CI: 1.03-1.21), lower education level (OR: 1.53, 95% CI: 1.01-2.32) and a diagnosis of MCI rather than dementia (OR: 1.52, 95% CI: 1.05-2.21). Potential drug-supplement interactions were identified in 107 (11.1%) patients. Supplement users had increased prevalence of polypharmacy compared to non-users (80.5% vs. 48.1%, p<0.001). *Conclusions:* Dietary supplements, including non-prescribed supplements, were commonly used by people attending memory clinics. Supplement use increased the prevalence of polypharmacy and resulted in potential supplement-drug interactions. Further research is required to assess the clinical outcomes of supplement use.

Key words: Dietary supplements, cognitive impairment, dementia, memory clinic.

Introduction

Dietary supplement use is increasing and almost 50% of older people use supplements (1-4). The decision to use supplements is often made by patients which creates a challenge for health professionals (5). The majority of patients who use supplements believe that they are safe, natural and cause no adverse effects; almost half do not disclose their use of supplements to their physician (6-8). Consequently, health professionals often underestimate supplement use (9). Dietary supplements can increase the risk of polypharmacy, adverse drug reactions, drug interactions and mortality (7, 10, 11).

Research into supplement use in patients attending memory clinics has been limited to a small Canadian study of 115 patients attending one dementia clinic, which reported that 39.1% of patients used one or more supplements, and 9.6% used them specifically to help with memory (12). There has been no large, multi-centre study exploring the prevalence of supplement use and the characteristics of supplement users in the specialist memory clinic setting.

The aim of this study was to explore the use of dietary supplements, in older people attending nine Australian memory clinics.

Methods

Design, setting and participants

This study was a cross-sectional analysis of baseline data from the Prospective Research In MEmory clinics (PRIME) study (National Institute of Health Clinical Trials registry number: NCT00297271). The PRIME study recruited patients from nine out-patient memory clinics affiliated to hospitals across four states of Australia between April 2005 and July 2008 (inclusive). Patients were eligible for inclusion if they had been diagnosed with dementia using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (13) or MCI using the Petersen criteria (14). Participants had to be community dwelling with <40 hours/week nursing care, be fluent in English, be able to provide written informed consent directly or through a legal guardian/proxy, and have a caregiver willing to provide consent. Further details of the PRIME study have been previously published (15).

Data collection

Data were collected by clinic staff (physicians and nurses) and trained research nurses. Demographic and clinical data included age, gender, level of education, living arrangements, caregiver relationship to participant, age at diagnosis of MCI/dementia, cognitive impairment diagnosis group, and Mini-

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Mental State Examination (MMSE) score (16).

Medication and dietary supplement data included name and duration of use. Dosage information, reason for use and source (prescribed versus self-selected) were not collected. Medication and supplement data were collected via patient and caregiver interviews conducted at the clinic or hospital. Patients' medication packages were inspected, if available.

Measures

Dietary supplement: defined as a product (other than tobacco) that contains one or more: vitamin, mineral, herb or other botanical, amino acid or other dietary substance (17). All supplement dose-forms (e.g. tablets/capsules, liquids) were included.

Non-prescribed supplement: defined as all dietary supplements excluding folic acid, calcium, vitamin D, vitamin B12, iron, potassium, magnesium, thiamine and herbal laxatives (e.g. senna), which are commonly prescribed by medical practitioners.

Total medication use: The sum total of all current, prescription and non-prescription medications, excluding all dietary supplements. Polypharmacy was defined as the use of five or more medications and hyperpolypharmacy as 10 or more (18).

Supplement-drug interactions: Potential supplement-drug interactions were identified according to Stockley's Drug Interactions 10th Edition (19).

Statistical analyses

Data analyses were conducted using the Statistical Package for Social Sciences (SPSS, version 22.0; IBM Corp. Armonk, USA).

Descriptive statistics were used to report the general demographics and features of medication use. Bivariate analyses were using Pearson $\chi2$, Mann-Whitney U test and independent samples t-test, as appropriate. A multivariate logistic regression model, incorporating all variables from bivariate analyses with p<0.2, was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs).

Results are presented as mean and standard deviation (SD), median and interquartile range (IQR), range, number and percentage, or OR with 95% CI.

Ethical Considerations

The PRIME study was approved by the research ethics committees of each participating institution. The analyses described in this manuscript received exemption from Monash University Human Research Ethics Committee.

Results

Participant characteristics

Of 967 participants included in the PRIME study, three were excluded due to missing data. Participants' (n=964) mean age (SD) was 77.6 (7.4) years; 456 (47.3%) were women and 121 (12.5%) had not completed a secondary level education. Caregivers were mostly spouses (n= 698, 72.4%), especially for male participants (n= 444, 87.4%). The median (IQR) MMSE score was 24/30 (20-27) (n=957).

The cognitive diagnoses of participants included Alzheimer's disease (n=521, 54.0%), MCI (n=185, 19.2%), vascular dementia (n=51, 5.3%), dementia with Lewy bodies (n=16, 1.7%), frontotemporal dementia (n=31, 3.2%), mixed Alzheimer's and vascular dementia (n=129, 13.4%) and other (n=31, 3.2%).

The median (IQR) number of medications (excluding all dietary supplements) was 5 (3-7). Polypharmacy was present in 498 (51.7%) patients, and hyperpolypharmacy was present in 73 (7.6%) patients.

Supplement use

Dietary supplements were used by 550 (57.1%) patients, with 353 (36.6%) using two or more. The median (IQR) number of dietary supplements was 1 (0-2), range zero to 14. Dietary supplements constituted 21.9% of all medications used. Supplements were mostly used in conjunction with other medication; 13 patients used only supplements. The ten most commonly used dietary supplements (Table 1) made up 82.1% of all dietary supplements used.

Table 1
Ten most common dietary supplements used by PRIME participants

Dietary Supplement	Patients (%)
Folic acid	176 (18.3)
Vitamin E	165 (17.1)
Fish oil/omega 3	147 (15.2)
Calcium (including combinations with vitamin D)	125 (13.0)
Vitamin B complex	111 (11.5)
Vitamin B12	84 (8.7)
Glucosamine (including combinations with chondroitin)	83 (8.6)
Ginkgo biloba	83 (8.6)
Vitamin D (excluding combinations with calcium)	59 (6.1)
Multivitamin	54 (5.6)
Total	**501 (52.**

* Total after removal of patients who took multiple supplements.

Non-prescribed supplements constituted 58.2% of all dietary supplements and were used by 364 (37.8%) patients (range zero to 13); 208 (21.6%) patients used both non-prescribed and prescribed supplements.

Table 2
Characteristics of users and non-users of dietary supplements and non-prescribed supplements

	All dietary supplements				Non-prescribed supplements			
	Users (n=550)	Non-users (n=414)	p value*	Odds Ratio (95% CI)^	Users (n=364)	Non-users (n=600)	p value*	Odds Ratio (95% CI)^
	n(%), unless specified				n(%), unless specified			
Age (years), mean (SD)	77.3 (7.7)	78.0 (7.0)	0.173	1.12 (1.03-1.21)	76.1 (7.9)	78.5 (7.0)	<0.001	**1.14 (1.05**
Age at diagnosis (years), mean (SD)	75.8 (7.9)	76.7 (7.3)	0.054	0.88 (0.82-0.96)	74.4 (7.9)	77.3 (7.3)	<0.001	**0.85 (0.78**
Gender (female)	254 (46.2)	202 (48.8)	0.460	-	152 (41.8)	304 (50.7)	0.009	0.89 (0.66-1.19)
Living alone	61 (11.1)	60 (14.5)	0.139	0.86 (0.53-1.41)	31 (8.5)	90 (15.0)	0.004	0.82 (0.47-1.44)
Spouse as caregiver	411 (74.7)	287 (69.3)	0.074	1.13 (0.77-1.64)	293 (80.5)	405 (67.5)	<0.001	**1.47 (0.96**
Education less than secondary level	80 (14.5)	41 (9.9)	0.040	1.53 (1.01-2.32)	60 (16.5)	61 (10.2)	0.006	2.18 (1.45-3.27)
Cognitive diagnosis								
- AD	288 (52.4)	233 (56.3)	0.253	-	189 (51.9)	332 (55.3)	0.335	-
- Other dementias#	142 (25.8)	116 (28.0)	0.490	-	79 (21.7)	179 (29.8)	0.006	0.70 (0.50-0.99)
- MCI	120 (21.8)	65 (15.7)	0.021	1.52 (1.05-2.21)	96 (26.4)	89 (14.8)	<0.001	**1.68 (1.14**
Total number of medications~, median (IQR)	5 (3-7)	4 (2-6)	0.003	1.09 (1.04-1.15)	4 (2-7)	5 (3-6)	0.409	-
MMSE Score (/30), median (IQR)	24 (20-27)	23 (20-26)	0.007	**1.03 (0.998**	25 (20-27)	23 (19-26)	<0.001	**1.04 (1.01**

* Bivariate p values based on Pearson χ2, Mann-Whitney U test and independent samples t-test as appropriate; ^ Odds Ratio, 95% Confidence Interval (CI) based on multivariate logistic regression incorporating variables from bivariate analyses with p<0.2; # Other dementias = vascular dementia, Lewy body dementia, frontotemporal dementia, mixed Alzheimer's and vascular dementia and other; ~ Total number of medications: defined as the sum total of all current, prescription and non-prescription medications, excluding all dietary supplements
Abbreviations: AD = Alzheimer's disease, MCI = Mild cognitive impairment, MMSE = Mini Mental State Examination

Characteristics of supplement users

In bivariate analyses (Table 2), dietary supplement users were less educated, were more likely to be diagnosed with MCI rather than dementia, had a higher MMSE score and were taking a greater total number of medications (excluding supplements). Additionally, non-prescribed supplement users were younger, diagnosed with cognitive impairment at a younger age, were more likely to be male, were not living alone and had a spouse as a caregiver.

In multivariate logistic regression models (Table 2) both supplement use and non-prescribed supplement use was associated with older age, diagnosis of cognitive impairment at a younger age, lower education level and a diagnosis of MCI rather than dementia. Supplement use was also associated with use of higher number of medications, and non-prescribed supplement use was associated with higher MMSE scores.

Dietary supplement impact on polypharmacy

The inclusion of dietary supplements in the total medication count resulted in supplement users having a statistically significant higher median number of medications (seven vs. four, p<0.001), and increased prevalence of polypharmacy (80.5% vs. 48.1%, p<0.001) and hyperpolypharmacy (27.5% vs. 4.6%, p<0.001) compared to non-users.

Supplement-drug interactions

Table 3 shows potential interactions between non-prescribed supplements and prescription medications taken by study participants. 107 (11.1%) patients were at risk of potential interactions.

Discussion

This is the first large, multi-centre study to explore the use of dietary supplements among older people attending memory clinics. It was found that the majority of participants used dietary supplements, mostly in conjunction with prescribed medications. This finding is consistent with research into supplement use in the general population (20, 21).

Five of the top ten supplements used by PRIME participants were supplements that may be used to support cognitive function, including folic acid, gingko biloba, omega 3, vitamin B12 and vitamin E (22). Despite their popularity, evidence of efficacy of dietary supplements to prevent cognitive decline is limited and inconsistent. Cochrane systematic reviews evaluating the efficacy of gingko biloba, omega 3 and vitamin E for preventing cognitive decline concluded that they have no convincing, predictable clinical benefit (23-25).

Patients diagnosed with MCI were more likely to use supplements than patients with dementia. This may suggest that patients or their families want to try alternative options in the early stages of cognitive decline despite limited evidence of efficacy. Another explanation could be that patients with MCI are more likely to use supplements to manage co-morbidities, including those associated with developing dementia (e.g. omega 3 for cardiovascular health) (26).

Unlike studies in non-dementia populations (1, 2, 4, 8), this study showed an inverse relationship between education level and supplement use and no association between female gender and supplement use. A possible explanation for these

Table 3
Possible interactions between non-prescribed dietary supplements and prescribed medications

Supplement (n)	Drug/s	Consequence of interaction	Patients with potential interactions
Garlic (8)	Warfarin	May increase severity of bleeding	4
Ginkgo biloba (83)	Aspirin, clopidogrel, warfarin	May affect platelets, bleeding and clotting and increase risk of bleeding	41
	Phenytoin, valproate	May reduce effect of phenytoin and valproate	6
Omega 3 (147)	Aspirin, warfarin	May have additive effect on bleeding time	68
Vitamin E (165)	Warfarin	May potentiate effect and increase bleeding	9
Zinc (14)	Bisphosphonates	May interfere with absorption and reduce effect	1
		Total Patients	107*

* Total after removal of patients who had two or more interactions.

differences lies in the fact that patients were often reliant on caregivers. The input of female caregivers in the decision to use supplements in male patients may have impacted upon the profile of supplement users. The level of education of caregivers was not collected in the PRIME trial. These findings are important for health professionals to consider and a reminder of the complexities associated with managing people with dementia

As highlighted by prior research, supplement use can sometimes have negative consequences (1, 7). Supplement use increases prevalence of polypharmacy, which has been linked to poorer medication adherence and other negative outcomes such as increased risk of delirium and falls (27-29). While one study suggested that there was no significant association between supplement use and non-adherence (30), there has been no research in patients with MCI or dementia. Cognitive impairment is an independent predictor of non-adherence and reduced ability to manage multiple medications (31), thus the impact of supplement use on polypharmacy and medication regimen complexity may be particularly important in these patients. Further research is needed to assess the impact of supplement use on adherence and medication management in this population.

Another concern regarding supplement use is the potential for interactions with prescribed medication (19). The findings of this study suggest that potential drug-supplement interactions are common, especially those related to increased risk of bleeding. These risks may be further compounded by underestimation of supplement use by health care professionals (6-9). Health care professionals need to actively enquire about supplement use and provide evidence-based, non-judgmental advice to assist patients and caregivers in considering risk versus benefit of supplement use. Greater educational support for health care professionals, including reliable sources of information about supplement use, safety and potential for interactions, would be valuable (32).

Our study had some strengths and limitations. Strengths included the large sample size and inclusion of patients from nine memory clinics across Australia with a broad range of cognitive diagnoses.

A limitation is that the PRIME study was not designed to assess supplement use and patients may not have reported all supplement use. Underreporting could have resulted in underestimation of the prevalence of both supplement use and potential drug-supplement interactions. Information was not collected regarding patients' motivations for taking non-prescribed supplements, or whether their physicians were aware and/or involved in their decision to use supplements. To avoid over-estimating non-prescribed supplement use we took a conservative approach and excluded supplements such as calcium that maybe self-selected but are often prescribed for older people. This may have resulted in underestimation of the number of patients self-selecting supplements.

The PRIME study excluded patients who did not speak English or who received high level nursing care; hence patterns of supplement use reported here may not be generalizable to these groups.

Finally, our study included data that were collected between 2005 and 2008 and supplement use patterns may have changed since that time. For example, Souvenaid (33), a specifically formulated drink for the dietary management of the early stages of Alzheimer's disease became available in Australia in 2013.

In conclusion, the majority of patients with cognitive impairment attending memory clinics were using dietary supplements. Supplement use increased the prevalence of polypharmacy and led to potential supplement-drug interactions. Further research is needed into the impact of supplement use on cognition, medication management, adherence, adverse effects and clinically significant drug interactions in this population.

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Potentially Inappropriate Medication, Anticholinergic Burden, and Mortality in People Attending Memory Clinics

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Abstract.

Background: There is limited evidence regarding the association between potentially inappropriate medications (PIM) and mortality in older people with cognitive impairment.

Objective: To examine whether use of medications considered to be potentially inappropriate in older people with cognitive impairment (PIMcog) and anticholinergic cognitive burden (ACB) were associated with mortality in people who attended memory clinics.

Methods: Cross-sectional and longitudinal analyses of data from the Prospective Research In MEmory clinics (PRIME) study. Participants were community-dwelling people who attended nine memory clinics and had a diagnosis of mild cognitive impairment or dementia. PIMcog was defined as any medication considered potentially inappropriate for a person with cognitive impairment according to Beers or STOPP criteria. Anticholinergic burden was calculated using the ACB scale. Time-dependent Cox-proportional hazards regression was used to analyze associations between PIMcog use/ACB score and all-cause mortality over a three-year follow-up period. The regression model included the baseline variables: age, gender, education, cognitive diagnoses, total number of medications, disease-burden, cognition, physical function, and neuropsychiatric symptoms.

Results: Of 964 participants, 360 (37.3%) used one or more PIMcog at some time during the study; most commonly anticholinergics and sedatives. 624 (64.7%) participants used a medication with potential or definite anticholinergic properties (ACB>0) at some point during the study. Both PIMcog use (adjusted hazard ratio: 1.42 95% CI: 1.12–1.80) and ACB score (adjusted hazard ratio: 1.18 95% CI: 1.06–1.32) were associated with mortality.

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Conclusion: Use of PIMcogs and medications with anticholinergic properties was common among memory clinic patients and both were associated with mortality.

Keywords: Alzheimer's disease, cholinergic antagonists, cognitive dysfunction, dementia, inappropriate prescribing, mortality, potentially inappropriate medication list

INTRODUCTION

Older people are more susceptible to adverse drug events than younger adults due to factors including altered pharmacokinetics and pharmacodynamics, multiple comorbidities, polypharmacy, and drug interactions [1, 2]. Inappropriate medication use further increases the risk of adverse drug events including hospitalizations, morbidity, and mortality [1, 3–9].

Cognitive impairment is common in older people, with around 5% of people aged ≥65 years having dementia [10] and a further 20% having mild cognitive impairment [11]. Older people with cognitive impairment have increased susceptibility to adverse central nervous system effects of medications, especially sedatives and anticholinergics [1, 2].

While there are tools for identifying potentially inappropriate medications (PIM) in people with advanced dementia [12], there are no specific tools for identifying PIM use in people with mild to moderate cognitive impairment. However, the Beers Criteria [13] and the Screening Tool of Older People's Prescriptions (STOPP) [14] criteria list medications which should be avoided in older people with cognitive impairment.

Anticholinergic medications increase the risk of cognitive impairment, functional impairment, and mortality [15–17]. There are a number of tools for measuring anticholinergic burden; however, there is no 'gold standard'. The anticholinergic cognitive burden scale (ACB) [18, 19] is particularly useful for identifying medications that may have a negative impact on cognition [20]. Each one point increase in ACB score has been associated with a 26% increase in the risk of death in older people [15].

There is limited research regarding the association between PIM use and mortality in older people with cognitive impairment, and no data specifically in people attending memory clinics. Memory clinics in Australia are ambulatory assessment services for people with suspected memory and related cognitive disorders [21]. We have reported earlier that nearly one in four patients attending memory clinics use a PIM or have a clinically significant anticholinergic burden [22].

The aim of this study was to examine whether medications considered to be potentially inappropriate in older people with cognitive impairment (PIMcog) and anticholinergic burden were associated with mortality in older people who attended memory clinics.

METHODS

Design, setting, and participants

Participants were from the Prospective Research In MEmory clinics (PRIME) study (National Institute of Health Clinical Trials registry number: NCT00297271). PRIME was a three-year multi-center observational cohort study assessing the management of patients who attended nine memory clinics affiliated with secondary or tertiary care hospitals across four of the eight states/territories of Australia. Patients were recruited at their initial assessment visit or a subsequent follow-up appointment between April 2005 and July 2008, and then followed up by a research nurse and/or their specialist physician at 3, 6, 12, 24, and 36 months from baseline, or until their death or withdrawal from the study.

Patients were eligible for inclusion in the PRIME study if they had been diagnosed with dementia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria [23] or mild cognitive impairment (MCI) according to the Petersen criteria [24]. Participants had to be community dwelling with <40 h/week nursing care, be fluent in English, be able to provide written informed consent directly or through a legal guardian/proxy, and have a carer willing to provide consent. Further details of the PRIME study have been previously published [25].

Data collection and measures

Data were collected by clinic staff (physicians and nurses) and trained research nurses. Demographic and diagnostic data were collected at baseline. Medication data and clinical assessments were completed at baseline and at each follow-up appointment. Cognition was assessed using the Mini-Mental State

Examination (MMSE) [26], functional ability was assessed using the Functional Autonomy Measurement System (SMAF) [27], and neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI) [28].

Medication use

Medication data were collected via patient and carer interviews conducted at the memory clinic. Secondary sources, including hospital/clinic records, patients' medication packages, and medication lists, were examined if available. Current exposure to all medications, including prescription and non-prescription, regular and when required, was recorded. Medication names (brand and generic) were recorded, but no information regarding strength or dose was collected. Medications were coded using the Anatomical Therapeutic Chemical Classification System 2015 [29].

Medication-based disease burden index (MDBI)

Data regarding co-morbidities were not collected in the PRIME study. Therefore, an MDBI score was calculated for each participant based on their baseline medication regimen to give an estimation of their disease burden. The MDBI is a validated measure for quantifying disease burden using participant medication lists [30]. Chronic conditions, identified by the medication used to manage that condition, are scored based on their contribution to global deaths [30]. We excluded the score for 'Alzheimer's disease and other dementias' from the total MDBI calculation given cognitive diagnoses were recorded separately.

PIMcog use

PIMcog was defined as any medication that was considered potentially inappropriate for use in older people with cognitive impairment according to the Beers 2012 [13] or STOPP 2014 criteria [14]. This included anticholinergics, sedatives, histamine-2 receptor antagonists, and systemic corticosteroids, which are associated with adverse central nervous system effects. Criteria unrelated to cognitive impairment were excluded. The PIMcog list consisted of 14 medication classes and 89 individual medications [22].

ACB score

The ACB scale assigns a score of zero for medications with no known anticholinergic activity, one for medication with possible anticholinergic properties

(*in vitro* evidence of muscarinic receptor antagonism), two for medications with definite clinical anticholinergic properties, and three for medications with definite anticholinergic properties that may cause delirium [18, 31]. A score was given for each medication listed on the ACB 2012 scale [18, 32], and a total ACB score for each participant was calculated by adding the individual scores of different medications in a participant's regimen.

Time-dependent measures of both PIMcog use and anticholinergic burden were defined using medication lists within one month of each follow up appointment. Participants were considered to be exposed to medications identified at each appointment until their next scheduled follow up, or until their date of death or date of withdrawal from the study. Medications that were started and ceased in between follow-up appointments were not known to the investigators.

Sensitivity analyses were conducted which excluded antipsychotics from the PIMcog list and ACB score as antipsychotic use has previously been associated with mortality [33].

Mortality

The primary outcome measure was all-cause mortality. Dates of death were recorded by memory clinic staff and research nurses, and confirmed using state registry records. Participant deaths that occurred within 90 days of completing or withdrawing from the study (determined by state registries search) were also included (hence total maximum duration of follow-up for the primary outcome was three years and 90 days).

Statistical analyses

Data analyses were conducted using the Statistical Package for Social Sciences (SPSS, version 22.0; IBM Corp. Armonk, USA).

Descriptive statistics were used to report the general demographics and features of medication use. Pearson χ^2 test, Mann-Whitney U test and independent samples *t*-test were used, as appropriate, for exploratory bivariate analyses.

Cox proportional hazards regression analyses were conducted to quantify the association between baseline PIMcog use (yes or no) or ACB score and time to all-cause mortality with censoring at scheduled end of three-year follow-up or withdrawal/loss to follow-up. Both unadjusted and adjusted hazard ratios (HRs) were calculated. Variables associated

with mortality or withdrawal from the study, as identified in exploratory analyses ($p < 0.05$), were adjusted for in the regression model. These variables included baseline age, gender, education, dementia/MCI diagnosis, total number of medications, MDBI score, MMSE, SMAF, and NPI score.

Time-dependent Cox proportional hazards regression analyses were used to determine the association between longitudinal PIMcog use (number of PIMcogs used at each time point) or ACB scores (at each time point) and mortality. From intraclass correlation coefficients (ICC), it was determined that between person variability was substantially higher than within-person variability in the medication exposure (i.e., ICC>0.80) and hence the time-dependent Cox models were appropriate [34, 35].

Results are presented as mean and standard deviation (SD), median and interquartile range (IQR), range, number and percentage and HR with 95% confidence interval. *p*-values less than 0.05 were considered to be statistically significant.

Ethical considerations

The PRIME study was approved by the research ethics committees of each participating institution. The analyses described in this manuscript received exemption from the Monash University Human Research Ethics Committee.

RESULTS

Participant baseline characteristics

There were 964 participants included at baseline with mean (SD) age 77.6 (7.4) years (Table 1). The cognitive diagnoses of participants included MCI ($n = 185$, 19.2%), Alzheimer's disease ($n = 521$, 54.0%), vascular dementia ($n = 51$, 5.3%), dementia with Lewy bodies ($n = 16$, 1.7%), frontotemporal dementia ($n = 31$, 3.2%), mixed Alzheimer's and vascular dementia ($n = 129$, 13.4%), and other dementia ($n = 31$, 3.2%).

At baseline the median (IQR) MMSE score was 24/30 (20 to 27) ($n = 957$, missing data from seven participants), the median (IQR) SMAF score was –14 (–23 to –7, $n = 905$, missing data from 59 participants), and the median (IQR) NPI score was 7.5 (2 to 18, $n = 826$, missing data from 138 participants). The median (IQR) number of medications was 6 (4 to 8), range 0 to 20. The median (IQR) MDBI score was 0 (0 to 0.21), range 0 to 1.74.

Participant follow up

Of the 964 participants, 310 (32.2%) did not complete the study. Reasons included withdrawal of carer/proxy consent ($n = 114$), lost to follow up ($n = 75$), self-withdrawal ($n = 55$), admission to nursing home or high level care and unable to participate in follow up ($n = 35$), carer illness/death ($n = 14$), moved interstate/overseas ($n = 10$), participant illness ($n = 4$) and discharged from the memory clinic ($n = 3$).

One hundred and forty-six (15.1%) participants died during the study or within 90 days from the date of completion or withdrawal from the study. The mean (SD) length of participation in the study was 2.37 (0.93) years.

Demographic and baseline clinical features of the participants who completed, died, and did not complete the study are summarized in Table 1. Participants who did not complete the study were older, had a lower level of education, were more likely to be diagnosed with dementia, and had a higher disease burden, lower cognitive ability, lower functional ability, and more severe neuropsychiatric symptoms at baseline than those who completed the study. Participants who did not complete the study had similar PIMcog use and ACB scores compared to those who completed.

PIMcog use and mortality

Three hundred and sixty (37.3%) participants used at least one PIMcog (range 0 to 7) at some point over the three-year study period. Two hundred and six (22.4%) participants were using a PIMcog at baseline, and 211 (21.9%) had a PIMcog initiated after recruitment. The most common PIMcogs were anticholinergics and sedatives (Table 2).

Baseline PIMcog use was associated with mortality in the unadjusted analysis (unadjusted HR: 1.71, 95% CI: 1.20–2.43) but was not statistically significant in the adjusted analysis (Model 1, Table 3).

Time-dependent PIMcog use was associated with mortality in both the unadjusted (HR: 1.52, 95%, CI: 1.26–1.83) and adjusted (HR: 1.42, 95%, CI: 1.12–1.80) analyses (Model 2, Table 3).

Sensitivity analyses, which excluded antipsychotics from the PIMcog list, showed similar results to the full PIMcog list (baseline PIMcog use adjusted HR: 1.33, 95% CI: 0.87–2.03 and longitudinal time-dependent PIMcog use adjusted HR: 1.46, 95% CI: 1.14–1.87).

Table 1
Characteristics of participants

Characteristic	Overall (n = 964)	Completed (n = 508)	Deceased (n = 146)	p-value*	Withdrawn or lost to follow up (n = 310)	p-value^
Age (years), mean (SD)	77.6 (7.4)	76.1 (7.7)	80.3 (6.4)	<0.001	78.7 (6.9)	<0.001
Sex (female), n (%)	456 (47.3)	244 (48.0)	54 (37.0)	0.023	158 (51.0)	0.458
Weight (kg), mean (SD)	71.1 (13.71)	71.0 (13.7)	72.0 (13.4)	0.485	70.8 (13.9)	0.861
Living alone, n (%)	121 (12.6)	58 (11.4)	18 (12.3)	0.876	45 (14.5)	0.235
Education (less than secondary level), n (%)	121 (12.6)	43 (8.5)	23 (15.8)	0.015	55 (17.7)	<0.001
Family history of dementia, n (%)	346 (35.9)	185 (36.4)	54 (37.0)	0.977	107 (34.4)	0.635
Cognitive diagnosis, n (%)						
- MCI	185 (19.2)	124 (24.4)	10 (6.8)	<0.001	51 (16.5)	0.009
- Dementia	779 (80.8)	384 (75.6)	136 (93.2)		259 (83.5)	
Total number of medications, median (IQR)	6 (4–8)	6 (4–8)	7 (5–10)	<0.001	6 (3–8)	0.906
Baseline disease burden (MDBI score), median (IQR)	0 (0–0.21)	0 (0–0.11)	0 (0–0.35)	<0.001	0 (0–0.21)	0.032
Baseline cognition (MMSE Score), median (IQR)	24 (20–27)	25 (21–27)	22 (16–25)	<0.001	23 (18–26)	<0.001
Baseline function (SMAF score), median (IQR)	–14 (–23 to –7)	–11 (–19 to –4.5)	–20.5 (–31.8 to –12.5)	<0.001	–18 (–27.3 to –9.5)	<0.001
Baseline neuropsychiatric (NPI score), median (IQR)	7.5 (2–18)	6 (2–15)	9 (3–20)	0.004	10 (3–23)	<0.001
Baseline PIMcog use (yes), n (%)	206 (21.4)	100 (19.7)	45 (30.8)	0.006	61 (19.7)	1.000
PIMcog use at some point (yes), n (%)	360 (37.3)	182 (35.8)	80 (54.8)	<0.001	98 (31.6)	0.248
Baseline ACB score, median (IQR)	0 (0-1)	0 (0-1)	1 (0–2)	<0.001	0 (0-1)	0.110
ACB medication use at some point (yes), n (%)	624 (64.7)	318 (62.6)	120 (82.2)	<0.001	186 (60.0)	0.505

Bivariate p-values based on Pearson χ^2, Mann-Whitney U test and independent samples t-test as appropriate. *p-values indicate difference between participants who died during the study or within 90 days of completing or withdrawing from the study (n = 146) versus those who completed the study (n = 508). ^p-values indicate differences between participants who withdrew or were lost to follow up (n = 310) versus those who completed the study (n = 508). ACB, Anticholinergic Cognitive Burden; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PIMcog, potentially inappropriate medication for a person with cognitive impairment; SMAF, Functional Autonomy Measurement System.

Table 2
Potentially inappropriate medications for people with cognitive impairment (PIMcog) by medication class

PIMcog Class	Baseline^	Initiated subsequently	Total
Anticholinergics	104	120	224
Antipsychotics (with anticholinergic properties)	27	42	69
Tricyclic antidepressants	27	11	38
Antimuscarinics (urinary)	20	21	41
Antispasmodics	13	32	45
First generation antihistamines	7	6	13
Other antidepressants (with anticholinergic properties)	7	1	8
Antiparkinson agents	3	2	5
Other antihistamines (with anticholinergic properties)	0	5	5
Skeletal muscle relaxants	0	0	0
Sedatives and hypnotics	103	158	261
Benzodiazepines (BZD)	95	157	252
Non-BZD hypnotics	7	1	8
Barbiturates	1	0	1
Others medications that can induce delirium	50	43	93
Systemic corticosteroids	26	29	55
Histamine-$_2$ receptor antagonists	24	14	38
Total	257	321	578
*Total participants**	206	211	360

^Details of baseline PIMcog use have been published previously [22]. *Total after removal of participants who took multiple PIMcogs.

ACB score and mortality

According to the ACB scale, 624 participants (64.7%) took a medication with potential or definite anticholinergic properties at some point during the study, and 431 (44.7%) had a baseline ACB score greater than zero. The most common ACB medications were risperidone (n = 166), frusemide (n = 138),

Table 3
Unadjusted and adjusted hazard ratios for the associations of PIMcog use with mortality over three years of follow up

Characteristic	Unadjusted HR (95% CI)	Model 1 Adjusted HR (95% CI)	Model 2^ Adjusted HR (95% CI)
Age (HR per year)	1.07 (1.05–1.10)	1.05 (1.02–1.08)	1.05 (1.02–1.08)
Sex (female)	0.66 (0.47–0.92)	0.55 (0.38–0.81)	0.54 (0.37–0.79)
Education (less than secondary level)	1.57 (1.01–2.46)	1.05 (0.64–1.70)	0.99 (0.61–1.62)
Dementia diagnosis (not MCI)	3.83 (2.01–7.28)	2.18 (1.03–4.64)	2.16 (1.02–4.59)
Total number of medications (HR per medication)	1.08 (1.04–1.13)	1.01 (0.95–1.07)	0.99 (0.94–1.05)
Baseline disease burden (HR per 1 unit MDBI score)	4.16 (2.55–6.81)	2.08 (1.11–3.91)	2.27 (1.21–4.26)
Baseline cognition (HR per 1 unit MMSE score)	0.92 (0.90–0.95)	0.96 (0.92–0.99)	0.95 (0.92–0.99)
Baseline function (HR per 1 unit SMAF score)	0.95 (0.94–0.96)	0.97 (0.95–0.99)	0.97 (0.95–0.99)
Baseline neuropsychiatric symptoms (HR per 1 unit NPI score)	1.01 (1.00–1.02)	1.00 (0.98–1.01)	1.00 (0.98–1.01)
Baseline PIMcog use (yes)	1.71 (1.20–2.43)	1.26 (0.83–1.91)	
PIMcog use over study period (HR per 1 unit PIMcog)^	1.52 (1.26–1.83)		1.42 (1.12–1.80)

^Time-dependent Cox-proportional hazards regression. CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PIMcog, potentially inappropriate medication for a person with cognitive impairment; SMAF, Functional Autonomy Measurement System.

warfarin ($n = 97$), atenolol ($n = 95$), and digoxin ($n = 81$), which all have an ACB score of one. The most common medications with an ACB score of three were olanzapine ($n = 30$), oxybutynin ($n = 27$), quetiapine ($n = 19$), and amitriptyline ($n = 17$).

Baseline total ACB score was associated with mortality in the unadjusted (HR: 1.27, 95% CI: 1.15–1.40) and adjusted (HR: 1.15, 95% CI: 1.01–1.31) analyses (Model 1, Table 4).

Time-dependent ACB scores were also associated with mortality in both the unadjusted (HR: 1.29, 95% CI: 1.19–1.39) and adjusted (HR: 1.18, 95% CI: 1.06–1.32) analyses (Model 2, Table 4).

Sensitivity analyses, which excluded antipsychotics from the ACB score, showed similar results (baseline ACB score adjusted HR: 1.18, 95% CI: 1.02–1.36 and longitudinal time-dependent PIMcog use adjusted HR: 1.16, 95% CI: 1.02–1.31).

DISCUSSION

More than one-third of patients attending the memory clinics in our study used a PIMcog and almost two-thirds were exposed to potential or definite anticholinergic cognitive burden over a three-year period. Explicit prescribing tools such as the Beers and STOPP criteria, and the ACB score, do not take individual patients' clinical picture or circumstances into consideration, so some of the usage of PIMcogs and ACB medications in our study population may have been clinically appropriate for individual patients. Nevertheless, their usage was high, and they were initiated both prior to the study and through-

out the three years of follow up despite the patients' diagnoses of MCI or dementia. This finding and the fact that their usage was associated with increased risk of mortality highlight a need to raise awareness among prescribers and pharmacists about the risks associated with these agents in people with cognitive impairment.

Baseline PIMcog use was not significantly associated with mortality over a three-year horizon when adjusting for other variables. However, longitudinal time-dependent PIMcog use was associated with a 40% increased risk of mortality. This may suggest that knowledge of longitudinal exposure to PIMcogs allows for better prediction of mortality than exposure at a single time point. The time-dependent exposure may also have demonstrated a stronger association with mortality due to its proximity to the occurrence of the outcome compared to baseline exposure.

A number of large population studies have shown that PIM use is associated with adverse drug events, hospitalizations, emergency department visits, and mortality in general populations of older people [7, 36]. A recent study found the risk of death in a community-based population of older adults was 44% higher in users of at least one PIM (measured using the 2012 Beers Criteria) [37]. However, there has been limited research regarding the association between PIM or PIMcog use and mortality in people with cognitive impairment. One study found a dose-response relationship between anticholinergic and sedative drug burden and mortality in people with Alzheimer's disease [5]. Other studies, using the Swedish National Board of Health and Welfare indicators [7] and the 1997 Beers criteria [38] to define

Table 4
Unadjusted and adjusted hazard ratios for the association of anticholinergic use with mortality over three years follow up

Characteristic	Unadjusted HR (95% CI)	Model 1 Adjusted HR (95% CI)	Model 2^ Adjusted HR (95% CI)
Age (HR per year)	1.07 (1.05–1.10)	1.05 (1.02–1.08)	1.05 (1.02–1.08)
Sex (female)	0.66 (0.47–0.92)	0.56 (0.38–0.82)	0.57 (0.39–0.83)
Education (less than secondary level)	1.57 (1.01–2.46)	1.08 (0.66–1.76)	1.02 (0.62–1.67)
Dementia diagnosis (not MCI)	3.83 (2.01–7.28)	2.09 (0.98–4.46)	2.08 (0.98–4.42)
Total number of medications (HR per medication)	1.08 (1.04–1.13)	0.99 (0.94–1.05)	1.00 (0.94–1.05)
Baseline disease burden (HR per 1 unit MDBI score)	4.16 (2.55–6.81)	2.05 (1.10–3.84)	1.99 (1.06–3.74)
Baseline cognition (HR per 1 unit MMSE Score)	0.92 (0.90–0.95)	0.96 (0.92–0.99)	0.96 (0.92–0.99)
Baseline function (HR per 1 unit SMAF score)	0.95 (0.94–0.96)	0.97 (0.95–0.99)	0.97 (0.95–0.99)
Baseline neuropsychiatric symptoms (HR per 1 unit NPI score)	1.01 (1.00–1.02)	1.00 (0.98–1.01)	1.00 (0.99–1.01)
Baseline ACB score (HR per 1 unit ACB score)	1.27 (1.15–1.40)	1.15 (1.01–1.31)	
ACB scores over study period (HR per 1 unit ACB score)^	1.29 (1.19–1.39)		1.18 (1.06–1.32)

^Time-dependent Cox-proportional hazards regression. ACB, Anticholinergic Cognitive Burden; CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; SMAF, Functional Autonomy Measurement System.

PIM use, found no significant association with mortality in people with dementia. Further research is needed to confirm the long-term effects of PIMcog use on mortality, and to test the potential benefits of deprescribing PIMcogs in this population.

In our study, higher baseline and longitudinal exposure to anticholinergic medications were both associated with mortality. In the time-dependent model, each one point increase in anticholinergic burden was associated with an 18% increase in risk of mortality for people attending memory clinics. This suggests that prescribers need to be cautious not only with the prescribing of individual anticholinergics, but also the potential cumulative anticholinergic burden of patients' entire regimens. These results are consistent with past research using the ACB scale in the general older population, where the odds of dying increased by 26% for every additional point scored on the ACB [15]. Other measures of anticholinergic burden have shown inconsistent associations with mortality [17, 39–41].

PIMcogs, particularly anticholinergic medications, are commonly prescribed for older people with cognitive impairment across many clinical settings [42]. Increasing polypharmacy, and recognition of potentially inappropriate prescribing, has led to a growing focus on deprescribing, the process of tapering or stopping medications, to minimize polypharmacy and improve patient outcomes [43]. Prescriber barriers to deprescribing include deficits in knowledge and skill (e.g., assessing benefits and harms of therapy, and recognizing adverse drug effects), lack of time, therapeutic inertia, fear of negative consequences, reluctance to stop medications prescribed by other physicians and patient resis-

tance to change [44]. Cognitive impairment, and involvement of carers, also creates barriers to deprescribing as it can be challenging to balance carer and patient preferences, and carers may have difficulties being surrogate decision makers [45]. More physicians providing care and lack of access to a complete medication history are further barriers [46, 47]. The long-term effects of deprescribing on clinical, economical, and quality of life outcomes are yet to be established in large prospective studies.

In general, studies suggest that interdisciplinary care and improved communication between health professionals can improve appropriateness of prescribing [48, 49]. A recent systematic review suggested that clinical medication review is beneficial in improving the quality use of medications [50]. A small Australian study reported that placing a pharmacist in a specialist memory clinic improved the accuracy of medication histories and identification of medication-related problems [47]. Further research is needed to evaluate the long-term clinical impact of interventions to improve appropriateness of medication use in this population.

Our study had strengths and limitations. Strengths included the large sample size with a wide geographical distribution, longitudinal study design with six time points of data collection over three years, inclusion of participants from nine memory clinics with a range of cognitive diagnoses and mortality data confirmed by state registry records. Our study also included sensitivity analyses to show that the association of PIMcogs and anticholinergic burden with mortality was independent of antipsychotic use. Our PIMcog list was a composite of both the Beers and STOPP criteria, which

enhanced the sensitivity in detecting adverse drug events [36].

A limitation of our study was that lack of information on medication doses prevented us from using dose-specific measures of PIM burden such as the Drug Burden Index [51]. A dose-specific measure could have differentiated the effect of high and low doses, and regular and when required (prn) use of medications. Limited information regarding patients' co-morbidities (other than dementia) may have resulted in residual confounding that was not accounted for within the medication-based disease burden index. Residual confounding may also have been present due to analyses only adjusting for baseline covariates. Participant withdrawal or loss to follow up in the PRIME study was 32% at three years. Similar rates of attrition have been seen in other cohort studies of patients with dementia due to both patient and caregiver factors [52]. Although we adjusted for relevant covariates and censored all participants at their time of drop out from the study, participant withdrawal may still have affected the results. Finally, recruitment from specialist memory clinics, exclusion of people living in residential care or receiving 40 or more hours per week of nursing care, and the lower than expected proportion of women in our study may limit the extent to which the findings apply to the wider population of people with cognitive impairment.

Conclusion

More than one-third of patients attending Australian memory clinics used a PIMcog and almost two-thirds were exposed to anticholinergic medications over a three-year period. Both longitudinal PIMcog use and anticholinergic burden were independent predictors of mortality. Further research on interventions for improving the appropriateness of prescribing for people with cognitive impairment and their effect on cognitive and health outcomes are needed.

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3.5 <u>Chapter summary</u>

The research presented in this chapter highlighted the high prevalence of potentially inappropriate and unnecessary medication use in people attending memory clinics. One in five patients used a PIMcog, one in ten patients had clinically significant anticholinergic burden and more than 50% of patients used one or more dietary supplements. PIMcog and anticholinergic medications were both initiated and continued during the three year study follow-up. Given that memory clinic patients remain under the primary care of their GP, the data likely reflects a combination of primary care prescribing and possible recommendations (or lack thereof) for medication changes from memory clinic doctors.

This chapter also highlighted potential consequences of inappropriate and unnecessary medication use on polypharmacy, drug interactions and mortality. The inclusion of dietary supplements in the total medication count increased the prevalence of polypharmacy (81% vs 48%), and one in ten people had a potential drug-supplement interaction. Anticholinergic medications at baseline, and both PIMcog use and ACB scores over the study period were associated with a higher risk of mortality. The impact of inappropriate medication use on cognition could not be assessed due to incomplete follow-up data on cognition in the PRIME study.

These findings support the urgent need for research investigating interventions for improving the appropriateness of medication use in people attending memory clinics, such as deprescribing.

4. CHAPTER FOUR: Deprescribing potentially inappropriate medications in people attending memory clinics

4.1 <u>Preface</u>

Chapter three identified high levels of potentially inappropriate and unnecessary medication use in people attending memory clinics, but to date, there have been no intervention studies to improve medication use in this setting. Lack of access to a complete medication history for patients attending memory clinics has been reported as a barrier to identifying MRPs, thus any patient-centred intervention should begin with a comprehensive medication history and medication review.

Research suggests that successful deprescribing requires a comprehensive medication review, patient-specific medication recommendations and multi-disciplinary collaboration. Despite there being limited research in people with cognitive impairment, chapter two (Cochrane review) suggested that pharmacist-led mixed educational and behavioural interventions (e.g. medication review, patient education and regimen simplification) may improve medication adherence in older adults.

This chapter aimed to apply the findings from the earlier chapters of this thesis, and evaluate the feasibility of adding a pharmacist into a memory clinic team to conduct medication reviews and lead an interdisciplinary deprescribing intervention. A feasibility study was conducted because of the limited previous research in this setting, and the potential challenges associated with recruiting and deprescribing medications in people with cognitive impairment. Stakeholder perspectives were also explored given this is a novel practice setting for pharmacists and deprescribing.

4.2 <u>Chapter objective</u>

To evaluate the feasibility of a pharmacist-led, interdisciplinary deprescribing intervention aimed at improving the appropriateness of medications used by people attending a memory clinic.

4.3 <u>Publications</u>

Cross AJ, George J, Woodward MC, Le VJ, Elliott RA. *Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM): a feasibility study* [submitted].

Cross AJ, Le VJ, George J, Woodward MC, Elliott RA. *Stakeholder perspectives on pharmacist involvement in a memory clinic to review patients' medication management and assist with deprescribing* [submitted].

4.4 <u>Appendices</u>

Appendix 4: Institutional research ethics approvals

Appendix 5: Participant information and consent forms

Appendix 6: Data collection forms

Appendix 7: Focus group and interview guides

Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM): a feasibility study

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Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM): a feasibility study

Abstract

Objective: To evaluate the feasibility of a pharmacist-led interdisciplinary deprescribing intervention study in a memory clinic.

Methods: A pre- post-intervention study conducted at an outpatient memory clinic. Participants were community-dwelling patients at risk of a medication-related problem, or their carers. Participants received a medication review in their home from a consultant pharmacist who collaborated with the patient/carer, memory clinic, general practitioner and community pharmacist to develop a plan for optimising medication use. The primary outcome was feasibility, based on i) proportion of clinic patients eligible to participate in the study , ii) proportion of eligible patients consented, iii) proportion of inappropriate/unnecessary medications reduced or ceased at six months.

Results: One-third of clinic patient/carers were eligible (n=82/238) and 60% (n=50/82) consented to participate. Pharmacists recommended deprescribing 124 medications, 53 (42.7%) had been ceased or dose-reduced at six months.

Conclusion: It is feasible to recruit study participants and deliver a pharmacist-led interdisciplinary deprescribing intervention in a memory clinic setting.

MeSH key words: dementia, deprescriptions, outpatients, pharmacists

Impact statement: This paper highlights the need for, and feasibility of, pharmacist-led interdisciplinary deprescribing for people attending memory clinics. Over a third of clinic patients were at risk of medication-related problems, 60% of these patients consented to participate, and 43% of medications recommended for deprescribing were ceased or reduced at six months.

Introduction

Older people, particularly those with cognitive impairment, are more susceptible to medication-related problems (MRPs) and adverse drug events (ADEs) than younger adults. Reasons include altered pharmacokinetics and pharmacodynamics, comorbidities, inappropriate/unnecessary polypharmacy and drug interactions [1, 2]. Impaired cognition can have a significant impact on a person's ability to manage their medications safely, leading to unintentional non-adherence, medication errors, and medication-related hospitalisations [3-5].

Deprescribing, the systematic, evidence-based process of discontinuing potentially inappropriate or unnecessary medications [6], is a growing area of focus in clinical practice and research. Deprescribing has the potential to reduce inappropriate medication use, improve health outcomes and reduce mortality [7].

Memory clinics are multi-disciplinary, specialist clinics for the assessment of a person with suspected cognitive impairment, diagnosis of a memory disorder (if applicable), and creation of a management plan [8]. Memory clinics may be an ideal setting for identifying medications that can be deprescribed because the benefits and harms of medications and health-related treatment goals may change as a result of new/developing cognitive impairment. Our earlier research showed that 40% of people attending a memory clinic take potentially unnecessary/inappropriate medication [9], with 20% taking medication considered specifically inappropriate for a person with cognitive impairment (e.g. anticholinergics and sedatives) [10, 11].

Memory clinics have input from many health professionals including physicians, nurses, neuropsychologists and social workers [8]. Pharmacists are not typically involved. We have previously shown that a pharmacist interview and medication review conducted in a memory clinic resulted in more comprehensive medication histories and identified more unresolved MRPs compared to standard practice [9].

To date, there have been no deprescribing intervention studies in people attending memory clinics. Deprescribing for people with cognitive impairment can be challenging as patients may have diminished decision making capacity and carers may have difficulties being surrogate decision makers [12]. Recruitment of people with dementia for research studies is also challenging, as the decision to enrol is generally made by two people; the patient and their carer [13]. Deprescribing in an outpatient clinic setting has potential barriers such as incomplete medical histories, risk of disrupting trust in patient-general practitioner (GP)

relationships and potential miscommunication between the clinic and GP [12, 14]. Given the limited research in this setting, this study aimed to evaluate the feasibility of a pharmacist-led, interdisciplinary deprescribing intervention study targeting people attending a memory clinic.

Methods

Study design and setting: Pre- and post-intervention feasibility study conducted in an outpatient memory clinic at an Australian tertiary care public hospital.

Participant characteristics:

Inclusion criteria:

1. Living at home within 20 km of clinic
2. Able to communicate in English
3. At risk of a MRP because of the presence of ≥1 of the following;
   a. ≥10 regular medications (including prescribed and over-the-counter medications), OR
   b. ≥1 medication considered potentially inappropriate for a person with cognitive impairment (PIMcog)[10] according to the Beer's 2015 Criteria [15] or the 2015 Screening Tool of Older Peoples Prescriptions (STOPP) [16], OR
   c. Answers 'yes' to ≥3 questions on the modified Medication-Risk Questionnaire (mMRQ) [17] (Supplementary Table 1)
4. Willing and able to provide informed consent or have a carer willing to participate in the intervention and provide informed consent.

Exclusion criteria:

1. Residents of an aged care facility
2. Patients for whom clinic staff deemed involvement in the study was inappropriate (e.g. with acute/unstable mental health conditions)

Participant recruitment and consent:

All patients attending the memory clinic (September 2017 to February 2018) were screened for eligibility using medical records and/or telephone/in-person questionnaire. Eligible participants and carers were provided with a participant information sheet and invited to participate. Written informed consent was obtained from the patient or their nominated carer.

A letter was sent to the participants' GP to advise them of their patient's involvement in the study.

Intervention pharmacist recruitment and training:

Two experienced consultant pharmacists were recruited to deliver the intervention. Prior to commencing, the pharmacists participated in a half-day, study-specific training session run by the investigators, which covered the study protocol, identification of inappropriate medications and application of evidence-based deprescribing algorithms.

Intervention:

The interdisciplinary deprescribing intervention followed a five-step patient-centred deprescribing process [46].

Step 1: Obtain comprehensive medication history

Following their clinic appointment, all participants were visited at home by a consultant pharmacist, to obtain a comprehensive medication history (including all prescription and over-the-counter medications).

Step 2: Identify PIMs and other MRPs

The pharmacist conducted a patient-centred implicit medication review to assess the clinical appropriateness of the participant's medications, and participant's ability to manage their medications (e.g. medication adherence).

Step 3: Determine whether medication could be ceased and prioritize

The pharmacist used their clinical judgement and, guided by a deprescribing algorithm [18], formulated and prioritised their deprescribing recommendations. They also considered the responses from the patient's attitude towards deprescribing (PATD) questionnaire [19] and information obtained during the patient or carer interviews.

Step 4: Plan and initiate medication withdrawal

The pharmacist prepared a written medication management and deprescribing report, which included a complete medication list, identified MRPs, actions already completed (e.g. administration counselling) and recommendations for:

- Dose reduction/cessation and/or modification of inappropriate medication(s); and

- Monitoring, management and follow up, including monitoring for potential ADEs and adverse drug withdrawal events.

This report was first sent to the participant's memory clinic doctor for review. If necessary, the report was modified to incorporate their opinions, then it was sent to the participant's GP, and to their community pharmacy if appropriate.

Step 5: Monitoring, support and documentation

The pharmacist telephoned the participant's GP to ensure receipt of the report, discuss recommendations and offer ongoing assistance as appropriate.

Data collection:

At baseline, a structured questionnaire was administered by an investigator (AC), either face-to-face during the participant's memory clinic visit or via telephone after their appointment.

Three and six-month follow-ups were also conducted in person (by AC) (in the participant's home or at the memory clinic) or via telephone, and involved collecting an updated medication history and determining if pharmacist recommendations had been implemented. A structured questionnaire was administered at six-months.

Outcomes

The primary outcome was the feasibility of a pharmacist-led interdisciplinary deprescribing intervention study in a memory clinic, as measured using the following;

a) Proportion of memory clinic patients eligible for the study
b) Proportion of eligible patients who consented to participate
c) Proportion of inappropriate and/or unnecessary medications, as identified by the pharmacist, which were ceased or dose reduced at six months.

Secondary outcomes were:

1. PATD [19]

2. Efficacy of the intervention
   a. Enhancing the accuracy of medication histories: Proportion of participants with discrepancies between actual medications used (identified during home visit) and medications documented in memory clinic records

    b.   Uptake of pharmacist recommendations: Proportion of pharmacist recommendations to address MRPs (all types) that were implemented/actioned at six months.

3.   Change in medication regimens at six months compared to baseline, including:
    a.   Total number of medications used
    b.   Medication Regimen Complexity Index (MRCI) [20] calculated based on pharmacist medication list and any recommended administration directions as per Australian Medicines Handbook [21]
    c.   Use of PIMcogs [10]
    d.   Drug Burden Index (DBI) score [22] – calculated for regular medications only.

4.   Change in health outcomes and health behaviours at six months compared to baseline, including:
    a.   Medication adherence (Tool for Adherence Behaviour Screening (TABS) [23])
    b.   Healthcare utilisation (number of visits to GP/specialists and number of unplanned hospitalisations)
    c.   ADEs (self-reported)
    d.   Quality of life (EQ-5D) [24]
    e.   Mini-Mental State Examination (MMSE) [25].

Statistical methods and analyses:

Data were analysed using Statistical Package for Social Sciences (SPSS) for Windows version 22.0 (IBM Corp. Armonk, USA). Data are presented as mean and standard deviation (SD), median and interquartile range (IQR), number and percentage. Pearson χ^2 test, Mann-Whitney U test and independent samples t-test were used to test group differences, as appropriate. Changes in outcomes at six months versus baseline were compared using McNemar's test for categorical variables and paired t-test or Wilcoxon signed rank test, as appropriate, for continuous variables. P-values less than 0.05 were considered statistically significant.

Sample size:

A pragmatic target sample size of 50 participants was set to allow for exploration of the primary outcome (feasibility) and inform sample size calculations for future effectiveness studies.

Ethics:

The study was approved by the Human Research Ethics Committees of the participating institutions.

Results

Primary outcome

Recruitment

Two hundred and thirty eight patients attended the memory clinic during the recruitment period, of whom 82 (34.5%) were screened as eligible. Of the eligible patients, 50 (61.0%) provided consent to participate and 46 received the intervention (Figure 1).

Participants had a median (IQR) age of 80.5 (71.5-85.0) years and 36% were female (Table 1). The median (IQR) number of previous visits to the memory clinic was 1 (0-3), and 22 (44%) were attending the clinic for the first time. The most prevalent cognitive impairment diagnoses were mild cognitive impairment (13, 26%), Alzheimer's disease (8, 16%) and mixed dementia (7, 14%); 13 (26%) did not have a confirmed diagnosis at the time of recruitment. There were no significant differences in age (p=0.38), sex (p=0.07), MMSE score (p=0.65, missing data for 4 patients) or MRP eligibility criteria (p=0.77) between participants and non-participants.

Deprescribing

Participants who received the intervention were taking a median (IQR) of 11 (8-13.25) medications. Pharmacists made deprescribing recommendations for 43 (93%) patients and 124 medications. Thirty (65%) patients had medications ceased or dose-reduced. Forty (32%) medications with a deprescribing recommendation were ceased, 8 (6%) had their dose reduced and 5 (4%) were changed to a safer alternative. Deprescribing was attempted, but was unsuccessful for a further five medications. Medications most commonly deprescribed were vitamins/complementary medications 21 (39.6%) and PIMcogs 11 (20.8%).

Those who had medications deprescribed (n=30) were similar to those who did not (n=16), in terms of their age, sex, and number of medications.

Secondary outcomes

Attitudes towards deprescribing

PATD questionnaire responses (Table 2) indicated that 27 (54%) participants felt they were taking a large number of medications and 44 (88%) were willing to stop one or more medications if their doctor agreed. Over two-thirds (68%) of participants felt comfortable if a pharmacist was involved in ceasing one or more of their regular medications if their doctor was kept informed of the progress.

Efficacy of the intervention

Accuracy of medication histories: Thirty-five (76.1%) participants had one or more discrepancy between actual medications used (as obtained by the pharmacist at the home visit) compared to the medication history documented in memory clinic records.

Uptake of pharmacist recommendations: Pharmacists made 261 recommendations, relating to deprescribing (n=121), adherence and medication management (n=52) and other aspects of care such as monitoring/investigative tests required (n=88). One hundred and thirty six (52.1%) recommendations were partially or completely implemented at six months.

Changes in medication regimen and health outcomes

There were no significant changes in the number of medications, MRCI score, number of people using PIMcogs, DBI score, TABS or health outcomes (doctor visits, hospitalisations, ADEs or quality of life) in the overall cohort following the intervention. Median (IQR) MMSE scores had declined at six months (24.0 (21.5-28.0), n=37) compared to baseline (26 (22.0-28.0), n=48, p=0.003).

Post-hoc analysis in participants who had potentially inappropriate or unnecessary medications ceased or dose-reduced (n=30) showed that at six months follow-up, participants were taking less medications (median [IQR] 9 [8-13] vs 11 [9-14], p=0.01), had a lower MRCI (median [IQR] 19.5 [14.75-23.75] vs 19.5 [15.88-28.88], p=0.01) and fewer people self-reported dizziness (n=12 vs n=6, p=0.03) compared to baseline.

Discussion

Recruitment of pharmacists for a pharmacist-led interdisciplinary deprescribing intervention study in a memory clinic setting is feasible. Over a third of people attending the memory

clinic were eligible to participate in the study, and more than 60% of those eligible consented to participate.

The intervention was able to facilitate deprescribing for study participants. Forty-three percent of medications that pharmacists recommended for deprescribing were reduced or ceased at six months. Although no significant changes were observed in total medications or medication burden in the whole cohort, there was a fall in median number of medications and regimen complexity in those who had medications deprescribed. PATD results suggest memory clinic patients are open to deprescribing if their doctor says it is possible, which is consistent with findings from a study using a recently published revised PATD for people with cognitive impairment [26].

Higher rates of successful deprescribing may require a more intensive and ongoing intervention with longer follow-up [27]. Participants were commonly seeing multiple health professionals and had a number of medications added/changed during follow-up that occurred independent of the intervention. Furthermore, a six-month follow-up may not be sufficient to implement all pharmacist recommendations, as there was evidence in our study that further deprescribing was planned for some participants but had not been implemented at six months.

Our intervention identified that three-quarters of participants had discrepancies between medications actually being taken compared to memory clinic records. Comprehensive clinical medication reviews, especially those that are pharmacist-led, have been shown to improve quality use of medications and health outcomes [28]. Review of medication is recommended as part of the diagnostic process for dementia [29] and an accurate mediation history may help to prevent misdiagnosis and medication harm (e.g. drug interactions).

The study was not powered to detect changes in health outcomes or quality of life, but this data was collected to help inform future studies and ensure it was feasible to collect this data in a memory clinic cohort. Overall, participants did not report changes in health outcomes or quality of life, which is consistent with recent systematic reviews of deprescribing interventions [30-32] that showed limited impact on clinical outcomes. On the other hand, if medications are reduced with no ill-effects for the patient, then this may be a benefit in itself [33]. Participants who had medications ceased or dose-reduced in our study did have a significant reduction in total number of medications, regimen complexity and self-reported

dizziness. This may suggest that positive outcomes are possible, but studies involving larger sample sizes, longer follow-up periods and randomized controlled design are warranted [33].

This study had some strengths and limitations. Strengths included that it is the first deprescribing study in a memory clinic setting, it involved an interdisciplinary team and it had 6-month follow-up. Limitations include no formal sample size calculation, single memory clinic and no control group. Lack of blinding may also have contributed to observation bias. GPs' reasons for/against implementation of recommendations were not ascertained, and there may have been sound clinical reasons for not adopting some of the pharmacists' recommendations. Exclusion of non-English speaking patients may limit the generalisability of our findings. Furthermore, as we were unable to assess whether the non-English speaking patients were at risk of a MRP, the number of people eligible to participate in this study was likely an underestimation of the total proportion of memory clinic patients at risk of a MRP.

In conclusion, a pharmacist-led interdisciplinary deprescribing study in a memory clinic setting is feasible. Over a third of memory clinic patients were eligible, sixty percent of eligible patients consented, and forty-three percent of medications recommended for deprescribing were ceased or reduced at six months. While there were no changes in medication burden or health outcomes overall, there was evidence of positive outcomes in the two-thirds of participants who had successful deprescribing. A larger, multi-centre randomised controlled trial with additional pharmacist follow-up is required to further evaluate clinical outcomes and cost-effectiveness.

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Graphics

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│   Patients seen by memory clinic during the study period (n=238)     │
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         │        │ Excluded (n=156)                                  │
         │        │   -   Not identified as at risk of MRP (n=80)     │
         ├────────│   -   Unable to communicate in English            │
         │        │       (n=51)                                      │
         │        │   -   Living in an aged care facility (n=11)      │
         │        │   -   Living >20km from clinic (n=7)              │
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│     Patients screened as eligible (n=82)    │
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         │        │ Not recruited (n=32)                            │
         ├────────│   -   Declined to participate (n= 24)           │
         │        │   -   Not suitable – as per clinic (n=4)        │
         │        │   -   Not invited – no time to invite (n=4)     │
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│        Participants recruited (n=50)        │
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         │        │ Did not receive the intervention (n=4)          │
         ├────────│   -   Declined when pharmacist called (n=       │
         │        │       3)                                        │
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│  Participants received intervention (n=46)  │
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         │        │ Uncontactable (n=3)                             │
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│   Completed six-month follow-up (n=43)      │
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Figure 1: Participant flow

Abbreviations: MRP: Medication-related problem

Table 1: Participant characteristics at baseline

Characteristic	n = 50
Age (years), median (IQR)	80.5 (71.5-85.0)
Gender (female), n (%)	18 (36)
Born in Australia, n (%)	33 (66)
Speaks primarily in English at home, n (%)	38 (76)
Completed high school or higher education, n (%)	10 (20)
Participant providing consent, n (%)	
- Patient	39 (78)
- Carer	11 (22)
Living arrangements, n (%)	
- With spouse/partner	32 (64)
- With family/friends	7 (14)
- Alone	11 (22)
First visit to memory clinic, n (%)	22 (44)
MMSE score (/30), median (IQR)	26 (22-28)^
CCI (inc. age), mean (SD)	4.94 (1.89)
Number of GP visits in past six months, median (IQR)	4.5 (3-6)
≥1 unplanned hospitalisation in past six months, n (%)	15 (30)
EQ-5D, reported problems in:	
- Mobility	23 (46%)
- Self-care	13 (26%)
- Usual activities	13 (26%)
- Pain/discomfort	16 (32%)
- Anxiety/depression	27 (54%)
EQ-5D VAS (0-100), median (IQR)	70 (60-85.75)
TABS	
- Adherence$, median (IQR)	20 (18-20)
- Non-adherence#, median (IQR)	5.5 (4-7.25)
Uses dose-administration aid, n (%)	36 (72)
Requires assistance from family/friends to use or take medication, n (%)	24 (48)
Pharmacist medication review in past 12 months (self-reported), n (%)	7 (14)

Total no. of medications at home visit, median (IQR)	11 (8-13.25)*
MRCI, median (IQR)	19.5 (15.375-25.625)*
Using ≥1 PIMcog, n (%)	25 (54.3)*
DBI, median (IQR)	0.63 (0.00-0.94)*
DBI >0, n (%)	31 (67.4)*

* n=46 as based on medication history obtained at pharmacist visit, ^ n=48, $ Adherence scores 4-20, higher scores better, # Non-adherence scores 4-20, lower scores better

Definitions: *CCI:* Charlson comorbidity index, *EQ-5D*: European quality of life - 5 dimensions, *GP:* general practitioner, *IQR:* inter-quartile range, *MMSE:* mini-mental state examination, MRCI: medication regimen complexity index, *PIMcog:* potentially inappropriate medication for a person with cognitive impairment, *SD:* standard deviation, *TABS:* tool for adherence behaviour screening, *VAS:* visual analogue scale

Table 2: Participant attitudes towards deprescribing (n=50) [19]

	Strongly agree (%)	Agree (%)	Unsure (%)	Disagree (%)	Strongly disagree (%)
1. I feel that I am taking a large number of medications	26	28	8	22	16
2. I am comfortable with the number of medications that I am taking	52	34	6	6	2
3. I believe that all my medications are necessary	54	22	18	4	2
4. If my doctor said it was possible I would be willing to stop one or more of my regular medications	76	12	8	2	2
5. I would like to reduce the number of medications that I am taking	46	16	20	14	4
6. I feel that I may be taking one or more medications that I no longer need	8	8	34	16	34
7. I would accept taking more medications for my health conditions	18	22	8	30	22
8. I have a good understanding of the reasons I was prescribed each of my medications	54	20	2	10	14
9. Having to pay for less medications would play a role in my willingness to stop one or more of my medications	6	2	6	22	64
10. I believe one or more of my medications is giving me side effects	20	14	20	12	34

Supplementary Data

Supplementary Table 1: Modified Medication-Risk Questionnaire (mMRQ) [17]

Does the patient	YES	NO
1. Currently take 5 or more medications (including prescription, non-prescription and dietary supplements)	☐	☐
2. Currently take 12 or more medication doses each day	☐	☐
3. Currently take any of the following medications: carbamazepine, lithium, phenytoin, quinidine, digoxin, phenobarbital, procainamide, theophylline, insulin, narcotics (opioids) or any oral anticoagulant	☐	☐
4. Have more than 1 physician prescribing medications on a regular basis	☐	☐
5. Currently take medications for 3 or more medical problems	☐	☐
6. Have prescriptions filled at more than 1 pharmacy	☐	☐
7. Have someone else bring their medications to their home for them	☐	☐
8. Find it difficult following medication regimen or sometimes chooses not to	☐	☐
9. Have a medication regimen (i.e. medications or instructions on how to take them) which has been changed 4 or more times in the past year	☐	☐
10. Not know the reasons for taking one or more medications	☐	☐

Stakeholder perspectives on pharmacist involvement in a memory clinic to review patients' medication management and assist with deprescribing

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ABSTRACT

Background: Memory clinics usually involve a team of health professionals who assess and review people with memory impairment. Memory clinic patients are typically older, and many have multiple comorbidities and potentially inappropriate polypharmacy. Pharmacists are not typically part of memory clinic teams.

Objective: To explore stakeholder perspectives on pharmacist involvement in a memory clinic to conduct medication reviews and assist with deprescribing potentially inappropriate/unnecessary medications.

Methods: Mixed-methods evaluation within the Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM) study. Patient/carer questionnaires were administered at 6-month follow-up. Fax-back surveys were sent to general practitioners (GPs) shortly after pharmacist medication reviews. A focus group was conducted with memory clinic staff and semi-structured interviews with pharmacists at conclusion of the study. Focus group/interviews were transcribed and thematically analysed.

Results: Most patients/carers found the pharmacist medication review helpful (86%, 37/43) and believed it was important to have pharmacists in the memory clinic (91%, 39/43). Twenty-one (47%) GPs responded to the survey; most found the pharmacist reports useful for identifying inappropriate medication and providing deprescribing recommendations (86% and 81%, respectively), and 90% thought a pharmacist review should be part of the memory clinic service. Feedback from memory clinic staff and pharmacists was largely positive; four themes emerged: memory clinic scope of practice; communication and collaboration; patient-centred care; and logistics and resources.

Conclusion: Patients, GPs and memory clinic staff were receptive to increased pharmacist involvement in the memory clinic. Stakeholder feedback will inform the development and delivery of pharmacist medication reviews and deprescribing in memory clinics.

Key words: Memory clinic, pharmacist, dementia, deprescribing, perspectives

INTRODUCTION

The prevalence of polypharmacy and medication regimen complexity in older people continue to increase and are associated with a range of health outcomes including falls, functional and cognitive impairment, adverse drug events, hospitalisation and mortality.[1, 2] Patients who have medications prescribed by multiple doctors, who attend multiple pharmacies and who have frequent medication changes are also at an increased risk of medication-related problems (MRPs).[3]

Multidisciplinary teams are a core aspect of geriatric medicine and are required to help manage the complex nature of care for many older people who may be experiencing multiple comorbid conditions and increasing physical and cognitive impairment. Pharmacists are increasingly being integrated into these multidisciplinary teams in various settings, including hospital wards, general practice, nursing homes and aged-care assessment teams. [4-10] Emerging research suggests that multi-disciplinary teams are effective for deprescribing (the systematic, evidence-based process of discontinuing potentially inappropriate or unnecessary medications).[11-13]

Dementia affects almost 50 million people worldwide,[14] and is the single greatest cause of disability in older Australians.[15] The burden of dementia is important in the context of medication as impaired cognition can have a significant impact on a person's ability to manage their medications safely, leading to increased unintentional non-adherence, medication errors, and medication-related hospitalisations.[16-19] People with dementia are also more sensitive to the cognitive side effects of some medications (e.g. sedatives and anticholinergics).[20, 21]

The prevalence of inappropriate and unnecessary medication use is high among people attending memory clinics,[22, 23] and has been associated with a higher risk of mortality.[24] Memory clinics are specialist, multi-disciplinary clinics that assist people experiencing changes in their cognition. In Australia, memory clinics are responsible for assessing people with suspected cognitive impairment, diagnosing a memory disorder and creating a management plan, if applicable.[25] Optimising medication use for people living with dementia can be challenging due to the changing goals of care as a result of progressive cognitive impairment.[26]

Pharmacists are not typically involved in memory clinics. There has been limited research regarding pharmacist involvement in memory clinics,[27] and no studies regarding

deprescribing in memory clinics. The aim of this study was to explore stakeholder acceptability of pharmacists in a memory clinic setting in the context of a pharmacist-led deprescribing feasibility study.[28]

METHODS

A mixed-methods exploration of the experiences and opinions of stakeholders from the Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM) feasibility study was conducted. The DePIMM study has been described separately.[28] Briefly, patients attending a tertiary care hospital outpatient memory clinic in Melbourne, Australia were screened for eligibility and risk of MRPs. Eligible participants and/or carers were provided a participant information sheet and invited to participate.

Following informed consent, participants received a comprehensive pharmacist medication review in their home. Reviews were conducted by one of two accredited pharmacists who were trained to deliver the intervention.[28] The pharmacist reviewed medication appropriateness, medication adherence and medication management, particularly in the context of the patient's cognitive impairment. The pharmacist then prepared a report which included a best possible medication history, any identified MRPs, actions the pharmacist had already completed (e.g. counselling on devices/storage) and recommendations for deprescribing, optimising medication adherence/management and suggested monitoring and/or follow up.

The pharmacist reports were first sent to the patient's memory clinic doctor for comment and review, and then to the patient's general practitioner (GP). The pharmacist telephoned the GP after sending the report to ensure receipt and to discuss recommendations, as appropriate. Patients were followed up at six months by an investigator (AC).

Recruitment and data collection

Experiences and opinions of stakeholders were explored using several methods:

Patients/Carers

A structured questionnaire was administered via telephone or in-person at the memory clinic or in the patient's home during six-month follow-up. Patients/carers were asked three questions, two on a 5-point Likert type scale (helpfulness and importance of pharmacist involvement), and one open item question (helpfulness of the medication review).

GPs

GPs were faxed a one-page, 5-item survey and participant information sheet with, or shortly after, receipt of their patient's pharmacist report. GPs were asked to fax the completed form to the investigators (with return of the survey indicating implied consent). The survey was re-sent once, two-four weeks later, if no response was received. GPs were asked three questions on a 5-point Likert type scale ranking the usefulness of the pharmacist's report, one question asking if the GP had discussed recommendations with the patient/carer, and one question asking if the GP felt pharmacist review should be a routine part of the memory clinic service.

Memory clinic staff

A focus group was conducted at the memory clinic at conclusion of the DePIMM study to get feedback on the intervention and explore opinions regarding the potential role for pharmacists and deprescribing in a memory clinic setting. All staff who had worked at the clinic during the study period were invited. A focus group was chosen in order to gain a multidisciplinary perspective by stimulation of group discussion, as well as being logistically convenient for participants. The focus group lasted approximately 40 minutes and was moderated by an investigator (AC), using a semi-structured topic guide. An observer/note-taker was also present (RE). One doctor, who was unable to attend the focus group, was interviewed one-on-one using the same topic guide. Written, informed consent was obtained from all participants.

Pharmacists

The intervention pharmacists were interviewed at the conclusion of the DePIMM study to get their feedback on the intervention and interactions with stakeholders. Written, informed consent was obtained. The interview lasted approximately 60 minutes and was led by one investigator (AC), using a semi-structured topic guide. An observer/note-taker was also present (VL).

Data analysis

Participant characteristics are presented descriptively. Data analysis was conducted using the Statistical Package for Social Sciences (SPSS, version 24.0: IBM Corp. Armonk, USA).

The interviews and focus groups were audio-recorded and transcribed verbatim. Transcripts were verified against audio recordings by two investigators (AC and VL). Data management was facilitated using NVivo Pro (version 12.0, QSR International Pty Ltd, Australia). Two

investigators (AC and VL) read the transcripts and independently analysed the data to identify emergent themes.[29] The initial coding and emerging themes were then discussed between AC and VL to reach a consensus. Results were presented to all investigators for discussion, where discrepancies were resolved and themes finalised. Following thematic analysis, theoretical frameworks were used to explain the findings. Illustrative quotes that represent a range of stakeholders and points of view were selected for reporting.

Ethics

The study was approved by the Human Research Ethics Committees of the participating institutions.

RESULTS

Patients/Carers

Forty-six patients received the pharmacist intervention. Three were lost to follow up and 43 patients/carers were interviewed at the six-month follow-up. At baseline, median (IQR) age of the 43 patients was 81 (72-85) years, 16 (37.2%) were female and median (IQR) mini-mental state examination score was 26/30 (21.75-28). Median (IQR) number of medications was 11 (8-14).

Majority of participants found the pharmacist medication review useful or very useful (83.8%, n=37) and thought it was important or very important to have pharmacist involvement in the memory clinic team (92.3%, n=39). Six and four participants, respectively, were unable to answer the questions due to cognitive impairment and/or not able to recall the intervention (Figure 1).

Patients/carers were asked the main reason why they found the home medication review helpful. The reported benefits included;

1. Greater understanding of, and confidence with, their medication regimen.

   "Helped to understand what I was taking" (Participant 4, 56 years, male)

   "*Better understanding of medication mix*" (Carer of participant 6, 88 years, female)

   "Always good to know more about medicines" (Participant 25, 77 years, female)

   "Very helpful…gives you confidence that you know what you are doing" (Carer of participant 35, 88 years, male)

2. Advice relating to medication use, storage and management, in particular, regimen simplification.

*"Changed vitamin into [dose administration aid] and changed vitamin timing… easier to manage medications" (*Participant 9, 80 years, male)

"Helped with [inhaler] spacer technique which improved my breathing" (Participant 12, 70 years, male)

"Removed old tablets" (Participant 23, 82 years, male)

"[Medication regimen] is very simple now" (Participant 32, 85 years, female)

3. Recommendations to the GP and collaboration with the GP to optimise medications.

*"Rang back and advised [of appropriate] dose after speaking to doctor" (*Participant 18, 85 years, male)

"[The pharmacist] suggested dose reduction. Good to refer to doctor to check if medicine still needed. [Patient] takes so many medicines we get confused" (Carer of participant 29, 79 years, male)

"Good [the pharmacist] was able to follow up with doctor" (Participant 39, 72 years, male)

"Reducing dose schedule was very good" (Participant 40, 88 years, male)

GPs

Surveys were sent to 44 GPs (regarding 46 patients) and 21 (48%) faxed back a completed survey. Majority of GPs found the pharmacist reports 'useful' or 'extremely useful' for identifying potentially unnecessary or inappropriate medications (86%, n=18), providing deprescribing recommendations (81%, n=17) and identifying other MRPs (76%, n=16) (Figure 2). Most GPs 15 (71%) stated that they had discussed the findings or recommendations from the report with the patient/carer.

Majority of GPs (19; 90%) believed that patients referred to a memory clinic should receive a medication review by a pharmacist as part of the service; 57% said in the home, 29% said in the clinic and 14% said either clinic or home.

Memory clinic staff and pharmacists

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Eleven staff, comprising three specialist physicians (2 specialising in geriatrics and 1 in nuclear medicine), one medical fellow, two medical registrars, two medical students, two registered nurses and one social worker participated in the focus group; one specialist physician (geriatrician) who could not attend the focus group was interviewed separately. The two intervention pharmacists participated in a semi-structured interview.

Four major themes emerged relating to the intervention and, more generally, to pharmacists and deprescribing in the memory clinic setting. Within each theme several sub-themes were identified (Table 1).

1. Scope of the memory clinic (Table 1, 1.1)

Memory clinics in Australia are primarily diagnostic clinics, thus questions were raised as to whether obtaining a comprehensive medication history and recommending deprescribing, especially of medications not related to cognition, was within the clinic's scope. Clinic doctors reported that they did not usually undertake a comprehensive medication review, and when reviewing patients' medications they focussed on medications with cognitive effects and were heavily reliant on GP referrals and/or patient-reported medication histories. Over-the-counter medications were usually not considered unless the patient initiated the conversation. Some doctors were comfortable making deprescribing recommendations to the GP, particularly relating to medications with known cognitive adverse effects. However, they had concerns regarding limited ability to follow up changes and needing to focus on the reason for presentation to the clinic (i.e. diagnosing memory disorder).

2. Patient-centred care (Table 1, 1.2)

Memory clinic staff agreed that a memory clinic pharmacist service would be beneficial for some patients (especially multimorbid patients with polypharmacy), but not as a routine service for all patients. The DePIMM study involved a screening process to identify patients at risk of MRPs, and the participating pharmacists believed this resulted in "quite well targeted patients". Pharmacists felt they were able to undertake an overall review of the patient's medical conditions and medication regimen and help engage all stakeholders in designing a patient-centred medication management plan. Pharmacists were able to educate patients and provide practical advice on regimen simplification to reduce medication-taking burden. Clinic doctors were uncertain whether the service resulted in any cognition-related outcomes, but felt that deprescribing and rationalising recommendations to the GP were useful.

3. Communication and collaboration (Table 1, 1.3)

Written pharmacist reports were well received by memory clinic staff, although they suggested a shorter format would be beneficial. Pharmacists cited that GP follow-up was the greatest challenge, particularly finding a mutually convenient time to discuss the patient's medication. Pharmacists enjoyed working in connection with the memory clinic and found the GPs were positive and interested in deprescribing for their patients.

4. Logistics and resources (Table 1, 1.4)

There were mixed views regarding the optimal timing for a pharmacist to visit patients in relation to their memory clinic appointment. Clinic staff and pharmacists suggested that two visits would be ideal, an initial visit before their clinic attendance to obtain a complete medication history and identify medications that may adversely affect cognition and other MRPs, and a subsequent visit to ensure implementation of changes and follow-up outcomes. A pharmacist home visit was preferred over a clinic consultation, although memory clinic staff would want the pharmacist to ask additional questions regarding the home environment if they were visiting the home. The single biggest barrier to extending pharmacist services to the memory clinic was cited to be lack of a funding model.

DISCUSSION

This study demonstrated that stakeholders, including patients/carers, GPs and clinic staff, accepted pharmacists as a member of the multi-disciplinary memory clinic team. Our results reflect international research and affirm pharmacists have skills to contribute to the complex care needs of older people living with cognitive impairment.[10, 27, 30, 31]

To our knowledge, this is the first study to explore stakeholder views on pharmacist involvement in a memory clinic team, but previous studies have explored pharmacist integration into other healthcare teams.[32, 33] Reported benefits for patients were similar to other studies, and included greater patient/carer understanding of their medication, more accurate medication histories, medication review, regimen simplification and deprescribing.[33-35]

Our study highlighted the need for clarity and consistency surrounding the scope of memory clinic practice. While patients/carers, GPs and pharmacists thought pharmacist medication review was an important aspect of the memory clinic service, memory clinic staff were unclear if medication review and deprescribing were a core role of a predominately

diagnostic clinic. The Australian clinical practice guidelines and principles of care for people with dementia recommend 'a review of medications in order to identify and minimise use of medications, including OTC products, that may adversely affect cognitive functioning and to simplify medication dosing' as part of the diagnosis process for dementia.[36] Research evidence is in support of pharmacist-led medication reviews[37] and memory clinic staff believed that pharmacist involvement was worthwhile in selected patients (i.e. for those patients at high risk of MRPs). Concerns raised by memory clinic staff were related to finite resources, thus future research should focus on evaluating the cost-effectiveness of pharmacist involvement, in addition to achieving clinical outcomes.

Another challenge identified in this study was the difficulty in establishing timely clinical communication between the memory clinic and GPs. This is consistent with existing literature surrounding communication challenges at transitions of care and during home medicines reviews.[38] Clinic-to-GP communication in this study relied on faxed or mailed written reports. Oral communication is most effective as it allows for bidirectional communication, but as was found in this study, it can be difficult to find a convenient time for all parties.[38] A planned patient-GP follow-up appointment, where the pharmacist/memory clinic could telephone in, may address communication challenges. Pharmacist follow-up at subsequent memory clinic visits may also assist with continuity of care. Financial incentives for health professional collaboration should be investigated.

This study had strengths and limitations. Its strengths included the mixed-methods evaluation, involvement of multiple stakeholders and very good participation/response rates from each of the stakeholder groups. A limitation was the involvement of only one memory clinic, which limits generalisability. Despite a good response rate from GPs, the fax-back survey method may have resulted in participation bias.

In conclusion, stakeholders are accepting of pharmacist involvement in memory clinics to assist with the management of people at high risk of MRPs. Pharmacists can assist with patient education, obtaining an accurate medication history, medication review, regimen simplification and deprescribing. Future research should address identified concerns relating to memory clinic scope of practice, memory clinic-GP communication and cost-effectiveness.

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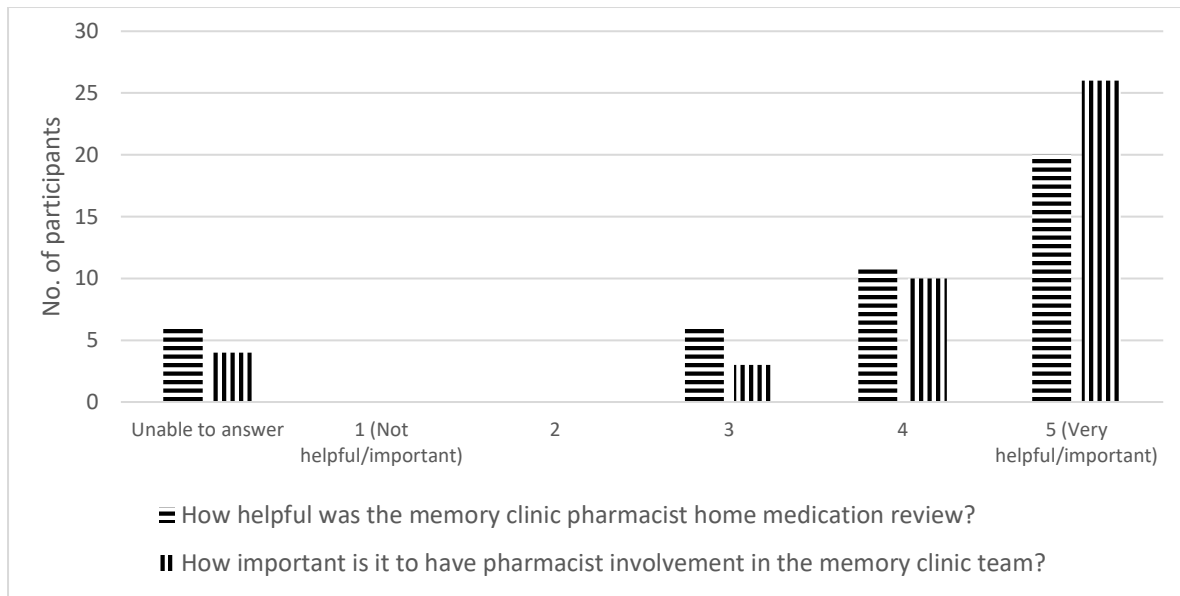**Figure 1: Patient/Carer feedback on helpfulness of pharmacist medication review and importance of pharmacist involvement in memory clinic (n=43)**
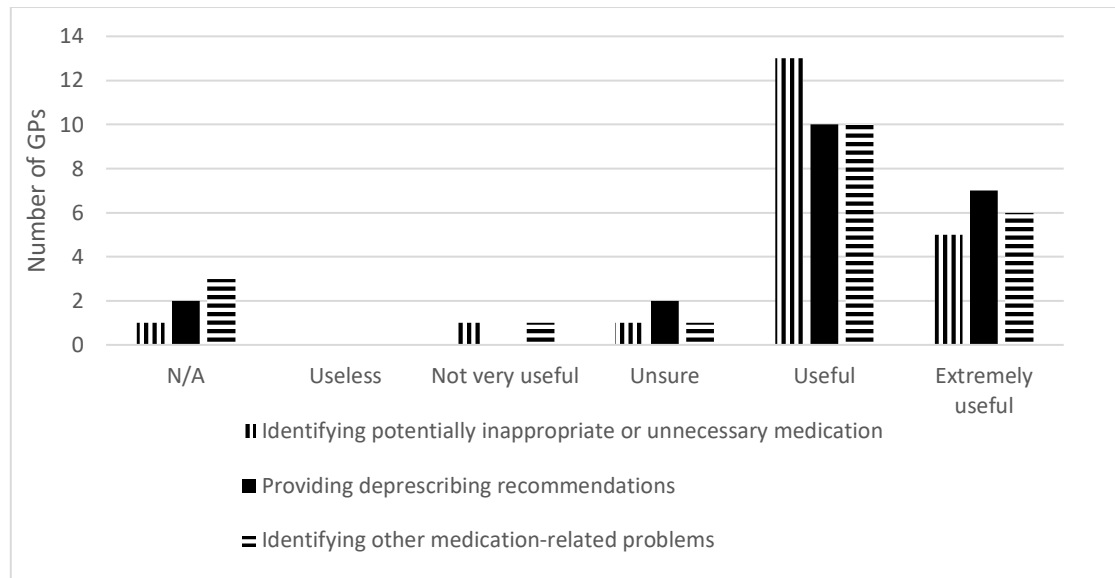
Figure 2: GP feedback on usefulness of pharmacist medication review/deprescribing report (n=20)

Table 1. Emergent themes from focus groups and interviews with memory clinic staff and intervention pharmacists regarding pharmacists and deprescribing in a memory clinic setting

Theme	Sub-themes and examples of quotes
1.1 Scope of memory clinic	*Obtaining and reviewing complete medication history*
	We are reliant on the GP referral usually to see how or what medications they [patients] are on. It doesn't always correlate [with] what they are actually taking. I think every clinic would have the same problem. (Specialist physician 2)
	Well I'm only interested in the medications that interfere with memory and I don't do a full medication listing and I don't aim to deprescribe or rationalise. (Specialist physician 3)
	I don't really delve into much over the counter [medications]…in memory clinic I don't see it as important (Specialist physician 2)
	… it's the patients that ask the doctors [about their OTC medications]. I'm on all these [OTC medications] are they going to make a difference? (Nurse 1)
	I don't [think the clinic] should be seeing patients without a full medication history (Pharmacist 1)
	Deprescribing in a memory clinic
	To be honest we don't pay much attention to drugs in the memory clinic, really. We record them, we might try and suggest we stop ones with strongly anticholinergic side effects. But we don't usually get as excited as we should when a

person is on 15 drugs. We know it isn't ideal but we don't do much about it. (Specialist physician 1)

I think our responsibility is to treat their reason for presenting to us, which is their memory problem. And certainly if we identify drugs that are contributing to that we've got to take care of that. But I don't see my role is to go through their entire medical history and list and rationalise their [medications]… I think that's outside of the scope of my work (Specialist physician 3)

Most of our clinicians are geriatricians first off. So I would expect that, you know, deprescribing is sort of '101' [fundamental]. It is when we've got a more focussed clinic [i.e. memory clinic] it's something that steps into the background. (Nurse 2)

We don't have any means to follow up either... for me to implement the changes in the clinic there is limited scope for that in that setting (Registrar 1)

1.2 Patient-centred care   *Patient selection & role for a pharmacist*

I'd like to be able [to] refer people reliably to a good pharmacist to do a medication review. But as you know, that's not as easy as it sounds. It's nicer if those pharmacists are embedded in your clinic. (Specialist physician 1)

I think that there's broadly 2 groups of people that come into the clinic. There's the ones that, the younger old, maybe 60 or 70, and they're coming with just a memory problem and they're otherwise quite well - probably not for them. But then we've got another subset who are frail, multimorbid, have

polypharmacy, they'd probably be better in a more general clinic and, I think in, in most geriatric clinics, where there are these sorts of multi morbid patients, I think, yeah, there is a role, …for ah, pharmacy (Specialist physician 4)

It has to be on a per case basis. Not a routine. It's a waste of resources (Specialist physician 3)

The patients were quite well targeted for us to go and see and I know that they really appreciated any advice they were given. (Pharmacist 1)

Every patient I saw was motivated or their carer was very motivated to change things for the better (Pharmacist 2)

Holistic care

Often the problem is that older people get, have, too many specialists and they don't have anyone taking, you know, an overarching view (Specialist physician 4)

GPs are very time poor …So they don't have an opportunity to really look at anything but the immediate problem…They are putting out fires, exactly. So that the medications just keep getting prescribed endlessly without reviews overall. (Pharmacist 1)

I think it's really engaging with all of the stakeholders to say let's go together in the same direction… we're all actually saying well this is our end game… this is how we can achieve it (Pharmacist 1)

Patient benefits

I think in terms of cognition I don't think it affected sort of you know, their cognitive outcomes. It's more deprescribing and rationalising medications. Which you'd hope GPs would do anyway. But they ah, they don't, not all of them anyway. So, I think it's a general deprescribing type outcome rather than a specific one for memory clinic… [Which] all aged care clinics could have. (Specialist physician 2)

[Patients] were very grateful for some information about possible improvement in their regimen that might improve their memory or their quality of life in general (Pharmacist 1)

[Regimen simplification] makes a huge difference to lifestyles and I think that that's probably looking at an angle that GPs wouldn't think about when they're ordering a medication daily or [twice daily], they don't actually think how is it being administered and community pharmacist don't either, they don't see the impact that that has on someone's lifestyle (Pharmacist 1)

1.3 Communication and Collaboration

Written communication – pharmacist reports

Very detailed reports about potential problems with medications, individual and in combination, and then suggested actions...I found them very useful and some very good deprescribing principles (Specialist physician 1)

They were good…it's good to have some extra impetus, and generally a lot of these people are on too many drugs to begin with. (Specialist physician 4)

One page [of the report] and the GPs are over it (Social worker 1)

Timely communication with GPs

… when the GP and the pharmacist are in partnership, the GP will almost always listen to the pharmacist. There is a lot of research that shows that. But where the GP has not requested a medication review and the high ivory tower of the hospital has just done it unsolicited, you are much less likely to get GP buy in. (Specialist physician 1)

What I found was the most frustrating thing was actually trying to get some feedback from the GPs…. they've got hundreds of patients so to ring them out of the blue and say, I want to talk to you about Mrs Smith, they'll go oh, god which patient, which patient is that. And conversely, when the receptionist says he'll ring you back, he's with a patient, 3 days later when they ring you back, and say, I'm ringing up to speak about Mr Brown, you think, oh my god, which one was that? That's really tricky. It is very hard to actually have a professional conversation at that moment in time. I want to actually read my report again, I want to think about the patient. (Pharmacist 1)

Interprofessional collaboration and cooperation

The GPs were pretty positive and really looking at ways to decrease the medication burden … but they just hadn't had time as everyone's got time pressure. (Pharmacist 2)

I also actually discussed it with the pharmacies that were packing the medications to say: I know this is going to be difficult but just prepare yourself there might be a weaning

schedule coming and all of them were on board. Fantastic.
That's great, we can handle it. (Pharmacist 1)

… it was fantastic being able to send the reports onto the
consultants at the clinics [for review before sending to the
GP]… I felt that the final report that went out to the GP had
more authority (Pharmacist 1)

1.4 Logistics & resources	*Timing of pharmacist review*

It [an accurate medication history] would be a good bit of
information to have prior to them coming into clinic because,
yeah, that one extra bit of information that we'd have that will
help us (Specialist physician 4)

It's not just about deprescribing, but a plan, is best when
you've got to know the patient fairly well. So in fact we'd
kinda like two levels of input. We'd like an accurate
medication list and what you'd do about it. And the first one
has to come early. (Specialist physician 1)

With the timing, sometimes say when we are doing our triage
calls. The family might have already identified that they're not
sure whether they're taking their medications or they know
what they're taking. So we'd know much earlier in the piece,
then it might be four months later that they come in here. So
then it would be something that you put in place then. Whereas
sometimes it's not until they come to that first appointment that
[the] son or daughter is aware of that. So that's going to vary.
(Nurse 1)

It would arm them [the clinic] with more information from the
very start but, it would be actually a good idea to re-visit them

[the patient] later after a diagnosis has been confirmed… and then you could actually implement some changes (Pharmacist 1)

Location of pharmacist review

I think people are very comfortable in their homes, and it is also a good way to see the other things that people are taking (Pharmacist 2)

If you were going to the home we'd probably load you up with more questions…what's the fridge look like, you know, gas stove, clutter all those types of things (Nurse 2)

A home assessment of medication is the best way to work out what a patient is actually taking. But you can get a reasonable idea if they do the paper bag trick…(Specialist physician 1)

Financial resources

I think in the real world it's unlikely that every memory clinic would be able to afford a pharmacist. (Specialist physician 1)

That's [pharmacists in memory clinics] a question of resources and cost effectiveness. (Specialist physician 3)

4.5 <u>Chapter summary</u>

This chapter has shown that it is feasible to recruit older adults with potential cognitive impairment (and their carers) for a deprescribing study and deliver a pharmacist-led interdisciplinary deprescribing intervention in a memory clinic setting. Over a third of memory clinic patients were eligible to participate in the study, and nearly 50% of those able to be assessed were at risk of a MRP, thus confirming chapter three's findings of high rates of potential MRPs in this setting. Sixty percent of eligible patients consented to participate, which, when combined with results of the PATD questionnaire, suggests that memory clinic patients are open to deprescribing. Results also showed that pharmacist recommendations were implemented, with 43% of medications that the pharmacist recommended for deprescribing being ceased or dose reduced at six months.

Stakeholders were accepting of pharmacist involvement in a memory clinic to assist with medication management and deprescribing. The majority of patients thought it was important to have a pharmacist involved in the memory clinic and GPs thought a pharmacist review should be part of the memory clinic service. Feedback from memory clinic staff was largely positive, although concerns relating to memory clinic scope of practice and finite resources were identified. Pharmacists expressed a desire for more structured and longer follow-up with both the patient and the GP to assist with implementation of deprescribing and medication management recommendations such as adherence and regimen simplification.

The DePIMM study was not powered to detect changes in secondary outcomes (health outcomes and quality of life), but data were collected to establish feasibility of data collection in a memory clinic and help inform the design of future studies. Post-hoc analyses of the two-thirds of participants who had medications deprescribed found there was a significant reduction in total number of medications, regimen complexity and self-reported dizziness at six months compared to baseline.

These results highlight the feasibility and acceptability of a pharmacist-led deprescribing intervention study in a memory clinic setting. Larger, controlled studies with longer follow-up, informed by the findings of this study, are needed to evaluate clinical outcomes and cost-effectiveness of the intervention.

5. CHAPTER FIVE: Discussion and conclusion

5.1 <u>Preface</u>

The purpose of this chapter is to summarise key findings of the research described in chapters two to four, discuss how it has collectively contributed to existing knowledge, and discuss the practice implications and future research directions.

5.2 <u>Summary of key findings</u>

The overall aim of this thesis was to review, explore and evaluate patterns of medication use and interventions for improving medication use and medication management in older people, particularly those living with cognitive impairment. To achieve this aim, three projects were undertaken as described in Chapters two, three and four.

In Chapter Two (Project One), a systematic review of the literature found that there was a lack of existing studies evaluating interventions for improving medication-taking ability and large variations in the study design, quality and effect of interventions for improving medication adherence in older people prescribed multiple medications. This made it difficult to draw any firm conclusions about the most effective interventions (including setting and provider) for improving medication-taking ability or medication adherence in older people prescribed multiple medications. Low quality evidence suggested that mixed educational and behavioural interventions, particularly those provided by pharmacists and those conducted at the interface between hospital and community (e.g. at discharge, post-discharge or in outpatient clinics), may improve medication adherence. Less than half of the identified studies included participants with cognitive impairment, and only two specifically focussed on people living with dementia.

In Chapter Three (Project Two) analysis of data from a large multi-centre cohort study of people attending memory clinics found that a high proportion were taking potentially inappropriate or unnecessary medication. One in five patients used a medication considered potentially inappropriate for a person with cognitive impairment (PIMcog), one in ten patients had a clinically significant anticholinergic burden and more than 50% of patients used one or more dietary supplements. Anticholinergic medications at baseline, and both PIMcog use and ACB scores over the three year study period, were independently associated with higher risk of mortality.

In Chapter Four (Project Three) it was found that recruitment of patients and delivery of a pharmacist-led interdisciplinary medication review and deprescribing intervention in a memory clinic setting were feasible. The design of this intervention was informed by the findings of chapters two and three. Pharmacists made 261 recommendations relating to deprescribing, adherence and medication management, along with other aspects of care such as monitoring/investigative tests required. Fifty-two percent of recommendations were partially or completely implemented at six months. Post-hoc sub-group analysis in participants who had medications successfully deprescribed identified a significant reduction in total number of medications, regimen complexity and self-reported dizziness. Stakeholder feedback on pharmacist involvement in the memory clinic team was positive, with 91% of patients believing it was important to have a pharmacist involved in the memory clinic and 90% of GPs stating that a pharmacist review should be part of the memory clinic service. Learnings from this study, including feedback from memory clinic staff and the intervention pharmacists can be used to guide the design of future deprescribing studies in this setting.

Together, the three projects have highlighted that medication-related problems are highly prevalent among people attending memory clinics, and that pharmacist-led interdisciplinary deprescribing and mixed educational and behavioural interventions targeting medication adherence may help to improve prescribing and medication management in older people.

5.3 <u>Strengths and limitations</u>

Specific strengths and limitations of individual studies have been discussed previously in Chapters Two to Four. Overall strengths and limitations of the research presented in this thesis are discussed below.

5.3.1 Strengths

Strengths of the research presented in this thesis include the use of a variety of research methods, study populations and statistical methods to review, explore and evaluate medication use in older people, particularly those living with cognitive impairment.

The Cochrane systematic review (Chapter Two) provided a rigorous, comprehensive review of randomised controlled studies. It is the first review to evaluate interventions for improving medication-taking ability, and the most extensive review to date of interventions to improve medication adherence in older adults prescribed multiple medications.

The exploration of medication use in people attending memory clinics across four of the eight states/territories of Australia (Chapter Three) involved a large cohort (n=964), with a broad range of cognitive diagnoses. There had been limited prior research regarding inappropriate medication use in this setting [216, 217], and no research exploring medication use across multiple clinics. The longitudinal study design was a further asset, allowing the first exploration of the association between inappropriate medication use and mortality in people attending memory clinics.

The DePIMM study (Chapter Four) was the first deprescribing study in a memory clinic setting, and it used mixed-methods to evaluate feasibility and acceptability from the perspectives of multiple stakeholders including patients/carers, GPs and multi-disciplinary memory clinic staff.

5.3.2   Limitations

There were some limitations to the research included in this thesis.

Firstly, the heterogeneous nature of RCTs included in the systematic review (Chapter Two) decreased the quality of the evidence and meant we were unable to draw firm conclusions regarding the most effective interventions for improving medication-taking ability and medication adherence. Our primary outcomes, medication-taking ability and medication adherence, were measured using numerous different methods, including subjective and objective measures, and many that had not been appropriately applied or validated. Outcomes were measured at various time-points, spanning from one month to two years for adherence, and were often not reported clearly or consistently across studies. Furthermore, while we broadly grouped interventions as educational, behavioural or mixed, there were still huge variations within these groups in terms of intervention components, provider, setting and duration. These inconsistencies were a major factor which impacted the strength of the overall systematic review recommendations. The limited number of studies focusing on people with cognitive impairment also meant we were unable to evaluate interventions targeting that population. The exclusion of non-RCTs is a further limitation of the systematic review. Conducting large RCTs involving complex interventions in older people with multiple morbidities is resource-intensive and challenging. Inclusion of studies with alternative methodologies, such as controlled before-and-after studies and interrupted time series studies, may have strengthened our findings. Moreover, updating the literature search to include research published post-2017 may also affect our findings, and will be undertaken

during manuscript review (post thesis submission) as per recommendations from the Cochrane Consumers and Communication Group.

The PRIME study, which formed the basis of Chapter Three, was not conducted for the purpose of analysing medication use patterns. The lack of specific information on medication doses prevented us from applying dose-specific measures of PIM burden such as the Drug Burden Index, and limited information regarding patients' co-morbidities may have resulted in residual confounding that was not accounted for within the Medication-based Disease Burden Index. Exclusion of people living in residential care or receiving 40 or more hours per week of nursing care, may limit the extent to which the findings can be applied to the wider population of people with cognitive impairment, especially those with greater frailty. The lack of data from memory clinic attendees in other countries may limit comparisons and application of our results internationally.

In Chapter Four, the single-centre, uncontrolled study design, exclusion of non-English speaking participants and small sample size may limit the generalisability and external validity of the results regarding inappropriate medication use and the feasibility of pharmacist-led deprescribing in a memory clinic setting. Nevertheless, the proportion of patients who were at risk of MRPs is likely to be an underestimate rather than overestimate. Lack of blinding may have contributed to observation bias, and the study was not powered to detect clinically significant changes in secondary outcomes. Whilst Chapter Two highlighted a need for robust, objective measures of medication-taking ability and medication adherence, as these outcomes were not the primary focus of the DePIMM feasibility study, medication-taking ability was not formally assessed and a self-reported measure of medication-adherence was used. GPs' reasons for/against implementation of pharmacist recommendations were not ascertained, and there may have been sound clinical reasons for not adopting some of the pharmacists' recommendations.

5.4 <u>Significance and practice implications</u>

The research presented in this thesis has focussed on a group of patients who are at high risk of MRPs because they take multiple regular medications and have increasing levels of impairment, due to age and/or a cognitive disorder. It has also focussed on a setting (memory clinics) where many of these high-risk patients attend, but where prior research regarding

medication use has been limited. The research presented in this thesis has added to the understanding of three key medication related issues, namely: medication-taking ability, medication adherence and medication appropriateness. It has also contributed to the understanding of roles for pharmacists in addressing these issues.

5.4.1 Medication-taking ability

The Cochrane review (Chapter Two) was the first of its kind focusing on interventions for improving medication-taking ability in older adults. Only five randomised controlled studies were identified in this review and no two studies used the same outcome measure. Managing one's own medications is a skill that is necessary for independent living [71]. Reduced ability to self-administer medications often necessitates the need for carer support [91] and is also associated with increased risk of ADEs [75], hospitalisation [218], and transfer into residential aged care [219]. Thus, finding effective interventions to improve medication-taking ability needs to be a priority.

A necessary first step would be to identify a 'gold-standard' measure of medication-taking ability. A 2009 systematic review of standardised assessments of a patient's capacity to manage medications identified thirty-two instruments, but concluded that "no published instrument currently has sufficient evidence of reliability and validity" [220]. Forerunners for preferred instruments included DRUGS (Drug Regimen Unassisted Grading Scale), MedMAIDE (Medication Management Instrument for Deficiencies in the Elderly) and MMAA (Medication Management Ability Assessment) [220, 221], however an updated review of the evidence is required. Only one study in the Cochrane review utilised any of these instruments [222].

When designing an intervention for improving medication-taking ability in community-dwelling older people with cognitive impairment, ideally both the patient and their carer should be targeted. This is because many older adults receive assistance from informal or non-professional carers for activities of daily living, including medication administration. The level of assistance also generally increases as patients get older or their level of cognitive or functional impairment progresses. Two of the five studies identified in the systematic review targeted both the patient and the carer, and these were the only two interventions to report a positive impact on medication-taking ability [222, 223]. In practice, this means that health professionals need to be mindful of potential involvement of carers in medication

administration and consider consulting carers when decisions are made (e.g. changes in medications). In the DePIMM study, the pharmacist conducted the home interview in the presence of both the patient and their carer, whenever possible. The pharmacist was able to explore problems with medication management with the patient and their carer, and make recommendations to simplify the medication regimen to help improve the patient's medication-taking ability (e.g. change in dose form, change in dose timing or number of doses per day, or recommending a dose administration aid [DAA]).

5.4.2 Medication adherence

Medication adherence is recognised as a major issue worldwide with the WHO suggesting that adherence rates in developed countries average about 50% [86]. Older people taking multiple medications represent a large and growing proportion of patients seen by health professionals, and given that adherence can be influenced by therapy-related factors including number of medications [86, 92], it is important to identify interventions that are effective in this population.

The systematic review (Chapter Two) identified 48 RCTs of interventions to improve medication adherence in older people prescribed multiple medications, but low quality of the studies prevented drawing any firm conclusions. This is consistent with two prior reviews of medication adherence in people taking multiple medications published over a decade ago [94, 224]. Two other reviews have been published since commencement of this thesis, one focussing on theory-based interventions [225] and one that included both cross-sectional analyses of prevalence of medication adherence and clinical trials/systematic reviews of interventions targeting adherence [226]. Neither was as comprehensive as the systematic review included in this thesis, and both concluded that high quality evidence was scarce.

Despite this, the systematic review did identify some promising results that could be used to guide future research or to assist consumers, health professionals and policy makers. Low quality evidence supported the use of mixed interventions, involving both educational and behavioural elements, for improving medication adherence, rather than educational or behavioural interventions delivered in isolation. This finding is consistent with an earlier review [94], and reflects the complex multi-factorial nature of non-adherence. In practice, this suggests that health professionals should not rely on patient education and/or medication review in isolation to improve medication adherence. Patients and their carers require

behavioural interventions targeted towards the specific patient factors contributing to their non-adherence [93]. For example, regimen simplification and DAAs may address therapy-related factors such as medication regimen complexity, where-as motivational interviewing and follow-up/monitoring may target patient-related factors such as lack of motivation or poor medication knowledge. In the DePIMM study the pharmacists incorporated both educational and behavioural components into their intervention. Pharmacists made both deprescribing and regimen simplification recommendations to reduce the total burden of medications, recommended dose-administration aids to improve medication adherence, and provided education to patients about their medications. However, no change in self-reported adherence was noted, potentially due to the high baseline self-reported adherence levels in the study population. Moreover, the DePIMM study was not powered to detect change in secondary outcomes such as adherence.

A further finding from the systematic review was the limited number of studies that have focussed on people living with cognitive impairment. Dementia is a national health priority [126] and medication non-adherence in dementia is associated with an increased risk of hospitalisation and death [227]. A recent review of medication adherence in older adults with dementia reported that telehealth home-monitoring and treatment modification improved adherence, however these findings were based on uncontrolled, observational studies [227]. Similar to other reviews [76, 227], our systematic review was unable to make any firm evidence-based recommendations regarding interventions to improve medication-taking ability and medication adherence in this population, and further research is urgently needed.

5.4.3   *Medication appropriateness*
Chapters Three and Four explored medication appropriateness, in particular, the use of potentially inappropriate and/or unnecessary medications in people attending memory clinics.

Cross-sectional analyses of medication use in patients attending nine Australian memory clinics (Chapter Three) found that almost one in four patients used a PIMcog or had a clinically significantly anticholinergic burden. This finding is consistent with one prior study conducted in a single memory clinic [216] and a 2015 systematic review of 22 studies investigating PIM use in people with cognitive impairment or dementia that showed prevalence ranged from 10% to 56% [228]. Higher rates of PIM use were observed in some

studies in the systematic review because they used more general measures of inappropriate medication use in older adults (i.e. did not focus on medications that may adversely affect cognitive function) [228]. The systematic review also found higher prevalence of PIM use in residential aged care populations [228].

PIMcog use and higher anticholinergic burden were associated with a higher risk of mortality over the three year follow-up period. This was the first study to explore the relationship between PIM use and mortality in people attending memory clinics. Prior research in the general population of older people with dementia has shown inconsistent associations between PIM use and mortality depending on the criteria used to define a PIM. One study found a dose-response relationship between anticholinergic and sedative drug burden and mortality in people with Alzheimer's disease [229]. Other studies, using the Swedish National Board of Health and Welfare indicators [230] and the 1997 Beers criteria [231] to define PIM use, found no significant association with mortality in people with dementia. Our results relating to anticholinergic burden are consistent with past research using the ACB scale in the general older population [58], while other measures of anticholinergic burden have shown inconsistent associations with mortality [232-235]. In the DePIMM study, the use of a PIMcog by a patient attending the memory clinic was successfully used to identify a patient who may benefit from a pharmacist review. In practice, these findings suggest that the use of a PIMcog, or a medication regimen with high anticholinergic burden, should trigger regular review of a person's medication regimen by health professionals.

Cross-sectional analysis of medication use in patients attending memory clinics also found that 57% of patients used dietary supplements, and 37% used two or more. Dietary supplements contribute to polypharmacy and medication regimen complexity, and may increase the risk of drug interactions, ADEs and healthcare costs [40, 42]. Given the lack of evidence to support the use of many dietary supplements, they are often considered by health professionals as unnecessary. Unfortunately, patients often do not disclose their use of supplements to a physician [39, 40], and consequently health professionals may underestimate their use [41]. In the DePIMM study, pharmacist-led comprehensive medication review was able to identify dietary supplement use, and recommend deprescribing if supplements were unnecessary or inappropriate. Forty percent of the successfully deprescribed medications in the DePIMM study were vitamins/complementary medications.

5.4.4   Role for pharmacists

The high prevalence of potentially inappropriate and unnecessary medication use highlights the need for improved prescribing and medication review in people living with cognitive impairment, including people attending memory clinics. There has been limited prior research regarding pharmacist roles in memory clinics, but two studies have highlighted the potential role for pharmacists in reducing MRPs [156, 217].

The DePIMM study (Chapter Four) was the first intervention study involving pharmacists and deprescribing in a memory clinic setting. It showed that pharmacist medication review was able to identify potentially inappropriate and unnecessary medications in people attending a memory clinic, and that pharmacist-led deprescribing is feasible, acceptable and may result in positive patient outcomes including reduced number of medications, regimen complexity and self-reported dizziness. Despite the limitations (e.g. uncontrolled design, single centre and small sample size) of this feasibility study, our results may be useful for memory clinics and other outpatient clinics as they highlight the need for an accurate medication history and comprehensive medication review for their clients, and the potential benefits of adding a pharmacist into the interdisciplinary clinic team.

The DePIMM study, particularly the stakeholder feedback, can also be used to inform future interventions, clinical trials and practice change. Intervention pharmacists highlighted the need for at least one additional follow-up with patients to assist with implementation of recommendations and to review medication regimens after changes in medication or goals of care occur. The results of our pragmatic study also suggested that six-months may not be sufficient to implement all pharmacist recommendations as there was evidence that some further deprescribing was planned but had not yet been implemented. This is consistent with a 2017 narrative review of the evidence surrounding deprescribing that stated that follow-up periods in many studies are too short [119].

An interesting finding of the DePIMM study was that some memory clinic staff questioned whether medication reviews and deprescribing were within the scope of memory clinic practice and thus whether pharmacists were required to assist with that activity. Quality use of medicines should be the responsibility of all health professionals involved in a patient's care, and specialist clinicians not recognising medication review as a part of their role could have major implications. While pharmacists may be able to assist, justifying their role in a

memory clinic is difficult if medication optimisation is not viewed as core business by memory clinic clinicians, hospitals or government bodies. This issue of memory clinic scope of practice should ideally be addressed nationally to ensure consistent practice across all memory clinics, but could also be decided by each individual memory clinic. Further evidence supporting the clinical impact and cost effectiveness of pharmacists in memory clinics is also required.

The systematic review also supported the role for pharmacists in improving medication adherence, with findings suggesting that pharmacist-led interventions and interventions set at the hospital-community interface (including outpatient clinics) may have the greatest impact on adherence. This is consistent with a growing body of evidence that shows potential benefits of pharmacist-led medication reviews on a variety of health outcomes [236].

5.5 **Future research directions**

The research presented in this thesis has generated new knowledge but has also highlighted a range of issues and gaps in the evidence around quality use of medicines in older people, especially those with cognitive impairment and those attending memory clinics. High quality randomised controlled studies are needed to:

1. Identify and evaluate effective interventions for improving medication-taking ability in older people prescribed multiple medications. The efficacy and cost effectiveness of mixed educational and behavioural interventions with both the patient and carer should be explored further. Further research is also needed to establish standardised measures of medication-taking ability.

2. Identify and evaluate effective interventions for improving medication adherence in older people prescribed multiple medications. Mixed interventions delivered by pharmacists, especially at the hospital-community interface (e.g. at discharge, post-discharge or in outpatient clinics) should be explored further. Strategies to improve adherence in primary care settings also need further development and evaluation.

3. Further evaluate the clinical outcomes and cost-effectiveness of pharmacist-led medication review for people attending memory clinics. Pharmacist-led deprescribing in a memory clinic setting is feasible, but efficacy and effectiveness need to be confirmed in a large, multi-centre cluster randomised controlled trial with longer follow-up. The design of such a study/intervention can be informed by findings from

the feasibility study, and should include additional pharmacist follow-ups and more structured communication between the pharmacist and GP.

5.6 <u>Conclusions</u>

Ageing populations and the increasing proportion of people living with cognitive impairment, together with increasing polypharmacy, represent a growing challenge for health care systems across the globe. Impaired ability to self-manage medications, suboptimal adherence and inappropriate or unnecessary medication use are some of the MRPs which can contribute to ADEs, including hospitalisation, morbidity and mortality. The research in this thesis makes significant contributions to knowledge in this field by highlighting three main findings: 1) there is a lack of high quality research on interventions to improve medication-taking ability and medication adherence in older adults prescribed multiple medications, especially those with cognitive impairment; 2) inappropriate and unnecessary medication use is prevalent among people attending memory clinics and is associated with increased risk of mortality; and 3) pharmacist-led medication review and deprescribing is feasible in a memory clinic setting and is acceptable to stakeholders, and may offer a potential solution to the challenges of MRPs in this population. This thesis provides clear direction and strong justification for further research to help optimise medication use and medication management in older adults living with cognitive impairment.

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APPENDICES

Appendix 1: Chapter 2 – Search Strategies

- Medline
- CENTRAL
- CINAHL
- EMBASE
- IPA
- PsycINFO

MEDLINE (Ovid SP) search strategy

1. exp aged/
2. ((old or older or aged or senior) adj2 (person? or people or adult? or men or women or patient* or consumer* or carer* or caregiver* or care giver*)).ti,ab,kw.
3. (late life or ag?ing or old age or seniors).ti,ab,kw.
4. (elder* or geriatr* or gerontol* or geropsych* or veteran*).mp.
5. or/1-4
6. exp Pharmaceutical Preparations/
7. (medication* or medicine? or medicament* or pharmac* or drug? or polypharmac*).ti,ab,kw.
8. exp drug therapy/
9. exp pharmaceutical services/
10. exp therapeutic uses/
11. or/6-10
12. 5 and 11
13. primary health care/
14. (primary adj2 (care or healthcare)).ti,ab,kw.
15. ambulatory care/
16. ambulatory.ti,ab,kw.
17. exp general practice/
18. general practitioners/
19. gp?.ti,ab,kw.
20. physicians primary care/
21. physicians family/
22. ((general or family) adj practi*).ti,ab,kw.
23. exp ambulatory care facilities/
24. home care services/
25. exp community health services/
26. patient discharge/
27. (hospital adj3 discharge).ti,ab,kw.
28. continuity of patient care/
29. aftercare/
30. (community or home* or domicil* or outreach or out-reach or postdischarge or post-discharge or postacute or post-acute or discharge plan* or aftercare or after care).ti,ab,kw.
31. or/13-30
32. 12 and 31
33. patient education as topic/
34. ((educat* or instruct* or advis* or advice* or counsel* or teach* or train* or coach* or learn*) and (patient* or client* or consumer* or user* or carer* or caregiver* or care giver*)).mp.
35. exp counseling/

36. information services/

37. drug information services/

38. (inform* adj5 (patient* or client* or consumer* or user* or carer* or caregiver* or care giver*)).ti,ab,kw.

39. reminder systems/

40. drug packaging/

41. drug prescriptions/

42. medication therapy management/

43. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) and (manag* adj5 (medication* or medicines))).ti,ab,kw.

44. pharmac* care.ti,ab,kw.

45. or/33-44

46. medication adherence/ or patient compliance/

47. ((medication or treatment) adj (complian* or adheren* or noncomplian* or nonadheren*)).ti,ab,kw.

48. self efficacy/

49. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) and (competen* or confident or confidence or abilit* or capacit* or skill* or self-efficacy or cope? or coping or complian* or noncomplian* or adher* or nonadher* or underadheren* or concordan* or nonconcordan* or persisten* or nonpersist*)).ti,ab,kw.

50. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) adj5 (error* or mistak* or misus* or mismanag*)).ti,ab,kw.

51. (patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*).ti,ab,kw. and medication errors/

52. self-administration/

53. or/46-52

54. 32 and (45 or 53)

55. randomized controlled trial.pt.

56. controlled clinical trial.pt.

57. randomized.ab.

58. placebo.ab.

59. clinical trials as topic.sh.

60. randomly.ab.

61. trial.ti.

62. or/55-61

63. 54 and 62

Cochrane Central Register of Controlled Trials (CENTRAL) (Via Ovid)

1. aged:kw
2. ((old or older or aged or senior) near/2 (person* or people or adult* or men or women or patient* or consumer* or carer* or caregiver* or care-giver*)):ti,ab,kw
3. ("late life" or ag*ing or "old age" or seniors):ti,ab,kw
4. (elder* or geriatri* or gerontol* or geropsych* or veteran*):ti,ab,kw
5. {or 1-4}
6. [mh "pharmaceutical preparations"]
7. [mh "drug therapy"]
8. [mh "pharmaceutical services"]
9. [mh "therapeutic uses"]
10. (medication* or medicine* or medicament* or pharmac* or drug or drugs or polypharmac*):ti,ab,kw
11. {or 6-10}
12. 5 and 11
13. ((primary near/2 *care) or primary-nursing):ti,ab,kw
14. ambulatory:ti,ab,kw
15. (((general or family) next (practi* or physician* or doctor*)) or gp or gps or family-medicine):ti,ab,kw
16. [mh "ambulatory care facilities"]
17. outpatient-department:ti,ab,kw
18. [mh "community health services"]
19. ((patient* or hospital*) near/3 discharg*):ti,ab,kw
20. (continu* near/3 care):ti,ab,kw
21. (community or home* or domicil* or outreach or out-reach or postdischarge or post-discharge or postacute or post-acute or discharge-plan* or aftercare or after-care):ti,ab,kw
22. {or 13-21}
23. 12 and 22
24. ((educat* or instruct* or advis* or advice* or counsel* or teach* or train* or coach* or learn*) and (patient* or client* or consumer* or user* or carer* or caregiver* or care-giver*)):ti,ab,kw
25. counseling:kw
26. information-services:kw
27. ((medical or drug) next information):ti,ab,kw
28. (inform* near/5 (patient* or client* or consumer* or user* or carer* or caregiver* or care-giver*)):ti,ab,kw
29. reminder-system*:ti,ab,kw
30. (drug next (packaging or label*)):ti,ab,kw
31. medication-therapy-management:ti,ab,kw
32. ((patient* or client* or consumer* or user* or subject or subjects or carer* or caregiver* or care-giver*) and (manag* near/5 (medication* or medicine*))):ti,ab,kw
33. pharmac*-care:ti,ab,kw
34. {or 24-33}
35. ((medication or treatment) next (complian* or adheren* or noncomplian* or nonadheren*)):ti,ab,kw

36. (self next (efficacy or concept)):ti,ab,kw
37. ((patient* or client* or consumer* or user* or subject or subjects or carer* or caregiver* or care-giver*) and (competen* or confident or confidence* or abilit* or capacit* or skill* or self-efficacy or cope* or coping or complian* or noncomplian* or adher* or nonadher* or underadheren* or concordan* or nonconcordan* or persisten* or nonpersist*)):ti,ab,kw
38. ((patient* or client* or consumer* or user* or subject or subjects or carer* or caregiver* or care-giver*) near/5 (error* or mistak* or misus* or mismanag*)):ti,ab,kw
39. (patient* or client* or consumer* or user* or subject or subjects or carer* or caregiver* or care-giver*):ti,ab,kw and medication-error*:kw
40. self-administ*:ti,ab,kw
41. {or 35-40}
42. 23 and (34 or 41) in Trials

CINAHL (via EBSCOhost)

S1 MH aged+

S2 (old or older or aged or senior) N2 (person* or people or adult* or men or women or patient* or consumer* or carer* or caregiver* or "care giver*")

S3 "late life" or ag#ing or "old age" or seniors or elder* or geriatr* or gerontol* or geropsych* or veteran*

S4 MH health services for the aged

S5 s1 or s2 or s3 or s4

S6 MH "miscellaneous drugs and agents+"

S7 MH drug therapy+

S8 medication* or medicine* or medicament* or pharmac* or drug* or polypharmac*

S9 MH "Pharmacy and Pharmacology+"

S10 s6 or s7 or s8 or s9 or s10

S11 (primary N2 (care or healthcare or nursing)) or ambulatory or "nurse-managed center*"

S12 ((general or family) N1 (practi* or physician* or doctor*)) or "family medicine" or gp or gps

S13 community or home* or domicil* or outreach or "out-reach" or "post-discharge" or "post-acute" or "patient discharge" or "discharge plan*" or (hospital N3 discharg*) or aftercare or "after care"

S14 MH continuity of patient care

S15 s11 or s12 or s13 or s14

S16 s5 and s10 and s15

S17 MH patient education+

S18 (educat* or instruct* or advis* or advice* or counsel* or teach* or train* or coach* or learn*) and (patient* or client* or consumer* or user* or carer* or caregiver* or "care giver*")

S19 MH counseling

S20 MW information services

S21 inform* N5 (patient* or client* or consumer* or user* or carer* or caregiver* or "care giver*")

S22 reminder* or "drug packaging" or "drug label*" or "pharmac* care"

S23 (patient* or client* or consumer* or user* or subject* or carer* or caregiver* or "care giver*") and (manag* N5 (medication* or medicine*))

S24 s17 or s18 or s19 or s20 or s21 or s22 or s23

S25 (patient or medication or treatment) N5 (complian* or adheren* or noncomplian* or nonadheren*)

S26 "self efficacy"

S27 ((patient* or client* or consumer* or user* or subject* or carer* or caregiver* or "care giver*") and (competen* or confident or confidence or abilit* or capacit* or skill* or "self-efficacy" or cope* or coping or complian* or noncomplian* or adher* or nonadher* or underadheren* or concordan* or nonconcordan* or persist* or nonpersist*)

S28 (patient* or client* or consumer* or user* or subject* or carer* or caregiver* or "care giver*") and (error* or mistak* or misus* or mismanag* or (inappropriate* N2 prescri*)

S29 "self administ*"

S30 s25 or s26 or s27 or s28 or s29

S31 s16 and (s24 or s30)

S32 "randomi?ed controlled trial" or PT randomized controlled trial

S33 PT Clinical Trial

S34 MH Clinical Trials+

S35 MH Random Assignment

S36 MH Placebos

S37 MH Quantitative Studies

S38 AB (random* or trial or placebo*) or TI (random* or trial or placebo*)

S39 AB (singl* or doubl* or tripl* or trebl*) and AB (blind* or mask*)

S40 TI (singl* or doubl* or tripl* or trebl*) and TI (blind* or mask*)

S41 S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40

S42 s31 and s41

S43 s42

EMBASE (Via Ovid)

1. exp aged/
2. ((old or older or aged or senior) adj2 (person? or people or adult? or men or women or patient* or consumer* or carer* or caregiver* or care giver*)).ti,ab,kw.
3. (late life or ag?ing or old age or seniors).ti,ab,kw.
4. (elder* or geriatr* or gerontol* or geropsych* or veteran*).mp.
5. or/1-4
6. exp drug/
7. (medication* or medicine? or medicament* or pharmac* or drug? or polypharmac*).ti,ab,kw.
8. exp drug therapy/
9. pharmacy/
10. exp pharmaceutics/
11. or/6-10
12. 5 and 11
13. exp primary health care/
14. (primary adj2 (care or healthcare)).ti,ab,kw.
15. exp ambulatory care/
16. ambulatory.ti,ab,kw.
17. general practice/
18. general practitioner/
19. gp?.ti,ab,kw.
20. family medicine/
21. ((general or family) adj practi*).ti,ab,kw.
22. outpatient department/
23. exp home care/
24. exp community care/
25. hospital discharge/
26. (hospital adj3 discharge).ti,ab,kw.
27. aftercare/
28. (community or home* or domicil* or outreach or out-reach or postdischarge or post-discharge or postacute or post-acute or discharge plan* or aftercare or after care).ti,ab,kw.
29. or/13-28
30. 12 and 29
31. patient education/
32. ((educat* or instruct* or advis* or advice* or counsel* or teach* or train* or coach* or learn*) and (patient* or client* or consumer* or user* or carer* or caregiver* or care giver*)).mp.
33. counseling/ or patient counseling/
34. patient information/ or medical information/
35. drug information/
36. (inform* adj5 (patient* or client* or consumer* or user* or carer* or caregiver* or care giver*)).ti,ab,kw.
37. reminder system/
38. drug packaging/ or drug labeling/

39. medication therapy management/

40. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) and (manag* adj5 (medication* or medicines))).ti,ab,kw.

41. pharmaceutical care/

42. pharmac* care.ti,ab,kw.

43. or/31-42

44. medication compliance/ or patient compliance/

45. ((medication or treatment) adj (complian* or adheren* or noncomplian* or nonadheren*)).ti,ab,kw.

46. self concept/

47. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) and (competen* or confident or confidence or abilit* or capacit* or skill* or self-efficacy or cope? or coping or complian* or noncomplian* or adher* or nonadher* or underadheren* or concordan* or nonconcordan* or persisten* or nonpersist*)).ti,ab,kw.

48. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) adj5 (error* or mistak* or misus* or mismanag*)).ti,ab,kw.

49. (patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*).ti,ab,kw. and exp medication error/

50. drug self-administration/

51. or/44-50

52. 30 and (43 or 51)

53. randomized controlled trial/

54. controlled clinical trial/

55. single blind procedure/ or double blind procedure/

56. crossover procedure/

57. random*.tw.

58. placebo*.tw.

59. ((singl* or doubl*) adj (blind* or mask*)).tw.

60. (crossover or cross over or factorial* or latin square).tw.

61. (assign* or allocat* or volunteer*).tw.

62. or/53-61

63. 52 and 62

IPA (via Proquest)

1. ab,ti((old or older or aged or senior) n/2 (person$1 or people or adult$1 or patient* or consumer* or carer* or caregiver* or "care giver*"))
2. ab,ti(late life or ag$1ing or old age or seniors or elder* or geriatr* or gerontol* or geropsych* or veteran*)
3. 1 or 2
4. su(dosage forms or prescription drugs or drug utilization)
5. ab,ti(medication* or medicine$1 or medicament* or pharmac* or pharmacotherap* or drug$1 or polypharmac*)
6. su(combined therapy or polypharmacy)
7. su(pharmacy services)
8. or/4-7
9. 3 and 8
10. su(primary care)
11. ab,ti((primary) n/2 (care or healthcare))
12. su(ambulatory care)
13. ab,ti(ambulatory)
14. ab,ti((general or family) n/1 (practi*))
15. ab,ti(gp$1)
16. su(physicians)
17. su(health centers)
18. su(home health care)
19. ab,ti((hospital) n/3 (discharge))
20. su(patient care; continuity)
21. su(after hours service)
22. ab,ti(community or home or domicil* or outreach or out-reach or postdischarge or post-discharge or postacute or post-acute or discharge plan* or aftercare or "after care")
23. OR/10-22
24. 9 and 23
25. su(patient education)
26. ab,ti((educat* or instruct* or advis* or advice* or counsel* or teach* or train* or coach* or learn* or remind*) and (patient* or client* or consumer* or user* or carer* or caregiver* or "care giver*"))
27. su(counseling)
28. su(drug information)
29. ab,ti((inform*) n/5 (patient* or client* or consumer* or user* or carer* or caregiver* or "care giver*"))
30. ab,ti((remind*) and (system* or aid* or service* or package* or message* or call*))
31. su(drugs; packaging)
32. su(collaborative drug therapy management)
33. ab,ti((patient* or client* or consumer* or user* or subject$1 or carer* or caregiver* or "care giver*") and ((manag*) n/5 (medication* or medicine*)))
34. ab,ti(pharmac* care)
35. or/25-34
36. su(compliance)

37. su(self-medication)
38. ab,ti((medication or treatment) n/1 (complian* or adheren* or noncomplian* or nonadheren*))
39. ab,ti((patient* or client* or consumer* or user* or subject$1 or carer* or caregiver* or "care giver*") and (competen* or confident or confidence or abilit* or capacit* or skill* or self-efficacy or cope$1 or coping or complian* or noncomplian* or adher* or nonadher* or underadheren* or concordan* or nonconcordan* or persisten* or nonpersist*))
40. ab,ti((patient* or client* or consumer* or user* or subject$1 or carer* or caregiver* or "care giver*") n/5 (error* or mistak* or misus* or mismanag*))
41. ab,ti(patient* or client* or consumer* or user* or subject$1 or carer* or caregiver* or "care giver*") and su(medication errors)
42. OR/36-41
43. 24 and (35 or 42)
44. ab,ti(random* or controlled or control or placebo)
45. 43 and 44

PsycINFO (Via Ovid)

1. aged.id.
2. ((old or older or aged or senior) adj2 (person? or people or adult? or men or women or patient* or consumer* or carer* or caregiver* or care giver*)).ti,ab,id.
3. (late life or ag?ing or old age or seniors).ti,ab,hw,id.
4. (elder* or geriatric* or gerontolog* or geropsych* or veteran*).mp.
5. ("380" or "390").ag.
6. or/1-5
7. exp drugs/
8. exp pharmacology/
9. (medication* or medicine? or medicament* or pharmac* or drug? or polypharmac*).ti,ab,hw,id.
10. exp drug therapy/
11. or/7-10
12. 6 and 11
13. primary health care/
14. (primary adj2 (care or healthcare)).ti,ab,id.
15. exp outpatient treatment/
16. ambulatory.ti,ab,id.
17. family medicine/
18. general practitioners/
19. gp?.ti,ab,id.
20. family physicians/
21. ((general or family) adj practi*).ti,ab,id.
22. home care/
23. exp community services/
24. long term care/
25. aftercare/
26. exp facility discharge/
27. ((patient or hospital) adj3 discharge).ti,ab,hw,id.
28. "continuum of care"/
29. (community or home* or domicil* or outreach or out-reach or postdischarge or post-discharge or postacute or post-acute or discharge plan* or aftercare or after care).ti,ab,hw,id.
30. or/13-29
31. 12 and 30
32. client education/
33. ((educat* or instruct* or advis* or advice* or counsel* or teach* or train* or coach* or learn*) and (patient* or client* or consumer* or user* or carer* or caregiver* or care giver*)).mp.
34. exp counseling/
35. information services/
36. information/
37. (inform* adj5 (patient* or client* or consumer* or user* or carer* or caregiver* or care giver*)).ti,ab,id.
38. (reminder? or reminder system*).ti,ab,id.

39. warning labels/

40. "prescribing (drugs)"/

41. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) and (manag* adj5 (medication* or medicines))).ti,ab,hw,id.

42. pharmac* care.ti,ab,id.

43. or/32-42

44. treatment compliance/

45. ((medication or treatment) adj (complian* or adheren* or noncomplian* or nonadheren*)).ti,ab,id.

46. self efficacy/

47. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) and (competen* or confident or confidence or abilit* or capacit* or skill* or self-efficacy or cope? or coping or complian* or noncomplian* or adher* or nonadher* or underadheren* or concordan* or nonconcordan* or persisten* or nonpersist*)).ti,ab,hw,id.

48. ((patient* or client* or consumer* or user* or subject? or carer* or caregiver* or care giver*) and (error* or mistak* or misus* or mismanag*)).ti,ab,hw,id.

49. drug self-administration/

50. or/44-49

51. 31 and (43 or 50)

52. random*.ti,ab,hw,id.

53. trial*.ti,ab,hw,id.

54. controlled stud*.ti,ab,hw,id.

55. placebo*.ti,ab,hw,id.

56. ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti,ab,hw,id.

57. (cross over or crossover or factorial* or latin square).ti,ab,hw,id.

58. (assign* or allocat* or volunteer*).ti,ab,hw,id.

59. treatment effectiveness evaluation/

60. mental health program evaluation/

61. exp experimental design/

62. "2100".md.

63. or/52-62

64. 51 and 63

Appendix 2: Chapter 3 – Institutional Ethics Approval

- Monash University Ethics Approval

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

20 May 2015

Dear Researchers

|	
Project Number:	**CF15/1535 - 2015000756**
Project Title:	**Medication use in older people attending memory clinics in Australia, Prospective Research In MEmory clinics study (PRIME)**
Chief Investigator:	**Dr Johnson George**

The above application has been reviewed by the Chairs of the Monash University Human Research Ethics Committee (MUHREC) who determined that the proposal satisfies section 5.1.22 of the National Statement on Ethical Conduct in Human Research.

Therefore, the Committee has granted an exemption from ethical review for the research as described in your proposal.

Thank you for your assistance.
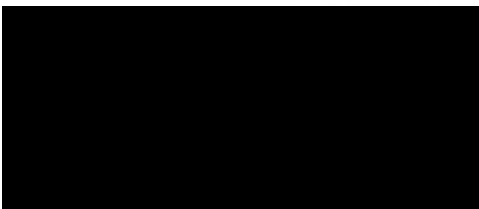
Professor Nip Thomson
Chair, MUHREC

cc: Dr Rohan Elliott, Mrs Amanda Cross

Appendix 3: Chapter 3 - Potentially Inappropriate Medications in cognitive impairment

- List of Potentially Inappropriate Medications in cognitive impairment (PIMcogs)

PIM	Number
Anticholinergic	**104**
Antipsychotics	
• Chlorpromazine	0
• Clozapine	1
• Fluphenazine	0
• Loxapine	0
• Olanzapine	4
• Perphenazine	0
• Pimozide	0
• Procholperazine	18
• Thioridazine	3
• Thiothixene	0
• Trifluoperazine	1
Tricyclic antidepressants	
• Amitriptyline	11
• Amoxapine	0
• Clomipramine	0
• Desipramine	0
• Dothiepin	7
• Doxepin	6
• Imipramine	1
• Nortriptyline	2
• Protriptyline	0
• Trimipramine	0
Antimuscarinics (urinary)	
• Darifenacin	0
• Fesoterodine	0
• Flavoxate	0

- Oxybutynin   15
- Solifenacin   2
- Tolterodine   3
- Trospium   0

Antispasmodics

- Atropine products   3
- Belladonna alkaloids   0
- Dicyclomine
- Homatropine   0
- Hyoscyamine products   1
- Loperamide   8
- Propantheline   1
- Scopolamine   0

First generation antihistamines

- Brompheniramine   0
- Carbinoxamine   0
- Chlorpheniramine   0
- Clemastine   0
- Cyproheptadine   3
- Dexbrompheniramine   0
- Dexchlorpheniramine   0
- Diphenhydramine   0
- Doxylamine   1
- Hydroxyzine   0
- Promethazine   3
- Triprolidine   0

Other antidepressants
(with anticholinergic properties)

- Paroxetine   7

Antiparkinson agents

- Benztropine   3
- Trihexyphenidyl   0

Other antihistamines (with anticholinergic properties)

- Dimenhydrinate   0
- Loratadine   0
- Meclizine   0

Skeletal Muscle Relaxants

- Carisoprodol   0
- Cyclobenzaprine   0
- Orphenadrine   0
- Tizanidine   0

Sedatives and hypnotics   **103**

Benzodiazepines (BZD)

- Alprazolam   3
- Clobazam   0
- Clonazepam   2
- Diazepam   11
- Flurazepam   0
- Lorazepam   0
- Midazolam   0
- Nitrazepam   7
- Oxazepam   23
- Temazepam   47
- Triazolam   2

Non-BZD hypnotics

- Zolpidem   1
- Zopiclone   6

Barbiturates

- Primidione   1
- Amobarbital   0
- Butabarbital   0
- Butalbitol   0
- Mephobarbital   0
- Pentobarbital   0

• Phenobarbital	0
• Secobarbital	0
Others medications that can induce delirium	**50**
Systemic corticosteroids	
• Betamethasone	0
• Dexamethasone	0
• Hydrocortisone	0
• Methylprednisolone	1
• Prednisolone/prednisone	25
• Triamcinolone	0
Histamine-2 receptor antagonists	
• Cimetidine	1
• Famotidine	3
• Nizatidine	4
• Ranitidine	16
Total	**257**

References:

1. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in oldeer adults. J Am Geriatr Soc 2012; 60: 616-31.

2. O' Mahony D, O' Sullivan D, Byrne S, O'connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015; 44: 213-8.

Appendix 4: Chapter 4 – Institutional Ethics Approval

- Austin Health Human Research Ethics

- Monash University Human Research Ethics

Austin Health

AUSTIN HEALTH HUMAN RESEARCH ETHICS COMMITTEE

ETHICAL APPROVAL

Dr Rohan Elliott
Austin Health

14 September 2017

Dear Dr Elliott

HREC Reference Number [AU RED HREC reference number]: HREC/17/Austin/277

Austin Health SITE REFERENCE Number: ND 17/277

Project Title: Deprescribing Potentially Inappropriate Medications in Memory Clinic Patients (DePIMM) - a feasibility study

I am pleased to advise that the above project has **received ethical approval** from the Austin Health Human Research Ethics Committee (HREC). The HREC confirms that your proposal meets the requirements of the National Statement on Ethical Conduct in Human Research (2007). This HREC is organised and operates in accordance with the National Health and Medical Research Council's (NHRMC) National Statement on Ethical Conduct in Human Research (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

HREC Approval Date: 14/09/2017

Ethical approval for this project applies at the following sites:

Site
Austin Health

Approved Documents:

The following documents have been reviewed and approved:

Document	Version	Date
NEAF	AU/1/2410314	08/08/2017
VSM		30/05/2017

Protocol	1.0	29/05/2017
Patient Information and Consent Form - Adult providing own consent	1.1	14/08/2017
Patient Information and Consent Form - Carer	1.1	14/08/2017
Participant Eligibility Criteria	1.0	30/06/2017
Participant Screening – Brief Verbal Explanatory Statement	1.0	30/06/2017
Baseline questionnaire	1.1	14/08/2017
Participant Questionnaire: 3 month follow up	1.1	14/08/2017
GP Introductory Letter	1.0	26/05/2017

Noted Document	Version	Date
Budget	1.0	07/07/2017

Governance Authorisation:

Governance Authorisation is required at each site participating in the study before the research project can commence at that site.

You are required to provide a copy of this HREC approval letter to the principal investigator for each site covered by this ethics approval for inclusion in the site specific assessment application.

Conditions of Ethics Approval:

- You are required to submit to the HREC:
    - An Annual Progress Report (that covers all sites listed on approval) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report, due within one month of the approval anniversary. Failure to comply with this requirement may result in suspension of the project by the HREC.
    - A comprehensive Final Report upon completion of the project.
- Submit to the reviewing HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure.
- Notify the reviewing HREC of any adverse events that have a material impact on the conduct of the research in accordance with the NHMRC Position Statement: *Monitoring and reporting of safety for clinical trials involving therapeutic products May 2009*.
- Notify the reviewing HREC of your inability to continue as Coordinating Principal Investigator.
- Notify the reviewing HREC of the failure to commence the study within 12 months of the HREC approval date or if a decision is taken to end the study at any of the sites prior to the expected date of completion.
- Notify the reviewing HREC of any matters which may impact the conduct of the project.
- **If your project involves radiation:**
    - **It is your responsibility to ensure the research is added to the site Management Licence issued by Department of Human Services – Radiation Safety Section prior to study commencement should it be required (check your Medical Physicist Report). The site RGO must be notified when the research has been added to the licence.**
    - **You are legally obliged to conduct your research in accordance with the Australian Radiation Protection and Nuclear Safety Agency Code of Practice 'Exposure of Humans to Ionizing Radiation for Research Purposes' Radiation Protection series Publication No.8 (May 2005)(ARPANSA Code).**

Please note: Template forms for reporting Amendments, Adverse events, Annual/Final reports, etc. can be accessed from: https://www2.health.vic.gov.au/about/clinical-trials-and-research/clinical-trial-research/how-to-make-an-hrec-application-for-clinical-trials.

The HREC may conduct an audit of the project at any time.

Yours sincerely

Austin Health

SITE SPECIFIC ASSESSMENT (SSA) AUTHORISATION

APPROVAL TO CONDUCT A NEW RESEARCH PROJECT AT AUSTIN HEALTH

Dr Rohan Elliott
Austin Health

14 September 2017

Dear Dr Elliott

AU RED HREC Reference Number: HREC/17/Austin/277

Austin Health Project Number: ND 17/277

Project Title: Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) - a feasibility study

AU RED SSA Reference Number: SSA/17/Austin/278

Reviewing HREC: Austin Health Human Research Ethics Committee (EC00204)

HREC Approval Date: 14/09/2017

SSA Authorisation Date: 14/09/2017

I am pleased to advise that the above project satisfies Austin Health's governance requirements and may now be conducted at Austin Health. Conduct of the project is subject to compliance with the conditions set out below and any additional conditions specified by the reviewing HREC.

SSA Approved Documents:

Document	Version	Date
Austin Health HREC approval letter		14/09/2017
Protocol	1.0	29/05/2017
Patient Information and Consent Form - Adult providing own consent	1.1	14/08/2017
Patient Information and Consent Form - Carer	1.1	14/08/2017
Participant Eligibility Criteria	1.0	30/06/2017
Participant Screening – Brief Verbal Explanatory Statement	1.0	30/06/2017
Baseline questionnaire	1.1	14/08/2017
GP Introductory Letter	1.0	26/05/2017
Participant Questionnaire: 3 month follow up	1.1	14/08/2017

Research governance

Condition of Governance Approval:

1. Researchers must comply with the Investigator's Responsibilities in Research Procedure and Good Clinical Practice (ICH GCP). The Principal Research is to ensure that all associate researchers are aware of terms of approval and to ensure the project is conducted as specified in the application and in accordance with the National Statement on Ethical Conduct in Human Research (updated March 2014).
2. The Principal Investigator must notify the 1) CPI, 2) Reviewing Human Research Ethics Committee (RHREC) and Sponsor (if applicable) of:
   - All related internal Serious Adverse Events (SAE) in accordance with the NHMRC Position Statement: *Monitoring and reporting of safety for clinical trials involving therapeutic products May 2009*.
   - Any other serious adverse effects to or complaints from Austin Health participants and steps taken to deal with them
   - Your inability to continue as Principal Investigator
   - Any unexpected developments in the project with ethical implications
   - Notify the RHREC of the failure to commence the study within 12 months of the RHREC approval date or if a decision is taken to end the study at any of the sites prior to the expected date of completion.
3. You are required to inform the Research Governance Office of;
   - The actual start date of the project at Austin Health
   - Any other matters which may impact the conduct of the project at Austin Health
   - Austin Health Investigators withdrawing from or joining the project.
4. Any amendments submitted to and approved by the RHREC, including changes to the protocol, approved documents and/or the addition of documents to be used at Austin Health, must be submitted for governance approval prior to implementation. After RHEC approval, the PI must submit a copy of all documents relating to the approved amendment, along with the RHREC approval certificate, to the Research Governance Office for approval.
5. Any changes to the indemnity, insurance arrangements or Clinical Trial Research Agreement for this project. This includes changes to the project budget or other changes which may have financial or other resource implications for Austin Health.
6. RHREC approval must remain current for the entire duration of the project. Investigators undertaking projects without current RHREC approval risk their indemnity, funding and publication rights.
7. **If your project involves radiation:**
   - **It is your responsibility to ensure the research is added to the site Management Licence issued by Department of Human Services – Radiation Safety Section prior to study commencement should it be required (check your Medical Physicist Report). The site RGO must be notified when the research has been added to the licence.**
   - **You are legally obliged to conduct your research in accordance with the Australian Radiation Protection and Nuclear Safety Agency Code of Practice 'Exposure of Humans to Ionizing Radiation for Research Purposes' Radiation Protection series Publication No.8 (May 2005)(ARPANSA Code).**

Clinical Trial projects:

8. For clinical trials where Austin Health is the Sponsor, you are required to contact the Research Governance Office to organise submission of the CTN to the TGA. This must be completed before commencement of your project.
9. Prior to commencement of the project a copy of the governance authorisation letter and CTN acknowledgement must be provided to the Clinical Trials Pharmacy.

10. It is the Principal Investigator's responsibility to ensure they receive a copy of the submitted clinical trial notification acknowledgement letter for their site.

You are also required to submit to the Office for Research:

11. In addition to the reporting requirements of the RHREC, you are required to submit an Annual Progress Report for the duration of the project. A copy of this report should also be submitted to the CPI. Continuation of SSA approval is contingent on submission of an annual report, due within one month of the approval anniversary. Continued SSA and HREC approval are contingent on receipt of an annual report by the RHREC and the Research Governance Office.

12. A comprehensive Final Report upon completion of the project.

The Office for Research may conduct an audit of the project at any time.

Yours sincerely

![Austin Health logo]

AUSTIN HEALTH HUMAN RESEARCH ETHICS COMMITTEE

ETHICAL APPROVAL FOR AMENDMENT

Dr Rohan Elliott
Austin Health
Heidelberg Repatriation Pharmacy, 300 Waterdale Road
Heidelberg
3081
Australia

02 March 2018

Dear Dr Rohan Elliott

AU RED HREC Reference Number: HREC/17/Austin/277

Austin Health Project Number: ND 17/277

Project Title: Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) - a feasibility study

I am pleased to advise that the above project amendment has **received ethical approval** from the Austin Health Human Research Ethics Committee (HREC). This HREC is organised and operates in accordance with the National Health and Medical Research Council's (NHRMC) National Statement on Ethical Conduct in Research Involving Humans (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

Original HREC Approval Date: 14/09/2017

Approved Documents:

The following documents have been reviewed and approved:

Document	Version	Date
DePIMM Protocol	1.1	23 February 2018
GP Survey	1.0	23 February 2018
CDAMS Consent	1.0	23 February 2018
CDAMS Focus Group	1.0	23 February 2018
Pharmacist Consent	1.0	23 February 2018
Pharmacist Interview	1.0	23 February 2018

Site Specific Assessment:

A copy of this letter must be forwarded to all Principal Investigators at every participating site and must be submitted to the relevant Research Governance Officer at each site.

Conditions of Ethics Approval:

- You are required to submit to the HREC:
    - An Annual Progress Report (that covers all sites listed on approval) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report, due within one month of the approval anniversary. Failure to comply with this requirement may result in suspension of the project by the HREC.
    - A comprehensive Final Report upon completion of the project.
- Submit to the reviewing HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure.
- Notify the reviewing HREC of any adverse events that have a material impact on the conduct of the research in accordance with the NHMRC Position Statement: *Monitoring and reporting of safety for clinical trials involving therapeutic products May 2009*.
- Notify the reviewing HREC of your inability to continue as Coordinating Principal Investigator.
- Notify the reviewing HREC of the failure to commence the study within 12 months of the HREC approval date or if a decision is taken to end the study at any of the sites prior to the expected date of completion.
- Notify the reviewing HREC of any matters which may impact the conduct of the project.
- If your project involves radiation, you are legally obliged to conduct your research in accordance with the Australian Radiation Protection and Nuclear Safety Agency Code of Practice 'Exposure of Humans to Ionizing Radiation for Research Purposes' Radiation Protection series Publication No.8 (May 2005)(ARPANSA Code).

The HREC may conduct an audit of the project at any time.

Yours sincerely

Ms Chelsea Webster
Ethics and Research Governance Manager
Office for Research, Austin Health
Level 8 HSB.
Phone: +61 3 9496 3248
E-mail: chelsea.webster@austin.org.au
Web: http://www.austin.org.au/researchethics

Carbon Copy: (PI) Mrs Amanda Cross

Austin Health

SITE SPECIFIC ASSESSMENT (SSA) AUTHORISATION

APPROVAL TO CONDUCT AN AMENDED RESEARCH PROJECT AT AUSTIN HEALTH

Dr Rohan Elliott
Austin Health
Heidelberg Repatriation Pharmacy, 300 Waterdale Road
Heidelberg 3081

02 March 2018

Dear Dr Rohan Elliott

AU RED HREC Reference Number: HREC/17/Austin/277

Austin Health Project Number: ND 17/277

Project Title: Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) - a feasibility study

AU RED SSA Reference Number:

I am pleased to advise that the above project amendment satisfies Austin Health's governance requirements and may now be conducted at Austin Health. Conduct of the project is subject to compliance with the conditions set out in the original authorisation and any additional conditions specified by the reviewing HREC.

Approved Documents:

Document	Date
Austin Health HREC Amendment Approval Letter – including all listed documents	02 March 2018

The Office for Research may conduct an audit of the project at any time.

Yours sincerely

Ms Chelsea Webster
Ethics and Research Governance Manager
Office for Research, Austin Health
Level 8 HSB.
Phone: +61 3 9496 3248
E-mail: chelsea.webster@austin.org.au
Web: http://www.austin.org.au/researchethics

Carbon Copy: (PI) Mrs Amanda Cross

Monash University Human Research Ethics Committee

Confirmation of Registration

Project Number: 11180

Project Title: Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM) - feasibility study

Chief Investigator: Dr Rohan Elliott

Expiry Date: 26/09/2022

Terms:

1. Registration is valid whilst you hold a position at Monash University and approval at the primary HREC is current.
2. This notification does not constitute an HREC approval. It is the responsibility of the Chief Investigator to ensure that approval from the primary HREC continues for the duration of the research.
3. End of project: You should notify MUHREC at the conclusion of the project or if the project is discontinued before the expected date of completion.
4. Retention and storage of data: The Chief Investigator is responsible for the storage and retention of the original data pertaining to this project in accordance with the *Australian Code for the Responsible Conduct of Research*.

Thank you for your assistance.

Professor Nip Thomson

Chair, MUHREC

CC: Dr Johnson George, Ms Amanda Cross

Appendix 5: Chapter 4 – Participant Information and Consent Forms

- Participant Information and Consent form – patient
- Participant Information and Consent form – carer
- Participant Information and Consent form (and survey) – general practitioner
- Participant Information and Consent form – memory clinic
- Participant Information and Consent form – pharmacist

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Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Austin Health Cognitive, Dementia and Memory Service

Title	Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM) – feasibility study
Short Title	DePIMM feasibility study
Protocol Number	1.0
Project Sponsor	Victorian Therapeutics Advisory Group (VicTAG)
Coordinating Principal Investigator/ Principal Investigator	Dr Rohan Elliott
Associate Investigator(s)	Dr Johnson George Dr Michael Woodward Mrs Amanda Cross
Location	Cognitive, Dementia and Memory Service (CDAMS) clinic, Heidelberg Repatriation Hospital, Austin Health

Part 1   What does my participation involve?

1   Introduction

You are invited to take part in this research project, which is called *Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM)*. You have been invited because you are attending the Austin Health memory clinic and you are taking medications. Your contact details were obtained from the Austin Health memory clinic.

This Participant Information Sheet/Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to be involved in the research described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

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2   What is the purpose of this research?

Some people may be at increased risk of experiencing problems with their medications. This may be because they use multiple medications which can interact, or because their medications cause unexpected side effects. Having multiple medical conditions or being under the care of more than one doctor or specialist can also increase the chance of problems with medication.

People with memory problems may be at increased risk of side effects from their medication or may have difficulties with managing their medications.

This study aims to test a new approach to identify medication problems and improve medication use in people who attend a memory clinic. The study involves using a pharmacist who is linked with the memory clinic to help identify possible medication problems and improve communication between the memory clinic, general practitioner (GP) and community pharmacist to address medication problems.

While there has been similar research around Australia and the world in older adults, this is the first time this type of study has been run in a memory clinic.

This research is being conducted by Dr Rohan Elliott from Austin Health and Monash University.

The results of this research will also be used by Amanda Cross as part of her Doctor of Philosophy studies at Monash University. Amanda Cross is supported by an Australian Government Research Training Program scholarship.

This research has been partially funded by the Victorian Therapeutics Advisory Group (VicTAG).

3   What does participation in this research involve?

If you agree to participate, you will receive the following **in addition** to usual clinic care.

1. A brief interview (approximately 15 minutes) with a researcher at the memory clinic (before or after your appointment), or via telephone. The interview will involve basic questions about your background, health and medication use.

2. A detailed interview (30 to 60 minutes) with a pharmacist from the memory clinic conducted in your own home. The pharmacist will contact you to arrange a convenient time. During the home interview the pharmacist will ask you about your medication use, including prescription and non-prescription medications, and how you manage your medications. The pharmacist will provide the memory clinic team and your GP with a report about any possible problems with your medications. The pharmacist, together with the memory clinic team, may make recommendations to your GP for stopping or reducing the dose of some medications or they may make other suggestions to make it easier for you to take your medications.

3. After the pharmacist visit, you will need to visit your GP to talk about your medications. This doesn't have to be an extra visit. You may wait until your next routine GP visit if you have one planned within the next four weeks. Based on the pharmacist's recommendations, you and your GP may decide to make changes to your medications to help avoid current or future medication-related problems and/or improve medication use.

4. At least one phone call from the memory clinic pharmacist within four weeks of the home interview. The pharmacist will contact you to follow-up on any changes that may have been made to

your medication and to answer any new questions or concerns you may have about your medication.

5. A <u>follow-up phone call (approximately 15 minutes)</u> with a researcher after three months. The researcher will ask you about your current medications and ask if there has been any changes to the way you use your medications. The researcher may also contact your GP or community pharmacist to ask about your current medications.

6. A <u>follow-up interview (approximately 30 minutes)</u> with a researcher in your home after six months. The researcher will ask about your medication use, medication management, health, memory and experiences with the study.

If you decide to participate in this study the investigator will inform your GP. You will remain under the care of your GP throughout the study.

There are no additional costs associated with participating in this research project, nor will you be paid. All home visits and follow-up from the memory clinic pharmacist will be provided to you free of charge.

However, there is a chance that you may need to make one or more extra visits to your GP and/or have additional tests (e.g. blood tests) if the medication review leads to changes to your medications. If you normally pay for these services than there may be additional costs involved (e.g. co-payment for visiting your GP). There is also a chance that you may be able to stop taking one or more of your medications as a result of the medication review.

4   What do I have to do?

You need to agree to have the memory clinic pharmacist visit you at home and review your medications, and you need to agree to have the researchers contact you, your GP and your community pharmacist over the next 6 months to collect information as described above.

As part of this study, the pharmacist may provide recommendations to you and your GP about the medications you take and how you manage your medications.

Some possible recommendations may include:
- Increase or decrease the dose of a medication to improve its benefits or reduce the chance of side effects
- Stop one or more medications that are no longer necessary or that may be causing problems
- Start a new medication to help manage an undertreated medical condition
- Change the timing of one or more medications to help simplify your medication regimen
- Lifestyle modification (e.g. diet or exercise) to help better manage your health

Changes to your medication will only occur if you and your GP agree. You will remain under the care of your GP throughout the study. You can discuss any questions or concerns you may have with the study pharmacist or your GP.

5   Other relevant information about the research project

The DePIMM study is a single site study running only at the Austin Health memory clinic.

Austin Health **MONASH** University

The study aims to recruit 50 people. The recruitment period will be from September 2017 until February 2018.

Each person will be followed up for six months. The study will be completed by 31st August 2018.

6   Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you can withdraw from at any time without being disadvantaged.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Austin Health.

7   What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this memory clinic. If you choose not to participate you will receive usual care from the memory clinic.

You may like to discuss the options with your local doctor.

8   What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research.

9   What are the possible risks and disadvantages of taking part?

The purpose of the medication review is to reduce the risk of side effects from medications. However, adjustments to medications, including stopping medications, may also cause side effects. *You will remain under the care of your local GP throughout the study*. If you have any side effects or your condition worsens, or you are worried about possible side effects, talk with your GP. Your GP and the study pharmacist will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your doctor immediately about any new or unusual symptoms that you get.

The possible risks of taking part will depend on the memory clinic pharmacist recommendations that you and your doctor choose to implement. For example;

- *If a medication is reduced or ceased* – you may experience a flare up in the condition that the medication was treating. For example, if a medication for reflux is reduced you may experience some symptoms of reflux. If severe or long lasting, your doctor may restart your medication.

- *If a new medication is started* – you may experience side effects. For example, if a new medication is started to better control your blood pressure you may experience some symptoms such as dizziness. If severe or long lasting, your doctor may cease the medication.

Austin Health   MONASH University

- *If your medication schedule is changed* – you may experience some difficulty as you get used to the new regimen. For example, if your medication is changed from night time to morning time this may take time to get used to the new routine. If you find the new routine too difficult then your doctor may change it back.

10   Can I have other treatments during this research project?

Yes. You can have any other treatments that you require during this project. However, it is important to tell your GP, your local pharmacist and/or the study pharmacist about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments.

11   What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team. This will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law.

12   Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as unacceptable side effects or the intervention being shown not to be effective.

13   What happens when the research project ends?

You will be followed up by a member of the research team at the end of the study (after six months).

After completion of the study you will then continue with regular care from the memory clinic, your GP and your community pharmacist.

Overall results from this study may be published in a journal(s) and/or presented at a conference and will be used by Amanda Cross as part of her Doctor of Philosophy degree at Monash University. The results may also be used to help us design future, larger studies.

If you would like to be provided with a summary of the results when the research project is completed then please contact the chief investigator (details listed below).

Part 2   How is the research project being conducted?

14   What will happen to information about me?

By signing the consent form you agree to the investigator and relevant research staff collecting and using personal information about you for the research project.

Any information obtained in connection with this research project that can identify you will remain confidential.

![Austin Health and Monash University logos]

Any personal information which can identify you (e.g. name and contact details) will only be accessible to the research team. It will be collected strictly for the purpose of the study to allow the study pharmacist to contact you and provide follow up. This information will be stored during the study in a locked filing cabinet at Austin Health. It will be destroyed at the end of the project.

All other information that is collected will be deidentified and recorded under your study identification number. This means that no details will be recorded that can be traced back to you individually. This information will be kept in a separate locked filing cabinet at Austin Health or Monash University, or a password protected computer file.

Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

15   Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the research team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

If you have any complaints about any aspects of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact the Austin Health Complaints Officer on 03 9496 4090.

16   Who is organising and funding the research?

This research project is being conducted by Dr Rohan Elliott and others from Austin Health and Monash University.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

Austin Health **MONASH** University

17   Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Austin Health HREC.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

18   Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the chief investigator Rohan Elliott on 03 9496 2334.

Clinical contact person

Name	Assoc/Prof Michael Woodward
Position	Head of Cognitive Decline And Memory Services clinic, Austin Health
Telephone	03 9496 2596
Email	Michael.WOODWARD@austin.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Complaints contact person

Position	Complaints Officer
Telephone	(03) 9496 4090 or (03) 9496 3248
Email	ethics@austin.org.au

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Austin Health Human Research Ethics Committee
HREC Executive Officer	Chelsea Webster
Telephone	03 9496 3248
Email	ethics@austin.org.au

Local HREC Office contact (Single Site - Research Governance Officer)

Name	Chelsea Webster
Position	Manager Ethics and Research Governance
Telephone	03 9496 3248
Email	ethics@austin.org.au

Consent Form - *Adult providing own consent*

Title	*Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) – feasibility study*
Short Title	*DePIMM feasibility study*
Protocol Number	*1.0*
Project Sponsor	*Victorian Therapeutics Advisory Group (VicTAG)*
Coordinating Principal Investigator/ Principal Investigator	*Dr Rohan Elliott*
Associate Investigator(s)	*Dr Johnson George Associate Professor Michael Woodward Mrs Amanda Cross*
Location	*Cognitive Dementia and Memory Service clinic, Heidelberg Repatriation Hospital, Austin Health*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors or other health professionals outside this hospital to release information to Austin Health concerning my treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print)	
Signature	Date

Declaration by Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher[†](please print)	
Signature	Date

[†] A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	*Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) – feasibility study*
Short Title	*DePIMM feasibility study*
Protocol Number	*1.0*
Project Sponsor	*Victorian Therapeutics Advisory Group (VicTAG)*
Coordinating Principal Investigator/ Principal Investigator	*Dr Rohan Elliott*
Associate Investigator(s)	*Dr Johnson George Associate Professor Michael Woodward Mrs Amanda Cross*
Location	*Cognitive Dementia and Memory Service clinic, Heidelberg Repatriation Hospital, Austin Health*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Austin Health.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the senior researcher will need to provide a description of the circumstances below.

Declaration by Researcher[†]

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Researcher[†](please print) _____

Signature _____ Date _____

[†] A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

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Participant Information Sheet/Consent Form – Person Responsible

| **Interventional Study** - *Person responsible consenting on behalf of participant* |

Austin Health Cognitive, Dementia and Memory Service

Title	Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM) – feasibility study
Short Title	DePIMM feasibility study
Protocol Number	1.0
Project Sponsor	Victorian Therapeutics Advisory Group (VicTAG)
Coordinating Principal Investigator/ Principal Investigator	Dr Rohan Elliott
Associate Investigator(s)	Dr Johnson George Dr Michael Woodward Mrs Amanda Cross
Location	Cognitive, Dementia and Memory Service (CDAMS) clinic, Heidelberg Repatriation Hospital, Austin Health

Part 1   What does participation involve?

1   Introduction

The participant is invited to take part in this research project, which is called *Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM)*. This is because the participant is attending the Austin Health memory clinic and is taking medication.

This Participant Information Sheet/Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not the participant can take part, you might want to talk about it with a relative, friend or the participant's local doctor.

Participation in this research is voluntary. If you don't wish the participant to take part, the participant doesn't have to. They will receive the best possible care whether or not they take part.

If you decide you want the participant to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
•   onsent to the participant taking part in the research project
•   onsent to the participant being involved in the research described
•   onsent to the use of the participant's personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

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2   What is the purpose of this research?

Some people may be at increased risk of experiencing problems with their medications. This may be because they use multiple medications which can interact, or because their medications cause unexpected side effects. Having multiple medical conditions or being under the care of more than one doctor or specialist can also increase the chance of problems with medication.

People with memory problems may be at increased risk of side effects from their medication or may have difficulties with managing their medications.

This study aims to test a new approach to identify medication problems and improve medication use in people who attend a memory clinic. The study involves using a pharmacist who is linked with the memory clinic to help identify possible medication problems and improve communication between the memory clinic, general practitioner (GP) and community pharmacist to address medication problems.

While there has been similar research around Australia and the world in older adults, this is the first time this type of study has been run in a memory clinic.

This research is being conducted by Dr Rohan Elliott from Austin Health and Monash University.

The results of this research will also be used by Amanda Cross as part of her Doctor of Philosophy studies at Monash University. Amanda Cross is supported by an Australian Government Research Training Program scholarship.

This research has been partially funded by the Victorian Therapeutics Advisory Group (VicTAG)

3   What does participation in this research involve?

If you agree, the participant will receive the following **in addition** to usual clinic care. You will be required to participate in all interviews, with or without the participant.

1. A brief interview (approximately 15 minutes) with a researcher at the memory clinic (before or after the participant's appointment), or via telephone. The interview will involve basic questions about the participant's background, health and medication use.

2. A detailed interview (30 to 60 minutes) with a pharmacist from the memory clinic conducted in the participant's home. The pharmacist will contact you to arrange a convenient time. During the home interview the pharmacist will ask about the participant's medication use, including prescription and non-prescription medications, and how you (and/or the participant) manage their medications. The pharmacist will provide the memory clinic team and the participant's GP with a report about any possible medication related problems. The pharmacist, together with the memory clinic team, may make recommendations to the GP for stopping or reducing the dose of some medications or they may make other suggestions to make it easier for the participant to take their medications.

3. After the pharmacist visit, the participant will need to visit their GP to talk about their medications. This doesn't have to be an extra visit. You may wait until the next routine GP visit if there is one planned within the next four weeks. Based on the pharmacist's recommendations, you, the participant and the GP may decide to make changes to the participant's medications to help avoid current or future medication-related problems and/or improve medication use.

4. At least one <u>phone call from the memory clinic pharmacist</u> within four weeks of the home interview. The pharmacist will contact you to follow-up on any changes that may have been made to the participant's medication and to answer any new questions or concerns you may have about their medication.

5. A <u>follow-up phone call (approximately 15 minutes)</u> with a researcher after three months. The researcher will ask you about the participant's current medications and ask if there has been any changes to the way they use their medications. The researcher may also contact the GP or community pharmacist to ask about the participant's current medications.

6. A <u>follow-up interview (approximately 30 minutes)</u> with a researcher in the participant's home after six months. The researcher will ask about medication use, medication management, health, memory and experiences with the study.

If you decide to participate in this study the investigator will inform the participant's GP. The participant will remain under the care of their GP throughout the study.

There are no additional costs associated with participating in this research project, nor will you or the participant be paid. All home visits and follow-up from the memory clinic pharmacist will be provided free of charge.

However, there is a chance that the participant may need to make one or more extra visits to their GP and/or have additional tests (e.g. blood tests) if the medication review leads to changes to their medications. If they normally pay for these services than there may be additional costs involved (e.g. co-payment for visiting your GP). There is also a chance that they may be able to stop taking one or more of their medications as a result of the medication review.

4   What does the participant have to do?

You need to agree to have the memory clinic pharmacist visit you and the participant at the participant's home and review their medications, and you need to agree to have the researchers contact you, the participant's GP and their community pharmacist over the next 6 months to collect information as described above.

As part of this study, the pharmacist may provide recommendations to you, the participant and the participant's GP about the medications the participant takes and how they manage their medications.

Some possible recommendations may include:
- Increase or decrease the dose of a medication to improve its benefits or reduce the chance of side effects
- Stop one or more medications that are no longer necessary or that may be causing problems
- Start a new medication to help manage an undertreated medical condition
- Change the timing of one or more medications to help simplify the medication regimen
- Lifestyle modification (e.g. diet or exercise) to help better manage the participant's health

Changes to the participant's medication will only occur if you (and the participant) and the participant's GP agree. The participant will remain under the care of their GP throughout the study. You can discuss any questions or concerns you may have with the study pharmacist or the participant's GP.

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5   Other relevant information about the research project

The DePIMM study is a single site study running only at the Austin Health memory clinic.

The study aims to recruit 50 people. The recruitment period will be from September 2017 until February 2018.

Each person will be followed up for six months. The study will be completed by 31st August 2018.

6   Does the participant have to take part in this research project?

Participation in any research project is voluntary. If you do not wish the participant to take part, the participant does not have to. If you decide that the participant can take part and later change your mind, you are free to withdraw the participant from the project at any stage.

If you do decide that the participant can take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether the participant can take part or not take part, or take part and then be withdrawn, will not affect the participant's routine treatment, your or the participant's relationship with those treating them, or the participant's relationship with Austin Health.

7   What are the alternatives to participation?

The participant does not have to take part in this research project to receive treatment at this memory clinic. If you choose not to participate, the participant will receive usual care from the memory clinic.

You may like to discuss the options with the participant's local doctor.

8   What are the possible benefits of taking part?

We cannot guarantee or promise that the participant will receive any benefits from this research.

9   What are the possible risks and disadvantages of taking part?

The purpose of the medication review is to reduce the risk of side effects from medications. However, adjustments to medications, including stopping medications, may also cause side effects. *The participant will remain under the care of their local GP throughout the study*. If they have any side effects or their condition worsens, or you are worried about possible side effects, talk with the participant's GP. The participant's GP and the study pharmacist will also be looking out for side effects

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell the participant's doctor immediately about any new or unusual symptoms that the participant experiences.

The possible risks of taking part will depend on the memory clinic pharmacist recommendations that you, the participant and their doctor choose to implement. For example;

- *If a medication is reduced or ceased* – the participant may experience a flare up in the condition that the medication was treating. For example, if a medication for reflux is

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reduced they may experience some symptoms of reflux. If severe or long lasting, the doctor may restart their medication.

- *If a new medication is started* – the participant may experience side effects. For example, if a new medication is started to better control blood pressure the participant may experience some symptoms such as dizziness. If severe or long lasting, their doctor may cease the medication.

- *If the medication schedule is changed* – you and/or the participant may experience some difficulty as you/they get used to the new regimen. For example, if the medication is changed from night time to morning time this may take time to get used to the new routine. If you/they find the new routine too difficult then the doctor may change it back.

10   Can the participant have other treatments during this research project?

Yes. The participant can have any other that they require during this project. However, it is important to tell their GP, their local pharmacist and/or the study pharmacist about any treatments or medications that the participant may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments.

11   What if I withdraw the participant from this research project?

If you decide to withdraw the participant from the project, please notify a member of the research team. This will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw the participant during the research project, the study staff will not collect additional personal information from the participant, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law.

12   Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as unacceptable side effects or the intervention being shown not to be effective.

13   What happens when the research project ends?

The participant will be followed up by a member of the research team at the end of the study (after six months).

After completion of the study the participant will then continue with regular care from the memory clinic, their GP and their community pharmacist.

Overall results from this study may be published in a journal(s) and/or presented at a conference and will be used by Amanda Cross as part of her Doctor of Philosophy degree at Monash University. The results may also be used to help us design future, larger studies.

If you would like to be provided with a summary of the results when the research project is completed then please contact the chief investigator (details listed below).

Part 2   How is the research project being conducted?
14   What will happen to information about the participant?

By signing the consent form you consent to the investigator and relevant research staff collecting and using personal information about the participant for the research project.

Any information obtained in connection with this research project that can identify the participant will remain confidential.

Any personal information which can identify you or the participant (e.g. name and contact details) will only be accessible to the research team. It will be collected strictly for the purpose of the study to allow the study pharmacist to contact you and provide follow up. This information will be stored during the study in a locked filing cabinet at Austin Health. It will be destroyed at the end of the project.

All other information that is collected will be deidentified and recorded under the participant's study identification number. This means that no details will be recorded that can be traced back to you or the participant. This information will be kept in a separate locked filing cabinet at Austin Health or Monash University, or a password protected computer file.

Information about the participant may be obtained from their health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to participation in this research project.

It is anticipated that the results of this research project will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that the participant cannot be identified.

Information about participation in this research project may be recorded in the participant's health records.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to the participant's information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access the participant's information.

Any information obtained for the purpose of this research project that can identify the participant will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

15   Complaints and Compensation

If the participant suffers any injuries or complications as a result of this research project, you should contact the research team as soon as possible and you will be assisted with arranging appropriate medical treatment for the participant. If the participant is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

If you have any complaints about any aspects of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact the Austin Health Complaints Officer on 03 9496 4090.

16   Who is organising and funding the research?

This research project is being conducted by Dr Rohan Elliott and others from Austin Health and Monash University.

No member of the research team will receive a personal financial benefit from the participant's involvement in this research project (other than their ordinary wages).

17   Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Austin Health HREC.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

18   Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if the participant has any problems which may be related to their involvement in the project, you can contact the chief investigator Rohan Elliott on 03 9496 2334.

Clinical contact person

Name	Assoc/Prof Michael Woodward
Position	Head of Cognitive Decline And Memory Services clinic, Austin Health
Telephone	03 9496 2596
Email	Michael.WOODWARD@austin.org.au

For matters relating to research at the site at which the participant is participating, the details of the local site complaints person are:

Complaints contact person

Position	Complaints Officer
Telephone	(03) 9496 4090 or (03) 9496 3248
Email	ethics@austin.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Austin Health Human Research Ethics Committee
HREC Executive Officer	Chelsea Webster
Telephone	03 9496 3248
Email	ethics@austin.org.au

Local HREC Office contact (Single Site - Research Governance Officer)

Name	Chelsea Webster
Position	Manager, Ethics and Research Governance
Telephone	03 9496 3248
Email	ethics@austin.org.au

Consent Form – Person Responsible

Title	*Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) – feasibility study*
Short Title	*DePIMM feasibility study*
Protocol Number	*1.0*
Project Sponsor	*Victorian Therapeutics Advisory Group (VicTAG)*
Coordinating Principal Investigator/ Principal Investigator	*Dr Rohan Elliott*
Associate Investigator(s)	*Dr Johnson George Associate Professor Michael Woodward Mrs Amanda Cross*
Location	*Cognitive Dementia and Memory Service clinic, Heidelberg Repatriation Hospital, Austin Health*

Declaration by Person Responsible

I am the Person Responsible for _____ (the Participant).

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I believe that the participation of the participant in this study is not contrary to their best interests.

I freely agree to the participant participating in this research project as described and understand that I am free to withdraw the participant at any time during the research project without affecting their future health care.

I am aware of my responsibilities as the Person Responsible for the participant and I understand that I will be assisting the participant in meeting their responsibilities whilst they are participating in this study.

I understand that I will be given a signed copy of this document to keep on behalf of the participant.

I give permission for the participant's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Austin Health concerning the participant's disease and treatment for the purposes of this research project. I understand that such information will remain confidential.

Name of Participant (please print) _____

Name of Person Responsible (please print) _____

Relationship of Person Responsible to Participant _____

Signature of Person Responsible _____ Date _____

Name of Witness* to
Person Responsible's Signature (please print) _____

Signature _____ Date _____

* Witness is <u>not</u> to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may <u>not</u> act as a witness to the consent process. Witness must be 18 years or older.

<u>Declaration by Researcher†</u>

I have given a verbal explanation of the research project, its procedures and risks and I believe that the person responsible has understood that explanation.

Name of Researcher†(please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation – Person Responsible

Title	*Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) – feasibility study*
Short Title	*DePIMM feasibility study*
Protocol Number	*1.0*
Project Sponsor	*Victorian Therapeutics Advisory Group (VicTAG)*
Coordinating Principal Investigator/ Principal Investigator	*Dr Rohan Elliott*
Associate Investigator(s)	*Dr Johnson George Associate Professor Michael Woodward Mrs Amanda Cross*
Location	*Cognitive Dementia and Memory Service clinic, Heidelberg Repatriation Hospital, Austin Health*

Declaration by Person Responsible

I wish to withdraw the participant from taking part in the above research project and understand that such withdrawal will not affect the participant's routine treatment, relationship with those treating them or their relationship with Austin Health.

Name of Participant (please print)

Name of Person Responsible (please print)

Relationship of Person Responsible to Participant

Signature of Person Responsible _____ Date _____

Name of Researcher (please print) _____

Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.

Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM)

Participant information sheet: General Practitioner questionnaire

The patient named on the attached fax-back form was recently seen by the Austin Health Cognitive Decline and Memory Service (aka memory clinic). He/she consented to participate in a research project evaluating a new approach for identifying medication related problems and improving medication use in people who attend a memory clinic. As part of the project we are seeking your feedback on the memory clinic pharmacist medication review/deprescribing report. A brief questionnaire is attached; participation is voluntary. It should only take 2-3 minutes.

Purpose of project

The purpose of the project is to evaluate the feasibility, acceptability and effectiveness of a patient-centred interdisciplinary medication review and deprescribing intervention for people referred to the memory clinic who may be at increased risk of a medication related problem.

Background & procedures

Previous research has found that a significant proportion of people who attend memory clinics used medications that may adversely affect cognitive function or that were otherwise potentially unnecessary of inappropriate. People who attend memory clinics may also be at high-risk for medication-related problems, due to multiple medication use together with functional and cognitive impairments. Most people referred to the memory clinic do not receive a comprehensive review of their medicines by a pharmacist.

As part of this project, your patient has received a comprehensive pharmacist medication review in their home. The pharmacist, in consultation with the memory clinic, then prepared a medication review/deprescribing report which was sent to the patient's preferred general practitioner and community pharmacy.

Privacy, Confidentiality and Disclosure of Information

Any information obtained in connection with this project that can identify participants will remain confidential. It will only be disclosed with your permission, except as required by law. We plan to publish the results in a scientific journal. In publication, information will be provided in such a way that participants cannot be identified.

Ethical Guidelines and Further Information

The ethical aspects of this project have been approved by the Human Research Ethics Committee of Austin Health.

If you wish to contact someone independent of the study about ethical issues or your rights or to make a complaint, you may contact the Austin Health Complaints Officer on 03 9496 4090 or ethics@austin.org.au.

If you require further information or if you have any concerns about this project, you can contact the principal investigator: Dr Rohan Elliott or Mrs Amanda Cross.

Dr Rohan Elliott	Mrs Amanda Cross
Pharmacy Department,	Centre for Medicine Use and Safety
Austin Health	Faculty of Pharmacy & Pharmaceutical Science,
PO Box 5555,	Monash University
Heidelberg, Vic, 3084	381 Royal Parade,
Ph: 03 9496 2334	Parkville, Vic, 3052
Fax: 03 9496 5900	Ph: 0408 311 814
Email: rohan.elliott@austin.org.au	Email : amanda.cross@monash.edu

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Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM)

FAX-BACK FORM

To:	Rohan Elliott, Senior Pharmacist, Heidelberg Repatriation Hospital
Fax Number:	**Please fax completed form to 03 9496 4260**
Re:	Mr/Mrs _____'s (DOB: ___/___/___) 'Memory Clinic Pharmacist Medication Review/Deprescribing Report'

1. How useful was the attached report for <u>identifying potentially unnecessary or inappropriate medications</u> used by this client?

☐ Extremely Useful ☐ Useful ☐ Unsure
☐ Not very Useful ☐ Useless ☐ N/A

2. How useful was the attached report for <u>providing deprescribing recommendations</u>* for this client?
 * Recommendations to reduce or stop a medication

☐ Extremely Useful ☐ Useful ☐ Unsure
☐ Not very Useful ☐ Useless ☐ N/A

3. How useful was the attached report for <u>identifying other medication-related issues</u>^ for this client?
 ^ e.g. issues relating to adherence or medication management

☐ Extremely Useful ☐ Useful ☐ Unsure
☐ Not very Useful ☐ Useless ☐ N/A

4. Did you discuss any of the findings or recommendations from the report with the client (or carer)?

☐ Yes
☐ No
☐ N/A

5. Most clients referred to memory clinics currently do **not** receive a medication review by a pharmacist. <u>Do you think clients should receive a pharmacist medication review as part of the service?</u>

☐ YES (in memory clinic)
☐ YES (in client's home)
☐ NO
☐ Other ………………………

Comments:

Thank you for your time and cooperation.

Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM)

<u>Participant information sheet: Memory Clinic Focus Group</u>

You are invited to participate in this research project. Please read this participant information sheet in full before deciding whether or not to take part in this research.

Why were you chosen for this research?

You have been invited to participate because one or more of your patients consented to participate in the DePIMM project, which is being conducted at the Austin Health Cognitive Decline and Memory Clinic Service.

Purpose of the research project

Previous research has found that a significant proportion of people who attend memory clinics used medications that may adversely affect cognitive function or that were otherwise potentially unnecessary of inappropriate. People who attend memory clinics may also be at high-risk for medication-related problems, due to multiple medication use together with functional and cognitive impairments. Most people referred to the memory clinic do not receive a comprehensive review of their medicines by a pharmacist.

The purpose of this project is to evaluate the feasibility, acceptability and effectiveness of a patient-centred, pharmacist-led, interdisciplinary medication review and deprescribing intervention for people referred to the memory clinic who may be at increased risk of a medication related problem.

Procedure

You are invited to attend a focus group to be held at a place and time convenient for you. To make sure that the research assistant does not miss any valuable information provided by you during the interview, the interview will be audio-recorded.

You will be asked for feedback on the DePIMM intervention, as well as the potential advantages and disadvantages of greater pharmacist involvement in the memory clinic.

The focus group with the research assistant will take approximately 60 minutes.

Consenting to participate in the project

Participating in any research project is voluntary. If you are willing to participate in this project, please sign and return the consent form below.

You have the right to withdraw from the project at any time by informing the research project team.

Possible benefits
We cannot guarantee or promise that you will receive any direct benefits from this research.

There is no payment for you to participate in the discussion, however light refreshments will be provided for the focus group.

Inconvenience/discomfort

We do not foresee any inconvenience or discomfort for you by participating in this study. You may choose to avoid answering questions during the discussion if you feel they are too personal or intrusive.

Confidentiality

The focus group will be transcribed verbatim. Any personal details that could reveal your identity will be removed from the transcripts. You will be identified only by a code and only the researchers will have access to the data collected. Only grouped findings from the session will be used in publications and presentations and no personal details that could reveal your identity will be reported.

Storage of data

Data collected will be stored in accordance with Austin Health and Monash University regulations. Data will be retained securely at the Pharmacy department, Austin Hospital or Faculty of Pharmacy and Pharmaceutical Science, Monash University for five years after project completion. After this time, the data will be confidentially destroyed.

Results

The results of this project will be published in a peer-reviewed journal and included as part of Amanda Cross' PhD thesis. If you wish to receive a copy of the results, please email your request to amanda.cross@monash.edu.

Ethical Guidelines

The ethical aspects of this project have been approved by the Human Research Ethics Committee of Austin Health.

Should you have any concerns or complaints about any aspect of this project, you are welcome to contact the Austin Health Complaints Officer on 03 9496 4090, or ethics@austin.org.au.

Further Information

If you require further information or if you have any concerns about this project, you can contact the principal investigator Dr Rohan Elliott or Mrs Amanda Cross.

Dr Rohan Elliott	Mrs Amanda Cross
Pharmacy Department, Austin Health PO Box 5555, Heidelberg, Vic, 3084 Ph: 03 9496 2334 Fax: 03 9496 5900 Email: rohan.elliott@austin.org.au	Centre for Medicine Use and Safety Faculty of Pharmacy & Pharmaceutical Science, Monash University 381 Royal Parade, Parkville, Vic, 3052 Ph: 0408 311 814 Email : amanda.cross@monash.edu

Austin Health   **MONASH** University

Consent Form: Memory Clinic Focus Group

Title	*Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) – feasibility study*
Project Sponsor	*Victorian Therapeutics Advisory Group (VicTAG)*
Principal Investigator	*Dr Rohan Elliott*
Associate Investigator(s)	*Dr Johnson George* *Associate Professor Michael Woodward* *Mrs Amanda Cross*
Location	*Cognitive Dementia and Memory Service clinic, Heidelberg Repatriation Hospital, Austin Health*

Declaration by Participant

I have read the Participant Information Sheet. I understand the purpose and procedures of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I consent to the following:	Yes	No
• **Taking part in a structured focus group facilitated by the research assistant**	☐	☐
• **Audiotaping of the discussion**	☐	☐

Name of Participant _____

Signature _____   Date _____

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Austin Health

MONASH University

Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM)

Participant information sheet: Intervention Pharmacist Interview

You are invited to participate in this research project. Please read this participant information sheet in full before deciding whether or not to take part in this research.

Why were you chosen for this research?

You have been invited to participate because you were the intervention pharmacist for the DePIMM project, which was conducted at the Austin Health Cognitive Decline and Memory Clinic Service.

Purpose of the research project

Previous research has found that a significant proportion of people who attend memory clinics used medications that may adversely affect cognitive function or that were otherwise potentially unnecessary of inappropriate. People who attend memory clinics may also be at high-risk for medication-related problems, due to multiple medication use together with functional and cognitive impairments. Most people referred to the memory clinic do not receive a comprehensive review of their medicines by a pharmacist.

The purpose of this project is to evaluate the feasibility, acceptability and effectiveness of a patient-centred, pharmacist-led, interdisciplinary medication review and deprescribing intervention for people referred to the memory clinic who may be at increased risk of a medication related problem.

Procedure

You are invited to attend a one-on-one interview to be held at a place and time convenient for you. To make sure that the research assistant does not miss any valuable information provided by you during the interview, the interview will be audio-recorded.

You will be asked for feedback on your experiences, both positive and negative, with the DePIMM intervention, and your opinions for improving the intervention. The interview will take approximately 30minutes.

Consenting to participate in the project

Participating in any research project is voluntary. If you are willing to participate in this project, please sign and return the consent form below. You have the right to withdraw from the project at any time by informing the research project team.

Possible benefits
We cannot guarantee or promise that you will receive any direct benefits from this research.

Payment
You will be paid $50 for your involvement in the interview.

Austin Health   **MONASH** University

Inconvenience/discomfort

We do not foresee any inconvenience or discomfort for you by participating in this study. You may choose to avoid answering questions during the discussion if you feel they are too personal or intrusive.

Confidentiality

The interview will be transcribed verbatim. Any details that could reveal the identity of any participants, carers or health professionals will be removed from the transcripts. Only generalised findings from the interview will be used in publications and presentations.

Your involvement in the study will be acknowledged in any publications resulting from this research. You may choose for your identity to remain confidential.

Storage of data

Data collected will be stored in accordance with Austin Health and Monash University regulations. Data will be retained securely at the Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University for five years after project completion. After this time, the data will be confidentially destroyed.

Results

The results of this project will be published in a peer-reviewed journal and included as part of Amanda Cross' PhD thesis. If you wish to receive a copy of the results, please email your request to amanda.cross@monash.edu.

Ethical Guidelines

The ethical aspects of this project have been approved by the Human Research Ethics Committee of Austin Health.

Should you have any concerns or complaints about any aspect of this project, you are welcome to contact the Austin Health Complaints Officer on 03 9496 4090, or ethics@austin.org.au.

Further Information

If you require further information or if you have any concerns about this project, you can contact the principal investigator Dr Rohan Elliott or Mrs Amanda Cross.

Dr Rohan Elliott	Mrs Amanda Cross
Pharmacy Department, Austin Health PO Box 5555, Heidelberg, Vic, 3084 Ph: 03 9496 2334 Fax: 03 9496 5900 Email: rohan.elliott@austin.org.au	Centre for Medicine Use and Safety Faculty of Pharmacy & Pharmaceutical Science, Monash University 381 Royal Parade, Parkville, Vic, 3052 Ph: 0408 311 814 Email : amanda.cross@monash.edu

Austin Health   MONASH University

Consent Form: Intervention Pharmacist Interview

Title	*Deprescribing Potentially Inappropriate Medications in Memory clinic patients (DePIMM) – feasibility study*
Project Sponsor	*Victorian Therapeutics Advisory Group (VicTAG)*
Principal Investigator	*Dr Rohan Elliott*
Associate Investigator(s)	*Dr Johnson George* *Associate Professor Michael Woodward* *Mrs Amanda Cross*
Location	*Cognitive Dementia and Memory Service clinic, Heidelberg Repatriation Hospital, Austin Health*

Declaration by Participant

I have read the Participant Information Sheet. I understand the purpose and procedures of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I consent to the following:	Yes	No
• **Taking part in a one-on-one interview with the research assistant**	☐	☐
• **Audio-recording of the discussion**	☐	☐
• **Being personally identified in publication acknowledgements**		

Name of Participant (please

Signature _____   Date _____

Appendix 6: Chapter 4 – Data Collection Forms

- Baseline questionnaire
- Follow-up questionnaire

Study ID: _____

Austin Health   **MONASH** University

<u>De</u>prescribing <u>P</u>otentially <u>I</u>nappropriate <u>M</u>edication in <u>M</u>emory clinic patients (DePIMM) – feasibility study

<u>Confidential Data</u>

Name: _____

Age in years: _____   Gender: ☐ Male   ☐ Female

Address: _____

Contact Telephone Number: _____

Best days of week, or times of day to call: _____

<u>Carer</u> ☐ Yes ☐ No

Name: _____   Relationship: _____

Contact Telephone Number: _____

<u>CDAMS</u>

Name of CDAMS clinic doctor: _____

<u>General Practitioner (GP)</u>

Name: _____ Ph: _____ Fax: _____

Postal Address: _____ _____

Email Address: _____

<u>Community Pharmacy</u>

Name: _____Ph: _____ Fax: _____

Postal Address: _____ _____

Email Address: _____

(Remove this page at the end of the interview and keep in the study folder in a locked cabinet)

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Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM) – feasibility study

Participant Questionnaire: Baseline

Date: _____ / _____ / _____

Part A: Some general questions about you

1. In which country were you born?

   ☐ Australia ☐ Other (specify) _____

2. In what language do you mainly speak to your family members?

   ☐ English ☐ Other (specify) _____

3. What is your <u>highest</u> level of education?

   ☐ No formal schooling ☐ Primary school

   ☐ High school (incomplete) ☐ Finished high school

   ☐ Technical/further education (including TAFE) ☐ University degree

   ☐ Other (specify) _____

4. What is your <u>current</u> employment status (tick as many as appropriate)?

   ☐ Employed (full-time) ☐ Employed (part-time)/casual ☐ Unemployed

   ☐ Retired ☐ Other: _____

5. What is your <u>current</u> marital status?

   ☐ Married/De-facto ☐ Single ☐ Other (specify) _____

6. What is your <u>current</u> living arrangement?

   ☐ Live with spouse or partner ☐ Live with friends ☐ Live alone at home

   ☐ Live with family members ☐ Other (specify) _____

Part B: Some questions about your health

7. In the last six (6) months, (approximately) how many times have you seen your regular GP? _____

8. a) In the last six (6) months, how many GPs and specialist doctors have you seen other than your regular GP? _____

   b) How many of those other GPs/specialists have prescribed medications for you? _____

9. In the last six (6) months, have you had any home visits from a nurse? ☐ Yes   ☐ No
   If Yes, what was the nature of the visit(s)? _____
   _____

10. In the last six (6) months, how many times have you had an unplanned admission to a hospital or a visit to an accident and emergency unit? _____
    If Yes, what was the reason for the admission/visit(s) _____
    _____

11. In the last six (6) months have you experienced any symptoms or problems that you think might have been side effects from your medications? For example:

    ☐ Dizziness   ☐ Falls   ☐ Drowsiness/tiredness

    ☐ Confusion   ☐ Hallucinations   ☐ Blurred vision

    ☐ Constipation   ☐ Diarrhoea   ☐ Dry mouth

    ☐ Others _____

12. Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems with walking around ❑

I have slight problems with walking around ❑

I have moderate problems with walking around ❑

I have severe problems with walking around ❑

I am unable to walk around ❑

PERSONAL CARE

I have no problems with washing or dressing myself ❑

I have slight problems with washing or dressing myself ❑

I have moderate problems with washing or dressing myself ❑

I have severe problems with washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

The best health
you can imagine

- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.

- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

The worst health
you can imagine

Part C: Some questions about your medication management

13. Do you collect your own medications from the pharmacy? ☐ Yes ☐ No

If no, how do you get them? _____

14. Are your prescriptions always dispensed at the same pharmacy? ☐ Yes ☐ No

If no, how many pharmacies do you use? _____

15. Does anyone help you to use or take your medication correctly? ☐ Yes ☐ No

If yes, please tell us who helps _____

16. Do you ever accidently forget to take your medication? ☐ Yes ☐ No

If yes, how many times in the last week have you forgotten to take one or more of your medications? ☐ Zero ☐ Once ☐ Twice or more

17. Do you ever intentionally not take your medication? ☐ Yes ☐ No

If yes, how many times in the last week have you intentionally not taken one or more of your medications? ☐ Zero ☐ Once ☐ Twice or more

18. Do you use anything to help you remember to use or take your medication?
    ☐ Alarm or beeper   ☐ Calendar or diary
    ☐ Medication pack (e.g. pill box, Webster) ☐ Medication list
    ☐ Mobile phone application   ☐ Other _____

19. Do you use any other medication aids?
    ☐ Eye drop aid   ☐ Inhaler aid
    ☐ Pill cutter   ☐ Other _____

20. Have you ever had a pharmacist medication review (where a pharmacist sat with you for at least half an hour to ask about all of the medications you take, answer questions about your medications, and check for side effects, medicine-interactions, doses etc)?
    ☐ Yes   ☐ No

If yes, how long ago? ☐ <3 month ☐ 3-6months ☐ 6-12 months ☐ >12 months

21. How would you rate the complexity or difficult of taking ALL of your medicines as prescribed on a scale from 1 (very simple) to 5 (very complex)?

(Very simple) 1---------2---------3---------4---------5   (Very complex)

22. For each statement, put a (✓) in the box that best describes your experiences.

Statements	Never	Rarely	Some-times	Often	Always
I have strict routines for using my regular medicines					
I keep my medicines close to where I need to use them					
I ensure I have enough medicines so that I don't run out					
I strive to follow the instructions of my doctors					
I get confused about my medicines					
I make changes in the recommended management to suit my lifestyle					
I put up with my medical problems before taking any action					
I alter my recommended management based on how I am feeling					

Study ID: _____

Part D: Some questions about your interest in deprescribing medications

23. For each statement, put a (✓) in the box that best describes your feelings/opinions

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
I feel that I am taking a large number of medications					
I am comfortable with the number of medications that I am taking					
I believe that all my medications are necessary					
If my doctor said it was possible I would be willing to stop one or more of my regular medications					
I would like to reduce the number of medications that I am taking					
I feel that I may be taking one or more medications that I no longer need					
I would accept taking more medications for my health conditions					
I have a good understanding of the reasons I was prescribed each of my medications					
Having to pay for less medications would play a role in my willingness to stop one or more of my medications					
I believe one or more of my medications is giving me side effects					

24. How many different tablets/capsules per day would you consider to be <u>a lot</u>?
    Please circle one of the below number ranges

     5-10   10-15   15-20   20-25   >25

25. What is the MAXIMUM number of tablets/capsules that you would be comfortable taking per day? *Please circle one of the below pictures*

26. How comfortable would you be if a pharmacist was involved in stopping one or more of your regular medications and provided the follow up (informing your doctor of the progress)?

    ☐ Uncomfortable   ☐ Unsure   ☐ Comfortable

27. If one of your regular medications was stopped, what follow up would you like?

    ☐ Face to face appointment

    ☐ Phone call(s)

    ☐ Written information via post

    ☐ Written information via email

    ☐ I wouldn't need planned follow up. I would be happy contacting a health professional if I had any problems.

Study ID: _____

Part E: Information to be <u>extracted</u> from CDAMS clinic records

28. Date of first visit to CDAMS clinic: _____

29. Number of previous visits to CDAMS clinic (excluding today's visit): _____

30. Duration of cognition impairment complaint: _____

31. Has a cognitive impairment diagnosis been made?

☐ Yes (specify diagnosis and date of diagnosis) _____

☐ Not yet (specify suspected diagnosis, if recorded) _____

☐ No

32. Mini-mental state score (/30): _____

33. Current health/medical conditions

Study ID: _____

34. Does the patient have any of the following conditions?

Assigned weight	Conditions	Please ✓if present
1	Myocardial infarction	
	Congestive heart failure	
	Peripheral vascular disease	
	Cerebrovascular disease	
	Dementia	
	Chronic pulmonary disease	
	Connective tissue disease	
	Ulcer disease	
	Mild liver disease	
	Diabetes	
2	Hemiplegia	
	Moderate or severe renal disease	
	Diabetes with end organ damage	
	Any tumour	
	Leukaemia	
	Lymphoma	
3	Moderate or severe liver disease	
6	Metastatic solid tumour	
	AIDS	
Total Charlson's Index score		

Appendix 6

Study ID: _____

35. Current medications (as listed in CDAMS clinic notes/referral correspondence)

Medication Name	Directions	Additional instructions	Any past prescribing or deprescribing recommendations made by CDAMS?

Medication History Source: _____Date: _____

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Study ID: _____

Austin Health   **MONASH** University

<u>D</u>eprescribing <u>P</u>otentially <u>I</u>nappropriate <u>M</u>edication in <u>M</u>emory clinic patients (DePIMM) – feasibility study

<u>**Participant Questionnaire: 3 month follow up**</u>

Date: ____ / ____ / _____

Part A: Current medications

Medication name & strength	Directions	Additional instructions	Dose change since baseline			
			Increase	Decrease	No Change	New
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐

Medication History Source: _____ Date: _____

Study ID: _____

Part B: Implementation of pharmacist recommendations

Has the patient had an appointment with their GP to discuss the pharmacist recommendations?

☐ Yes, date (if known) ___/___/____   ☐ No   ☐ Unsure

Pharmacist MRP Recommendation	Implementation			Details (e.g. description of change made, reasons not implemented)
	Yes	No	Partial	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	

Participant Questionnaire: 6 month follow up

Date: _____ / _____ / _____

Part A: Current medications

Medication name & strength	Directions	Additional instructions	Dose change since baseline			
			Increase	Decrease	No Change	New
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
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			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐

Medication History Source: _____ Date: _____

Study ID: _____

Part B: Implementation of pharmacist recommendations

Pharmacist MRP Recommendation	Implementation			Details (e.g. description of change made, reasons not implemented)
	Yes	No	Partial	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	
	☐	☐	☐	

Part C: Some questions about your medication management

1. Do you collect your own medications from the pharmacy? ☐ Yes ☐ No

   If no, how do you get them? _____

2. Are your prescriptions always dispensed at the same pharmacy? ☐ Yes ☐ No

   If no, how many pharmacies do you use? _____

3. Does anyone help you to use or take your medication correctly? ☐ Yes ☐ No

   If yes, please tell us who helps _____

4. Do you ever accidently forget to take your medication? ☐ Yes ☐ No

   If yes, how many times in the last week have you forgotten to take one or more of your

   medications? ☐ Zero ☐ Once ☐ Twice or more

5. Do you ever intentionally not take your medication? ☐ Yes ☐ No

   If yes, how many times in the last week have you intentionally not taken one or more

   of your medications? ☐ Zero ☐ Once ☐ Twice or more

6. Do you use anything to help you remember to use or take your medication?
   ☐ Alarm or beeper   ☐ Calendar or diary
   ☐ Medication pack (e.g. pill box, Webster)   ☐ Medication list
   ☐ Mobile phone application   ☐ Other _____

7. Do you use any other medication aids?
   ☐ Eye drop aid   ☐ Inhaler aid
   ☐ Pill cutter   ☐ Other _____

8. How would you rate the complexity or difficult of taking ALL of your medicines as
   prescribed on a scale from 1 (very simple) to 5 (very complex)?

   (Very simple) 1---------2---------3---------4---------5   (Very complex)

Study ID: _____

9. For each statement, put a (✓) in the box that best describes your experiences.

Statements	Never	Rarely	Some-times	Often	Always
I have strict routines for using my regular medicines					
I keep my medicines close to where I need to use them					
I ensure I have enough medicines so that I don't run out					
I strive to follow the instructions of my doctors					
I get confused about my medicines					
I make changes in the recommended management to suit my lifestyle					
I put up with my medical problems before taking any action					
I alter my recommended management based on how I am feeling					

Part D: Some questions about your health

10. Have your living arrangements changed in the last 6 months? ☐ Yes   ☐ No

    If Yes, what are your current living arrangements? _____

11. In the last six (6) months, (approximately) how many times have you seen your regular GP? _____

12. a) In the last six (6) months, how many GPs and specialist doctors have you seen other than your regular GP? _____

    b) How many of those other GPs/specialists have prescribed medications for you? _____

13. In the last six (6) months, have you had any home visits from a nurse? ☐ Yes   ☐ No

    If Yes, what was the nature of the visit(s)? _____

    _____

14. In the last six (6) months, how many times have you has an unplanned admission to a hospital or a visit to an accident and emergency unit? _____

15. In the last six (6) months have you experienced any symptoms or problems that you think might have been side effects from your medications?

    ☐ Dizziness   ☐ Falls   ☐ Drowsiness/tiredness

    ☐ Confusion   ☐ Hallucinations   ☐ Blurred vision

    ☐ Constipation   ☐ Diarrhoea   ☐ Dry mouth

    ☐ Others _____

16. In the last six months (since _____/_____ month/year) have you had any further appointments at the Austin Health CDAMS clinic? ☐ Yes   ☐ No

Study ID: _____

17. Mini-Mental State Examination

(To be administered by the investigator in accordance with guidelines for administration and scoring instructions)

STANDARDIZED MINI-MENTAL STATE EXAMINATION (SMMSE)

		QUESTION	TIME ALLOWED	SCORE
1	a.	*What year is this?*	10 seconds	/1
	b.	*Which season is this?*	10 seconds	/1
	c.	*What month is this?*	10 seconds	/1
	d.	*What is today's date?*	10 seconds	/1
	e.	*What day of the week is this?*	10 seconds	/1
2	a.	*What country are we in?*	10 seconds	/1
	b.	*What province are we in?*	10 seconds	/1
	c.	*What city/town are we in?*	10 seconds	/1
	d.	*IN HOME – What is the street address of this house?* *IN FACILITY – What is the name of this building?*	10 seconds	/1
	e.	*IN HOME – What room are we in? IN FACILITY – What floor are we on?*	10 seconds	/1
3		SAY: *I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.* Say the following words slowly at 1-second intervals - **ball/ car/ man**	20 seconds	/3
4		*Spell the word WORLD. Now spell it backwards.*	30 seconds	/5
5		*Now what were the three objects I asked you to remember?*	10 seconds	/3
6		SHOW wristwatch. ASK: *What is this called?*	10 seconds	/1
7		SHOW pencil. ASK: *What is this called?*	10 seconds	/1
8		SAY: *I would like you to repeat this phrase after me: No ifs, ands or buts.*	10 seconds	/1
9		SAY: *Read the words on the page and then do what it says.* Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads and does not close their eyes, repeat up to three times. Score only if subject closes eyes	10 seconds	/1
10		HAND the person a pencil and paper. SAY: *Write any complete sentence on that piece of paper.* (Note: The sentence must make sense. Ignore spelling errors)	30 seconds	/1
11		PLACE design, eraser and pencil in front of the person. SAY: *Copy this design please.* Allow multiple tries. Wait until person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between two 5-sided figures.	1 minute	/1
12		ASK the person if he is right or left-handed. Take a piece of paper and hold it up in front of the person. SAY: *Take this paper in your right/left hand* (whichever is non-dominant), *fold the paper in half once with both hands and put the paper down on the floor* . Score 1 point for each instruction executed correctly.	30 seconds	
		Takes paper correctly in hand		/1
		Folds it in half		/1
		Puts it on the floor		/1
		TOTAL TEST SCORE		**/30**

18. Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems with walking around ❑

I have slight problems with walking around ❑

I have moderate problems with walking around ❑

I have severe problems with walking around ❑

I am unable to walk around ❑

PERSONAL CARE

I have no problems with washing or dressing myself ❑

I have slight problems with washing or dressing myself ❑

I have moderate problems with washing or dressing myself ❑

I have severe problems with washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

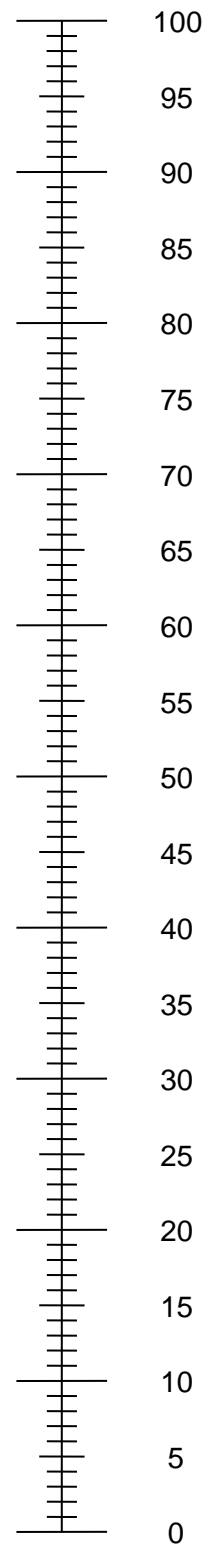**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

The best health
you can imagine

- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.

- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

100

95

90

85

80

75

70

65

60

55

50

45

40

35

30

25

20

15

10

5

0

The worst health
you can imagine

Part E: Some questions about your experiences in the study

Thinking about the memory clinic pharmacist home medication review that you had on _____/_____/_____, can you answer the following questions:

19. We would like to know whether you think the memory clinic pharmacist home medication review was helpful for you. Can you tell as whether it was helpful, on a scale from 1 (not helpful) to 5 (very helpful)?

    (Not helpful)   1---------2---------3---------4---------5   (Very helpful)

20. What was the main reason why you found the home medication review helpful/not helpful? _____

    _____

21. The memory clinic pharmacist contacted you after the home medication review to see how you were going and provided additional advice if it was needed. We would like to know whether this follow-up was helpful. How would you rate this follow-up on a scale from 1 (not helpful) to 5 (very helpful)?

    (Not helpful)   1---------2---------3---------4---------5   (Very helpful)

22. What was the main reason why you found the pharmacist follow-up helpful/not helpful? _____

    _____

23. The memory clinic pharmacist sent a report about your medication use to your local community pharmacist. Did your community pharmacist speak to you about the report?

    ☐ Yes   ☐ No   ☐ Unsure

24. *For patients who had medication changes as a result of the intervention:* Did your community pharmacist ask you how you were going with your medication after your doctor made changes?

    ☐ Yes   ☐ No   ☐ Unsure

25. How important do you think it is to have pharmacist involvement in the memory clinic team on a scale from 1 (not important) to 5 (very important)?

    (Not important)   1---------2---------3---------4---------5   (Very important)

26. How comfortable were you with a pharmacist being involved in stopping one or more of your regular medications (whilst informing your doctor of the progress)?

☐ Uncomfortable   ☐ Comfortable   ☐ Unsure

27. Are there any additional services or help you would have liked to receive from the pharmacist or the memory clinic which would have allowed you to better manage your medications?

☐ Yes   ☐ No   ☐ Unsure

If Yes, please describe: _____

_____

Appendix 7: Chapter 4 – Focus group and interview guides

- Memory clinic focus group guide

- Intervention pharmacist interview guide

Deprescribing Potentially Inappropriate Medication in Memory clinic patients

(DePIMM): Memory Clinic Focus Group Guide

Questions:

1. **Do you think it is the memory clinic's role to review patient's medication regimens and recommend deprescribing?**

   Prompts
   a. For medication known to affect cognition (e.g. anticholinergics)?
   b. For all prescription medications?
   c. For over-the counter medications (e.g. complementary medications)?

2. **How useful were the medication review/deprescribing reports prepared by the memory clinic pharmacist during this study?**

   Prompts
   a. Useful for providing a verified, accurate medication list/history?
   b. Useful for identifying potentially unnecessary or inappropriate medications?
   c. Useful for providing deprescribing recommendations?
   d. Useful for identifying other medication-related problems, such as issues relating to adherence or medication management?
   e. Advantages/disadvantages of the reports?
   f. Were the pharmacists' recommendations appropriate?
   g. Do you think the intervention improved patient care?

3. **Do you think memory clinic patients should have a pharmacist consultation as part of the memory clinic service?**

   Prompts
   a. Advantages or disadvantages of such a service?
   b. Best time for pharmacist consultation?
   c. Best setting for the consultation (e.g. clinic or home)?
   d. Should pharmacist be present during memory clinic or case conference? If so, what would their role be? Benefits and challenges with such a role?
   e. Would you prefer a dedicated 'memory clinic' pharmacist or would you be happy to use the hospital outreach service? What are the pros and cons?

4. **Do you have any other comments on the DePIMM study?**

Deprescribing Potentially Inappropriate Medication in Memory clinic patients (DePIMM): Intervention Pharmacist Interview Guide

General feedback

1. Overall, how did you find your experience working as the memory clinic pharmacist?
   - Like/dislike? What did you like? What did you not like so much?
   - Do you think the role is important?
   - Would it have been useful to spend time regularly in the clinic or attending case conference?
   - Any other suggestions for improvement?

Patients

2. How did you find the home consultations with the memory clinic patients?
   - Were they receptive?
   - Do you think they benefitted?
   - Did you have any challenges?
   - Do you think it was worth visiting them at home vs the memory clinic?

Memory Clinic Doctors

3. How did you find your interactions with the memory clinic doctors?
   - Were they supportive?
   - Did you receive much input regarding your pharmacist reports?
   - Was there sufficient, timely communication?
   - Did you experience any challenges?
   - Any suggestions to improve the interactions?

GP

4. How did you find your interactions with GPs?
   - Were they receptive to recommendations?
   - Did you get feedback on reasons for/against implementation?
   - Was there sufficient, timely communication?
   - Did you experience any challenges?
   - Any suggestions to improve the outcomes?

Community pharmacists

5. How did you find your interactions with community pharmacists?
   - What interactions occurred?
   - Were they receptive to recommendations?
   - Was there sufficient, timely communication?
   - Did you experience any challenges?
   - Any suggestions to improve the communication?