THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

Optimising prescribing in frail older people

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MSc Pharm

A thesis submitted for the degree of Doctor of Philosophy at
The University of Queensland in 2015

School of Pharmacy

Abstract

The ageing of the population, while a societal success, presents many challenges to healthcare systems. One such challenge relates to prescribing practices for older people. While many older people remain robust and independent, others become frail, suffer chronic diseases, receive multiple medications, and are susceptible to adverse drug events (ADEs). Prescribing is further influenced by age-related changes in drug pharmacokinetics and pharmacodynamics. Identifying ways for optimising prescribing and minimizing harm in this vulnerable population is increasingly a priority for health care providers and policy makers.

The overall aim of this thesis was to determine how to optimise medication prescribing in frail older people. Four connected study phases were conducted to address the overall aim and to inform the development of a best practice guideline for prescribing in frail older people.

The first part of this thesis explored the relationship between polypharmacy and adverse outcomes among older hospital inpatients stratified according to their frailty status. This was a secondary analysis of a prospective study of 1418 patients, aged 70 and older, admitted to 11 hospitals across Australia. Patients had a mean (SD) age of 81 (6.8) years and 55% were female. Polypharmacy (5-9 drugs per day) was observed in 684 (48.2%) and hyper-polypharmacy (≥10 drugs) in 497 (35.0%) patients. In total, 591 (42.5%) patients experienced at least one adverse outcome. The only adverse outcome associated with polypharmacy was delirium. Within each polypharmacy category, frailty was associated with adverse outcomes and the lowest overall incidence was among robust patients prescribed 10 or more drugs. While polypharmacy may be a useful signal for medication review, in this study it was not an independent predictor of adverse outcomes for older inpatients. Assessing the frailty status of patients better appraised risk. Extensive de-prescribing programs in all older inpatients may not be an intervention that directly improves outcomes.

The second part of this thesis assessed the frequency and nature of risk factors for potentially inappropriate prescribing (PIP) in patients discharged to residential aged care facilities (RACF) (from the larger cohort of 1418 patients in the previous study). The study

revealed that 54.4% of patients were on at least one potentially inappropriate medication (PIM) at admission to hospital with a non-significant trend to fewer PIMs on discharge (49.5%). The frailty status of patients and in-hospital cognitive decline were the only significant predictors of the number of PIMs received at both admission and discharge. The findings of this study provided a basis for designing interventions to rationalize prescribing in frail older patients in RACFs.

In third part of this thesis, the recommendations on medication by specialist geriatricians were evaluated in a prospective observational study conducted on residents in four RACFs in Queensland, Australia via video-conferencing (VC). Four geriatricians assessed a total of 153 patients. They were prescribed a mean (SD) of 9.6 (4.2) regular medications. Of total 1469medications prescribed, geriatricians recommended withdrawal of 145 (9.8%) and dose alteration of 51 (3.5%). New medications were initiated in 73 (47.7%) patients. Of the 151 (10.3%) medications considered as potentially inappropriate, 26 (17.2%) were stopped and the dose altered in 4 (2.6%). Geriatricians made relatively few changes, suggesting either that, on balance, prescription of these medications was appropriate or, because of other factors, there was a reluctance to adjust medications. A structured medication review using an algorithm for withdrawing medications of high disutility might help optimise medications in frail patients. A follow up study on 50 patients was also conducted to review the impact of these recommendations 3 months after the initial consultation to determine the extent to which the medication changes had been implemented and maintained. A total of 126 recommendations were made by a geriatrician of which only 17 (13.5%) were not followed.

In the final part of this thesis, we developed a pragmatic, easily applied algorithm for medication review to help clinicians identify and discontinue potentially inappropriate medications that predispose older patients, particularly those who are frail, to develop various geriatrics syndromes. The algorithm captures a range of different clinical situations in relation to PIMs and offers an evidence-based approach to identifying and, if appropriate, discontinuing such medications. Decision support resources were developed to complement the algorithm in ensuring a systematic and patient-centred approach to medication discontinuation. Further studies are required to evaluate the effects of the algorithm on prescribing decisions and ultimately, patient outcomes.

In conclusion, optimising prescribing in frail older people is achievable by accurate identification of frail patients in clinical settings and individualisation of medication prescribing based on each patient's own goals of care and frailty status. Future work should focus on the incorporation of frailty measures into clinical studies to improve medication use in frail older people. A routine use of a medication review algorithm may improve the quality of prescribing.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Peer-reviewed papers (published):

Poudel A, Hubbard RE, Nissen L, Mitchell C. Frailty: a key indicator to minimize inappropriate medication in older people. QJM. 2013; 106(10):969-75.

Poudel. A, Hubbard RE, Nissen L, Mitchell C. Are prescribing indicators essentially representing the frail older population? J Frailty Aging. 2013; 2(2):199.

Poudel A, Peel NM, Nissen L, Mitchell C, Hubbard RE. A systematic review of prescribing criteria to evaluate appropriateness of medications in frail older people. Rev Clin Gerontol. 2014; 24(04):304-18.

Poudel A, Peel NM, Nissen L, Mitchell C, Gray LC, Hubbard RE. Potentially Inappropriate Prescribing in Older Patients Discharged From Acute Care Hospitals to Residential Aged Care Facilities. Ann Pharmacother. 2014; 48(11):1425-33.

Hopcroft P, Peel NM, **Poudel A**, Scott IA, Gray LC, Hubbard RE. Prescribing for older people discharged from the acute sector to residential aged-care facilities. Intern Med J. 2014;44(10):1034-7.

Hubbard RE, Peel NM, Scott IA, Martin JH, Smith A, Pillans PI, **Poudel A**, Gray LC. Polypharmacy among inpatients aged 70 years or older in Australia. Med. J. Aust. 2015;202:373-377.

Poudel A, Peel NM, Mitchell CA, Gray LC, Nissen LM, Hubbard RE. Geriatrician interventions on medication prescribing for frail older people in residential aged care facilities. Clin Interv Aging. 2015.10

Poudel A, Ballokova A, Hubbard RE, Gray LC, Mitchell CA, Nissen LM, Scott IA. An algorithm of medication review in frail older people: focus on minimising use of potentially inappropriate medications. Geriatr and Gerontol Int. (in press)

Peer-reviewed papers (submitted):

Poudel A, Peel NM, Nissen LM, Mitchell CA, Gray LC, Hubbard RE. Adverse outcomes in relation to polypharmacy in robust and frail older inpatients. Journal of American Geriatrics Society. (Under review at time of thesis submission).

Conference abstracts:

Poudel A, Nissen L, Hubbard R, Mitchell C. Assessment of frailty and prescribing criteria in older people: A systematic review. Australian Pharmaceutical Science Association (APSA), Annual Conference: December 2-5, 2012, Sydney, Australia.

Poudel A, Nissen L, Mitchell C, Peel NM, Gray LC, Hubbard RE. Potentially inappropriate prescribing in older patients admitted to acute care hospitals and discharged to residential aged care facilities. The American Geriatrics Society, Annual Scientific Meeting: May 15-17, 2014, Florida, USA.

Poudel A, Peel NM, Nissen L, Mitchell C, Hubbard RE. The impact of frailty and polypharmacy on adverse outcomes in older inpatients. The American Geriatrics Society,Annual Scientific Meeting: May 15-17, 2014, Florida, USA.

Poudel A, Peel NM, Nissen L, Mitchell C, Gray LC, Hubbard RE. Inappropriate prescribing in older people. Universitas21 Graduate Research Conference- Celebrating Ageing Research. July 1-4, 2014, Auckland, New Zealand.

Poudel A, Nissen L, Mitchell C, Peel NM, Gray LC, Hubbard RE. Potentially Inappropriate Prescribing in Older People Discharged to Residential Aged Care Facilities. The 18th International Social Pharmacy Workshop: August 5-8, 2014, Boston, USA.

Poudel A, Gray LC, Mitchell C, Nissen LM, Hubbard RE. Geriatrician consultations on appropriate prescribing for frail older people in residential aged care facilities. British Geriatrics Society Autumn Scientific Meeting: October 15-17, 2014, Brighton, UK.

Poudel A, Ballokova A, Hubbard RE, Gray LC, Mitchell C, Nissen LM, Scott IA. An Algorithm of Medication Review in Residential Aged Care Facilities: Focus on Minimizing Use of High Risk Medications. Australian Pharmaceutical Science Association (APSA), Annual Conference: December 5-7, 2014, Brisbane, Australia.

Poudel A, Nissen L, Mitchell C, Peel NM, Gray LC, Hubbard RE. Effect of frailty status on adverse outcomes from polypharmacy in older inpatients. interRAI Network of Excellence in Acute Care (iNEAC) Symposium Meeting: April 21-22, 2015, Lausanne, Switzerland.

Publications included in this thesis

This thesis includes five original manuscripts, including published papers (n=3), paper accepted for publication (n=1) and paper submitted for publication (n=1) in peer-reviewed international journals.

Incorporated in Chapter 1

Poudel A, Peel NM, Nissen L, Mitchell C, Hubbard RE. A systematic review of prescribing criteria to evaluate appropriateness of medications in frail older people. Reviews in Clinical Gerontology. 2014; 24(04):304-18.

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Charles A Mitchell	Edited the paper (20%)
Ruth E Hubbard	Conception and design of the project (20%) Edited the paper (30%)

Incorporated as Chapter 2

Poudel A, Peel NM, Nissen LM, Mitchell CA, Gray LC, Hubbard RE. Adverse outcomes in relation to polypharmacy in robust and frail older inpatients.

Paper submitted as a research article to Journal of the American Geriatrics Society (Under review at time of thesis submission)

Contributor	Statement of contribution
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Nancye M Peel	Data analysis (20%) Edited the paper (30%)

Lisa M Nissen	Data analysis (10%) Edited the paper (15%)
Charles A Mitchell	Edited the paper (15%)
Leonard C Gray	Edited the paper (10%)
Ruth E Hubbard	Conception and design of the project (50%) Edited the paper (30%)

Incorporated as Chapter 3

Poudel A, Peel NM, Nissen L, Mitchell C, Gray LC, Hubbard RE. Potentially Inappropriate Prescribing in Older Patients Discharged From Acute Care Hospitals to Residential Aged Care Facilities. Annals of Pharmacotherapy. 2014; 48(11):1425-33.

Contributor	Statement of contribution
Arjun Poudel (Candidate)	Conception and design of the project (60%) Data analysis (80%) Wrote the paper (100%)
Nancye M Peel	Edited the paper (10%)
Lisa M Nissen	Conception and design of the project (20%) Edited the paper (30%)
Charles A Mitchell	Conception and design of the project (10%) Data analysis (20%) Edited the paper (30%)
Leonard C Gray	Edited the paper (10%)
Ruth E Hubbard	Conception and design of the project (10%) Edited the paper (20%)

Incorporated in Chapter 4

Poudel A, Peel NM, Mitchell CA, Gray LC, Nissen LM, Hubbard RE. Geriatrician interventions on medication prescribing for frail older people in residential aged care facilities. Clinical Interventions in Aging. 2015.10

Contributor	Statement of contribution
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Leonard C Gray	Edited the paper (10%)
Lisa M Nissen	Conception and design of the project (10%) Edited the paper (20%)
Ruth E Hubbard	Conception and design of the project (30%) Edited the paper (30%)

Incorporated as Chapter 5

Poudel A, Ballokova A, Hubbard RE, Gray LC, Mitchell CA, Nissen LM, Scott IA. An algorithm of medication review in frail older people: focus on minimising use of potentially inappropriate medications.

Paper has been accepted for publication in Geriatrics and Gerontology International. (in press)

Contributor	Statement of contribution
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Anna Ballokova	Conception and design of the project (20%) Analysis and interpretation of the results (20%)
Ruth E Hubbard	Conception and design of the project (10%) Edited the paper (30%)
Leonard C Gray	Edited the paper (10%)
Charles A Mitchell	Edited the paper (15%)
Lisa M Nissen	Edited the paper (15%)
Ian A Scott	Conception and design of the project (20%) Edited the paper (30%)

Contribution by others to the thesis

Professor Lisa Nissen was the principal doctorial academic advisor, Associate Professors Ruth Hubbard and Charles Mitchell were the associate advisors. All advisors oversaw all aspects of data collection, interpretation and analysis.

Dr. Nancye Peel is recognised for the intellectual support, help in data analysis and editing of the manuscripts.

Dr Melinda Martin Khan is recognised for her assistance in ethical application.

Professor Len Gray is recognised for the intellectual support in the planning of the study (chapter 4) and perusal and editing of the manuscripts.

A/Professor Ian Scott is recognised for the intellectual support in the interpretation of results and assistance in formulating an algorithm of medication review (chapter 5).

Statement of parts of the thesis submitted to qualify for the award of another degree

None

Acknowledgements

Attainment of this doctoral thesis was possible with the support from several people. I would sincerely like to thank them all for their help along the way.

Foremost, I would like to express my sincere gratitude to my three supervisors, Professor Lisa Nissen, Associate Professor Ruth Hubbard and Associate Professor Charles Mitchell. By possessing different scientific and personal skills, you have formed a high quality supervising team that has guided me professionally from day one through to the final day of submission.

Lisa, you have been a tremendous mentor for me. Your continued support and advice on both research as well as on my career have been priceless. You have oriented and supported me with promptness and care, and have always been patient and encouraging in times of difficulties. Ruth, thank you so much for your support and guidance throughout this PhD. I am very grateful that you accepted to supervise and involved me in the frailty research. Without your guidance and persistent help this dissertation would not have been possible. Charles, thank you very much for your supervision, inspiring advice and a constant support. Your timely words of wisdom and help to improve my scientific writing and presentation skills are greatly appreciated.

My special thanks go to Dr Nancye Peel for her help and crucial contribution to this project as a whole. You have always made time out of your busy schedule to assist me in all possible ways. I am so very grateful to have received advice and feedback from someone with such specialised knowledge and experience. Your involvement has triggered and nourished my intellectual maturity that I will benefit from, for a long time to come.

I am extremely thankful and indebted to Professor Len Gray for sincere and valuable guidance and encouragement extended to me. Also, I would like to acknowledge the scientific support and help that I received from Associate Professor Ian Scott. Many thanks to Dr Melinda Martin Khan for your assistance in ethical application.

I am very grateful to the International Postgraduate Research Scholarship (IPRS) and UQ Centennial Scholarship which provided invaluable financial support during my PhD. Thank you to the School of Pharmacy academics, staff, and students, for their assistance and

cooperation. To all my other colleagues at Centre for Research in Geriatric Medicine, thank you for your support and friendship over the last years.

My special thanks go to my dear friends and relatives who have always listened, encouraged and shared fun moments to make me forget study-related concerns. In particular, I would like to thank Saval, Sanjiv, Sundar, Sabbu, Suja, Sanjaya, Suraj, Sapana, Sarada, Anjali and Ramesh for invaluable friendship and help during the last three years in Brisbane.

To Anna, I am forever grateful for your friendship. Thank you for all the pep-talks, coffee breaks and precious memories alongside. My dear friend Palisma – thank you for everything. I would not have made it through this without your support. I thank Aarati and her wonderful family who have been considerate during tough times. They seemed to assume that I would do fine, and this helped me more than they know.

Finally, thanks to my family. Words cannot express how grateful I am for all of the sacrifices that you've made on my behalf. Your constant inspiration and unwavering belief kept me focused and motivated. I thank you so much for your love, support and significant influence in my life.

Keywords
adverse outcomes, algorithm, frailty, potentially inappropriate medications, inappropriate prescribing, medication review, older people, polypharmacy, residential aged care facilities

Australian and New Zealand Standard Research Classifications (ANZSRC)
ANZRC code: 110308, Geriatrics and Gerontology, 50%

ANZSRC code: 111702, Aged Health Care, 40%

ANZRC code: 111503, Clinical Pharmacy and Pharmacy Practice, 10%

Fields of Research (FoR) Classification
FoR code: 1103: Clinical Sciences, 70%

FoR code: 1117: Public Health and Health Services, 30%

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List of Abbreviations

AC	Acute Care
ACEI	Angiotensin Converting Enzyme Inhibitor
ACOVE	Assessing Care of Vulnerable Elders
ADR	Adverse drug Reaction
ADE	Adverse Drug Event
ADL	Activities of Daily Living
AGS	American Geriatrics Society
AOU	Assessment of Underutilization
ATC	Anatomical Therapeutic Chemical
BADL	Basic Activities of Daily Living
CAO	Composite Adverse Outcome
CDSS	Clinical Decision Support System
CES-D	Centre for Epidemiologic Studies Depression
CGA	Comprehensive Geriatric Assessment
COPD	Chronic Obstructive Pulmonary Disease
CNS	Central Nervous System
CPG	Clinical Practice Guideline
CPS	Cognitive Performance Scale
CRGM	Centre for Research in Geriatric Medicine
CSHA-CFS	Canadian Study of Health and Aging- Clinical Frailty Scale
DBI	Drug Burden Index
DDI	Drug Drug Interaction
DRP	Drug Related Problem
DUR	Drug Utilization Review
ECG	Electrocardiogram
ED	Emergency Department
FI	Frailty Index
GDS	Geriatric Depression Scale
GEMU	Geriatric Evaluation and Management Unit
GP	General Practitioners
HEDIS	Healthcare Effectiveness Data and Information Set
HMR	Home Medication Review
IADL	Instrumental Activities of Daily Living
IBM	International Business Machine

IMU & PIT	Inappropriate Medication Use and Prescribing Indicators Tool
interRAI	interResident Assessment Instrument.
IP	Inappropriate Prescribing
IPET	Improved Prescribing in the Elderly Tool
IQR	Interquartile Range
ISAR	Identification of Seniors at Risk
MAI	Medication Appropriateness Index
MAO	Monoamine Oxidase Inhibitors
MDS-HC	Minimum Data Set for Home Care
MeSH	Medical Subject Headings
MMSE	Mini-Mental State Examination
MW	Medical Ward
NH	Nursing Home
NORGEP	Norwegian General Practice
NSAIDs	Non-steroidal Anti-inflammatory Drugs
PAH	Princess Alexandra Hospital
PD	Pharmacodynamics
PIM	Potentially Inappropriate Medication
PIP	Potentially Inappropriate Prescribing
PK	Pharmacokinetics
PPO	Potential Prescribing Omission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RACF	Residential Aged Care Facility
RAND	Research and Development
SD	Standard Deviation
SPMSQ	Short Portable Mental Status Questionnaire
SPPB	Short Physical Performance Battery
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older Persons' potentially inappropriate Prescriptions
TCA	Tricyclic Antidepressants
TUG	Timed Up-and-Go Test
UK	United Kingdom
USA	United States of America

VA	Veterans Affairs
VC	Video Conferencing
WHO	World Health Organization

"Longevity is much more valuable if it is accompanied by freedom from suffering, pain or disability. The growing prevalence of chronic diseases and disabilities has brought into focus the need to seek a balance between the length and quality of life "

(World Health Organisation, 1997).

Chapter 1 – Introduction and Literature Review

1.0 Introduction

Old age is associated with chronic diseases and disabilities. Balancing the costs and benefits of healthcare will be the key aim for ageing societies. A strategic shift to prevention and early intervention for those at high risk for dependency and disability is necessary. There is limited evidence on the safety and efficacy of medications in older people, particularly in the frail, who often have multiple comorbidities and functional impairments.(1) The implementation of disease-specific guidelines for the management of the elderly with their multiple chronic diseases results in a large number of prescribed medications. An increasing number of medications is associated with a significantly greater risk of adverse health outcomes.(2) This has been a global problem and limited attention has been given to addressing the medication related factors in the frail older population. Understanding the concept of frailty may help to optimise medication prescribing in older people. Optimisation of prescribing in this vulnerable population using a multidisciplinary approach with frequent monitoring and review might have a major clinical impact.

This chapter describes the demographic changes seen in the elderly and considers prescribing practices in older people. The concept of frailty and its measurement are critically appraised. An overview of the assessment and prevalence of potentially inappropriate medications (PIMs) provides the context for a systematic review that evaluates appropriateness of medications in frail older people using different prescribing criteria.

1.1 The ageing population

The global perspective: In 2013, the population of older individuals aged 60 years or over was 841 million. This is projected to increase to more than 2 billion by 2050.(3)At that point, the older population will exceed the population of children (0-14 years). More than half of the world's older population is in Asia (55%) followed by Europe (21%). The oldest old (aged 80 years and over), account for 14% of those aged 60 years or over. This age group is the most rapidly increasing segment of the older population. It is projected that by 2050, 20% of the older population will be aged 80 years or over. The trend is even more rapidly growing in centenarians (aged 100 years or over) with a projected tenfold increase

from approximately 343,000 in 2012 to 3.2 million by 2050.(4)The demographic trends in both developed and developing countries are moving towards a society with an increasing percentage of people above 60 years of age as shown in Table 1.

Australians setting: The population of older people in Australia is growing absolutely because of an increasing life expectancy and relatively because of the sustained low fertility levels. Australia enjoys one of the highest life expectancies in the world. Among similarly developed countries, Australia was ranked sixth with a mean life expectancy at birth of 84.3 years for females and 79.9 years for males.(5)The population of Australian aged 65 years and over was 2.7 million in 2006, representing 13% of the total population. Of those aged 65 years and over,52% were aged 65-74 years, 36% aged 75-84 years and 12% were over 85 years. In 30 years, the projected growth in those aged 65 years and over is expected to be more than double, from 2.7 million to 6.3 million, representing 24% of the total population at that time.(6)

This demographic shift in the age distribution to an increasingly older population has significant social, health and economic impacts. It drives the current focus of governments worldwide in implementing healthy aging services, policies, guidelines and investigations so that the functional decline associated with aging that leads to poorer health outcomes and increased disability, dependence and chronic disease are addressed.(6)

Table 1: Demographic trend in developed and developing countries

Population aged 60 years or over						
Country or area	**Number (thousands)**		**Proportion of total population (percentage)**		**Share of persons aged 80 years or over* (percentage)**	
	2012	**2050**	**2012**	**2050**	**2012**	**2050**
WORLD	809,743	2,031,337	11	22	14	20
Developed countries	279,287	418,326	22	32	20	29
Less developed countries	530,455	1,613,011	9	20	11	17
Least developed countries	46,389	181,568	5	11	8	10

Source: United Nations. Department of Economic and Social Affairs Pd. Population Ageing and Development. 2012.
* Persons aged 80 years or over (the “oldest-old”) as a percentage of the population aged 60 years or over.

1.2 Pharmacotherapy in older people

Although pharmacotherapy represents one of the successes of modern medical interventions, it is a complex process that is not limited to drug prescribing. Pharmacotherapy is not synonymous with drug prescribing: it should encompass age-appropriate drug development and manufacturing, appropriate drug testing in clinical trials, improving quality of life, safety, ease of use, levels of patient adherence, reducing the overall caring costs and age-appropriate outcome monitoring.(7)Prescribing is a critical feature of geriatric medical care. The main aims of prescribing are to cure disease, eliminate or reduce symptoms relating to an underlying disease states and improve functional capacity of the patients.(8)

The appropriate use of available pharmacotherapy requires a balance between the risks and benefits of medications. In older people, prescribing is complex because of the limited evidence on effectiveness of medication in this age group.(9) While most research has focused on the middle-aged, there is a significant knowledge gap in the study of pharmacotherapy in older people. In this group, prescribing is guided mostly by evidence from randomized controlled trials, from which older people, particularly those who are frail, have been excluded.(10) Despite the fact that these populations are rapidly increasing along with the subsequent significant increase in consumption of health care services and their costs, elderly patients have seldom been involved in clinical trials. Regulatory authorities and healthcare industries have for a long time ignored the age-specific aspects of medications in older individuals. As such, the need for a detailed ‘geriatric’ approach in drug development and registration has been recognized and acknowledged by medicine agencies.(11)

1.2.1 Appropriate prescribing

“Safe”, “rational” and “optimal”, are words often used to define standards that should be achieved in prescribing. In the early 1970s, the term ‘appropriate prescribing’ was introduced,(12) as a general concept that comprises a range of different prescribing values and practices. According to the World Health Organization (WHO), appropriate prescribing or the rational use of medicines requires that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" (WHO 1985).(13)Appropriate prescribing is essentially a measure the quality of prescribing.(14) More general descriptions of what constitutes good prescribing have included: maximising

effectiveness, minimising risks, minimising costs and respecting patient choices.(15) While defining the appropriate prescribing practices for an individual patient, a number of factors need to be considered, such as:

- What the patient wants,
- What the patient needs and
- Scientific rationalism (that encompasses clinical pharmacology of certain drugs).

Buetow *et al.* defined appropriateness as "the outcome of a process of decision making that maximises net individual health gains within society's available resources".(16) Appropriateness is then the outcome if the patient receives the "right" drug; regardless of on what grounds the prescribing decision is based. Prescribing can be rational, regarding the process of decision making, but still inappropriate, if the decision is for example based on too little or incorrect information. A 'risk-benefit' approach to appropriate care is defined by the Research and Development (RAND) Corporation as that where 'the expected health benefit (e.g. increased life expectancy, relief of pain, reduction in anxiety, improved functional capacity) exceeds the expected negative consequences (e.g. mortality, morbidity, anxiety of anticipating the procedure, pain produced by the procedure, misleading or false diagnoses) by a sufficiently wide margin that it is worth providing'.(17) However, Hopkins made the point that many clinicians will view examinations of appropriateness as 'cost-cutting' exercises(18) and subsequently added two further dimensions to the definition of appropriateness: the individuality of the patient under consideration, and the availability of healthcare resources.(19)

Appropriate prescribing in older people is further complicated by a number of other factors that increase the complexity of prescribing. Hence, the operational definition of appropriate prescribing has been modified in relation to prescribing for older people as greater heterogeneity is observed in these populations as compared to others.(20, 21) In general, these definitions suggest that the expected benefits to health should outweigh any negative effects.(22) It has also been recommended that the term 'appropriate prescribing' be expanded to include misuse, overuse and underuse of treatments.(23) Since the clinical evidence for the effects of drugs in older people is limited, goals of treatment might change, and social and economic factors might be different or more important for these patients than for a younger population.(24)The following factors must be considered when prescribing for older people (25):

- Life expectancy of the patient
- The right therapeutic approach in patients with a poor prognosis
- Selection of the pharmacotherapy with the most favourable benefit/risk ratio

In theory, appropriate prescribing, can be identified by taking into account the factors that should be addressed in an ideal context. However in practice, many factors are difficult to quantify and they may influence the individual prescriber's decision.

1.2.2 Inappropriate prescribing

Inappropriate prescribing (IP) has been defined as the use of a particular medicine that poses greater risk of harm than benefit, especially when safer and more effective options are available for the same condition.(14, 26) The concept of IP recognises that there are no medications without any risk, whereby appropriate use of medications requires that the risks associated with its use outweigh the anticipated benefits.(27) IP also includes not prescribing sub-optimal doses of medication.(28) Based on the concept of risk-benefit definition of appropriateness, inappropriate medications has been defined as: (29)

1) overuse of a medication where there is no clear indication,
2) misuse of a medication in relation to wrong drug, dose, and duration, or
3) underuse of a medication where there is a clear indication.

Inappropriate prescribing can result from many components of the prescribing context(14, 28, 30-32) such as:

1) Polypharmacy: Polypharmacy indicates the prescribing practice of multiple medications that are considered clinically necessary.(28) The minimum number of medications used to define "polypharmacy" is variable, but generally ranges from 5 to 10.(33, 34) It also includes the practice of prescribing medications at a higher dose, greater frequency or for a period longer than is clinically indicated. Polypharmacy is associated with suboptimal and inappropriate prescribing. Many medications that have an increased tendency to cause problems for older patients have been labelled as inappropriate drugs.(14)

2) Unfavourable risk benefit ratio: IP occurs when the risks of an adverse event associated with a medication use outweigh the clinical benefits, where safe and more effective alternative therapy is available.(35)

3) Prescribing medications with high risk of drug-drug or drug-disease interactions.(35)

4) Prescribing certain medications where there are no specific indication and clinical significance for a specific patient.(14)

5) Under prescribing or underutilization of medications: IP occurs when there is the failure to prescribe a clinically significant medication for a patient for whom there is no valid reason not to prescribe the said medication and for which there is no contraindication to this beneficial pharmacotherapy e.g. if a patient is suffering from a particular disease and no drug is prescribed to treat that particular condition, or the dose of the medication is insufficient to treat that condition effectively.(14)

1.3 Frailty in older people

1.3.1 What is frailty?

While one person may appear fit and well, another, who had seemed just as robust (fit) in recent times, starts to weaken and slow down, sometimes as early as middle age. This is a central issue that is now being systematically addressed by many researchers – that being why some people age well and others do not, often heading along a path that ends up with a medical condition known as frailty.(36)Frailty is a fast emerging research area in geriatric medicine.(37)

In the past, the term “frailty” had many different definitions, often linked with disability and chronic diseases, with most definitions addressing the adverse health outcomes of frailty.(38, 39)Prior to the 1990s, the term frailty was not often used. Winograd *et al* .in 1991, suggested one of the first definitions of frailty based on specific criteria.(40)In the same year, Speechley and Tinetti defined frailty as the occurrence of at least four of the following characteristics: more than 80 years of age, depression, balance and gait difficulties, no exercise, consuming sedatives, diminished shoulder strength, any lower extremity disability, diminished knee strength, and loss of proximate vision.(41) Later

studies defined frailty based on certain types of impaired physiological functioning while the adverse outcomes were not considered.

For example, Buchner and Wagner in 1992 defined frailty as “the state of reduced physiologic reserve associated with increased susceptibility to disability.”(42) Similarly in 1997, Campbell and Buchner defined frailty as “a loss of the person’s capability to withstand minor environmental stresses”(43)In 1998, Woodhouse and colleagues tried to differentiate between fit and frail older people. According to their definition, fit older people were those individuals more than 65 years of age, freely ambulant and living independently at their home or in sheltered accommodation whereas, frail elderly were individuals aged 65 years and over, often living in institutional care with several diseases and highly dependent on others for activities of daily living.(44) A very frequently used definition by Fried *et al.* is criteria based, as a “phenotype characterizing an older people with a high risk of falls, disability, hospitalization and mortality.(45)

The term “frail” is intended to identify those older people at greatest risk of adverse outcomes. Although there is frequent use of this term in medical practice and published papers, there are not any widely accepted definitions or criteria for frailty. While there are different approaches to the definition and measurement of frailty, it is progressively used to identify a vulnerable group of older people at high risk of adverse outcomes including falls, worsening disability, prolonged hospital stays, institutionalization and death.(46)Studies in community-dwelling older populations reported that those who are frail are more likely to die, be admitted to an institution or become more disabled.(45, 47)Predominantly, frailty is linked with increasing age (48)and with co-morbidities.(49)However, frailty is not identical with either advanced age or the presence of disease. Chronological age alone cannot predict inpatient mortality, for example.(50)

1.3.2 Measurement of frailty

Frailty can be measured using three established methods as shown in Table 2. The **first** method; a rules-based approach identifies frailty as a ‘clinical syndrome or phenotype’ (a set of symptoms and signs that tend to occur together, thus characterizing a specific medical condition). The most well-known and widely used phenotype was developed by Fried *et al.* in 2001;it identifies frailty as the presence of ≥ 3 of 5 criteria: weight loss, exhaustion, weak grip strength, slow walking speed, and low physical activity.(45)People

having three or more of these deficits are considered to be frail and those with none are considered robust while when one or two of these deficits is present the term ‘pre-frail’ is used. This phenotype has been validated as a predictor of adverse outcomes in large epidemiological studies (51)and was used to define frailty as the most common condition leading to death in community-dwelling older people.(52) While this model is clinically coherent and reproducible, the omission of disorders of cognition and mood made it controversial since some argue that frailty consists of more than weakness, slowness and wasting.(53, 54)

The **second** method, is based on clinicians ‘subjective opinion’ (55, 56)though this has strong face validity, generalizability is limited.

The **third** method conceptualizes frailty as a ‘multidimensional risk state’ that measures frailty based on the quantity rather than by the nature of health problems.(48)This concept is termed Frailty Index (FI), deficits are counted as an aggregation of features such as symptoms, signs, diseases and disabilities with the principle that ‘the more deficits a person has, the more likely that person is to be frail.’(46)The FI is expressed as a ratio of deficits present to the total number of deficits considered. For example, if a patient has 14 of 40 assessed deficits, the FI of that person would be 14/40 = 0.35. Several studies have shown consistent results using the FI which suggests, the higher the deficit count, the frailer the person is and more vulnerable to adverse outcomes.(57-61)

These approaches differ not only in their processes for measuring frailty but also in their conceptualisation of the aetiology and implications of frailty itself. The frailty phenotype views frailty as a clinical syndrome with the core pathophysiological feature of sarcopenia (the loss of skeletal muscle mass and strength as a result of ageing) caused mainly by age-related changes in hormones.(62) In this model, co-morbidity is distinct from frailty, though the presence of multiple chronic diseases is recognised, somewhat separately, as necessitating a different approach to prescribing.(63) The Frailty Index approach, on the other hand, conceptualises frailty as a state of increased risk of adverse health outcomes due to a variety of accumulated health deficits.(64) These deficits may or may not relate to sarcopenia, and are sometimes, but not always, secondary to comorbid disease.

Table 2: Methods of frailty measurement

Authors	**Frailty (Definition)**	**Components**	**Grades of frailty**	**Measurement**	**Pros/Cons**
Fried *et al.*(45)	Phenotype/Rules-Based Approach	Performance on five variables	Robust: no problems Pre-frail: one or two problems Frail: three or more problems	Clinical Performance-based measures	Pros: Performance based, easy to apply Cons: challenging in immobile patients
Rockwood *et al.*(65)	Frailty Scale (e.g., Canadian Study of Health and Aging-Clinical Frailty Scale)	Single descriptor of a person's state of frailty (fitness)	CSHA-CFS: A 7 point scale ranging from 'very fit' to 'severely frail'	Clinical Judgment	Pros: Subjective, easy to use/implement Cons: Validated for use by specialists, insensitive in some populations
Mitnitski *et al*. (57)	Frailty Index (e.g., Rockwood-Mitnitski Frailty Index)	Deficit count or proportion of potential deficits that a person has accumulated	Range: 0-1.0 Empirical cut-off: <0.25 (robust/pre-frail) ≥ 0.25 (frail) 0.67 (99% upper limit of FI)	Comprehensive Geriatric Assessment Population-based data (survey)	Pros: Simple approach, robust indicator of frailty, reproducible mathematical properties, precise grading Cons: Burdensome in clinical setting

1.3.3 Frailty assessment as a part of a comprehensive geriatric assessment

Comprehensive geriatric assessment (CGA) is a multidimensional process that has long been recognised as the best approach to the management of the clinical complexity in older populations.(66) A CGA explores clinical, functional, cognitive, nutritional and social parameters, leading to an all-inclusive assessment which helps to optimize long-term management, resource planning and the use of services.(67) The proven benefit of CGA has been supported by several studies. One study that randomly assigned 63 frail elderly inpatients with a high probability of nursing-home placement to an innovative geriatric evaluation unit showed that a multidimensional assessment led to an improvement in functional status, discontinuation in the number of prescribed drugs, lower mortality and less time spent in hospital.(68) Another study showed an increased survival in frail older patients with a CGA admitted to a geriatric ward as opposed to a general medical ward.(69) CGA has the potential to optimize drug therapy by the detection of both over- and under-treated disease conditions.(70, 71)Importantly, a FI can be derived from the information collected as part of CGA.(72)

1.3.4 Pharmacokinetics/Pharmacodynamics changes in frail older people

Age and frailty are both likely to affect the pharmacokinetics and pharmacodynamics of medications, and hence should influence prescribing(73) as shown in Figure 1.(74) Age-related physiological changes affect drug absorption, distribution, metabolism and excretion; effects well documented in the literature.(75-78) However, the evidence on the drug responses and evaluation of differences in pharmacokinetics and pharmacodynamics in fit versus frail older people is limited to few studies.(79)

Pharmacokinetics

Absorption: Previous studies reported that age-related changes are associated with drug absorption (80)however recent findings suggest that there is no change in drug absorption with frailty.(81)

Distribution: In frailty, there are an increase in body fat, and decrease in lean body mass; these affect the volume of distribution of drugs. The increased body fat especially alters the distribution of lipophilic drugs such as lidocaine, verapamil and benzodiazepines.(82) This particularly impacts the drug's half-life and estimation of loading dose; shortening at the beginning and prolonged release later which may result in higher plasma levels.(73)

Hence, a smaller volume of distribution is observed in frail adults than in non-frail adults.(74)As well, the serum albumin level is significantly reduced in frail older people. Acidic drugs such as warfarin, valporic acid, lorazepam, digoxin, and ceftriaxone are bound strongly to albumin which makes frail older people receiving acidic drugs prone to toxicity even with normal drug levels.(73)

Metabolism: Drug biotransformation reactions are described as either phase I (oxidation, reduction, hydrolysis) or phase II (methylation, sulphation, glucuronidation). While no change was observed in phase I metabolism,(83) phase II metabolism is likely to be reduced in frail older people.(84) Some enzymes involved in drug metabolism are impacted by frailty but not by chronological age. Studies on paracetamol and metoclopramide revealed that paracetamol clearance was reduced in both fit and frail older people compared to younger controls but when corrected for liver size, the glucuronidation of paracetamol was markedly lower in frail older people compared to their fitter peers.(85) Similarly, clearance of metoclopramide by sulphation was similar in young controls and fit older people but significantly reduced in those with frailty.(86)A study by Hubbard *et al.* that compared the plasma esterase activity in fit and frail older patients found normal plasma esterase activity in the healthy volunteers, which fell significantly with increasing frailty.(87)

Elimination: Drug clearance is likely to be impaired with frailty due to the reduced hepatic and renal size and function in old age (88)which is aggravated by the development of a chronic inflammatory state.(89)There is limited evidence of reduced renal clearance in frail older people. However, older people with chronic renal insufficiency, as demonstrated by higher serum creatinine levels, are more likely to be frail.(90)

Pharmacodynamics: Pharmacodynamic changes in frail older people have not been well documented. Older people have an increased sensitivity to warfarin (91)and to benzodiazepines.(92) A study by Wynne *et al.* reported that frail older people are more sensitive to metoclopramide-related sedation.(86) Moreover, the pharmacodynamics of anticoagulant and immune-modulating medications are influenced by the presence of the procoagulant state seen in chronic inflammation in frail older people.(74)

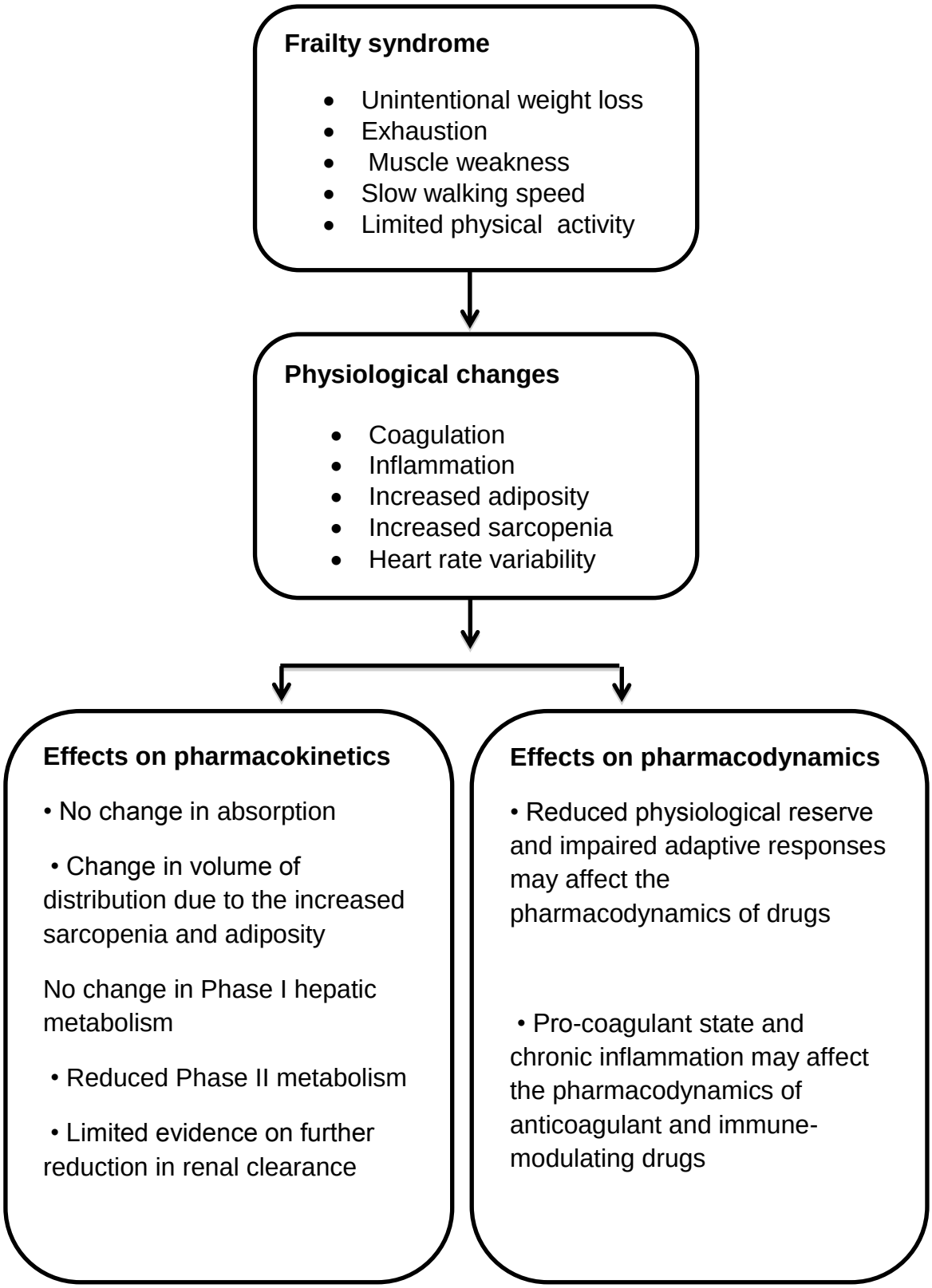


Figure 1: The effect of frailty-associated physiological changes on the pharmacological response in frail older people compared with non-frail older people.

1.3.5 Prescribing in frail older people

Frail older persons often have multiple comorbidities with signs of impairment in activities of daily living.(93) Prescribing drugs for these vulnerable individuals is a difficult and potentially unsafe activity as there is a lack of evidence on drug efficacy in these groups.(94) The anticipated outcome of medication in frail older people is usually generalized from non-frail or robust populations.(95) Rational prescribing in frail older people needs specific expertise knowledge of the factors that contribute to the differences in response to medicines in this group. Factors such as age-related changes in pharmacokinetics and pharmacodynamics, multiple comorbidities, polypharmacy and adherence issues modify drug responses that contribute to an augmented likelihood of adverse drug reactions (ADRs) in frail older people. (88, 96, 97) Also, the wide inter-individual variability with increasing age contributes to different drug responses between fit and frail older people. Avoiding inappropriate medications in the frail older people minimises the risk of adverse drug events (ADEs) since medication-related ADRs are common in frail older people.(98)

Prescribing in frail older people should differ from that in non-frail older people. The primary focus in frail patients with life-limiting conditions is to improve quality of life by reducing the severity of symptoms or by controlling a disease in the short term.(99) Many medications that are commonly prescribed in older people such as psychotropic drugs, cardiovascular agents, and analgesics, are commonly associated with high risk of ADRs.(100) It is essential that frailty status be considered when treatment plans shift away from a curative towards an individualized symptom controlling approach. Understanding frailty could assist the treating medical practitioner to better manage patients who do not fit well into clinical practice guidelines (CPG) and management algorithms.(101) Prescribers need to appreciate that following evidence-based clinical guidelines is appropriate for patients with no or minimal comorbidities but, in those who are frail and disabled, the goals of care and treatment targets need to be readjusted.(67)

Potentially vulnerable older patients should benefit from an approach that evaluates their frailty, considers their remaining life expectancy and identifies diseases with highest priority for treatment instead of treating all diseases. A common example in a frail patient with a life expectancy of few months is the use of statins to lower serum cholesterol levels and hence improve long term cardiovascular disease risk or antiresorptive therapy for osteoporosis, which will have no benefit as the onset of measurable effects, will occur too

late to be of any benefit.(67) If a disease with high priority for treatment is identified, the most appropriate therapy based on the recommendations of the CPGs could be followed, taking into consideration the frailty status of the patient. This involves the use of various tools, guidelines and algorithms to optimize appropriate use of medication. Unfortunately, the available guidelines are not practically applicable to frail older people.

1.4 Optimising pharmacotherapy in older people

The continuing challenge for prescribing physicians and patients is to thoroughly reconsider medications that are really needed (prioritization) and medications that could be stopped (discontinuation).(102) These aspects of pharmacotherapy are central, especially in the care of older people since the goals of care for older patients with reduced life expectancy becomes palliative rather than curative.(103)Discontinuation of unnecessary medications in this vulnerable population demands several considerations such as assessment of geriatric syndromes (those clinical conditions in older persons that do not fit into disease categories such as delirium, falls, incontinence), regular follow up and monitoring of effects, dose adjustments over time as well as discontinuation of medication when indicated.(104)

While many studies focus on the safe and effective initiation of medications in older people, only a handful of studies are conducted with particular attention on the cessation of medications that are no longer required.(79)The cessation of medications has been defined by terms such as deprescribing, discontinuation and withdrawal which should be considered in cases of polypharmacy, ineffective treatment, the presence of ADRs as well as with changes of treatment goals. However, deprescribing should be based on a principle of stopping one medication at a time and gradual weaning of doses over weeks or months.(105)Developing a pragmatic and easily applied algorithm for medication review that offers an evidence-based approach to identifying and, if appropriate, discontinuing such medications might help optimise medications in frail older people.

1.4.1 Screening tools to assess inappropriate medications

Given that pharmacotherapy in older people is challenging and complex, several criteria and tools have been developed to identify IP.(106)Inappropriate prescribing in older people can be detected using explicit (criterion-based) or implicit (judgment-based) methods. These criteria have been developed based on literature reviews, scientific and clinical expertise and on previous established criteria, most of which were validated using

consensus methods while others by using patient medical records.(106)The factors addressed by these tools and criteria in assessing quality of medication prescribing in older people are shown in Table 3. Some criteria assess medications alone; some assess medication and disease states and others factors related to the individual patient. Some approaches use a combination of all of these. None address frailty although several consider some surrogates of frailty.

1.4.1.1 Explicit Criteria: Explicit criteria are generally derived from expert reports or published reviews, consensus methods and pre-determined standards.(14) These criteria include the lists of drugs, dosages or drug classes that should be avoided in older people. They have high reliability and reproducibility but focus mainly on specific drugs and disease states.(74)They do not address patient related factors such as life expectancy, cognition, functional status, co-morbidities and patient preference.(107) Hence, one cannot rely only on explicit criteria for assessing the appropriateness of pharmacotherapy in an individual patient.(108) Yet, explicit criteria are considered applicable in detecting inappropriateness of prescribing in drug charts or databases of larger population. Some commonly used explicit criteria include:

Beers Criteria: The Beers criteria have been the most widely used tool to evaluate PIM use among older people since their development in the US in 1991.(109) Developed by a consensus panel of 13 experts in geriatric care, they were originally designed for older nursing home residents. They identified a total of 30 medications where 19 medications were to be avoided irrespective of diagnoses, doses, durations, and frequencies; while for 11 medications, certain doses, durations, and frequencies of medication therapy were not be exceeded. These criteria were updated in 1997 so that they were applicable to all adults of 65 years and older, regardless of their place of residence.(27) Later in 2003, the list was updated again to include 48 medications to be avoided regardless of diagnosis and 20 medical conditions in which certain drugs should be avoided.(110)Recently in 2012, the criteria have been revised again to address three main domains: i) PIMs to avoid in older people irrespective of diagnoses or conditions; ii) PIMs to avoid with certain drug disease/syndrome interactions; and iii) list of medications to be used with caution.(111) The quality of criteria has been improved using an evidence based approach that now includes a clear indication of the strength of the evidence and of the recommendation. Although the Beers criteria have widespread utilization, they possess several limitations. Many medications in the Beers list are not available in countries other than the USA and

some medications from the list, for example methyldopa, are rarely used in everyday clinical practice in older patients. Moreover, the Beers criteria do not address other important domains of IP such as under-prescribing, drug duplication and drug-drug interaction.(26)

Screening Tool of Older Person's potentially Inappropriate Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START): In 2008, a group of 18 specialists in geriatric pharmacotherapy from Ireland and the UK validated the Screening Tool of Older Person's potentially Inappropriate Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) using the Delphi consensus methodology (a widely used and accepted method for gathering data from respondents within their domain of expertise).(112)The STOPP criteria address 65 indicators of inappropriate prescribing with special attention to drugs that adversely affect older patients at risk of falls, drug-drug interaction, drug-disease interaction and drug duplication. Each criterion is supported by a concise description that explains why the specific medication is potentially inappropriate.(107)

The START criteria include 22 evidence-based prescribing indicators highlighting potentially serious errors of prescribing omission in older people.(112) In cases where the life expectancy and functional status of patients justifies the prescribed medicines and where there is no contraindication to prescribed medications, these criteria identify under-prescribing.(107) Both STOPP and START criteria have good inter-rater reliability between pharmacists and physicians.(113, 114) Studies using the STOPP criteria identified 21% of prescriptions as IP in primary care (115), 35% in hospitals (116) and 60% in long term residential care.(117) On the other hand, studies using the START criteria in primary care identified prescribing omission in 23% of patients and in 57% in hospitals.(117) However, the application of the STOPP and START criteria make them time consuming and further studies across different settings and countries are needed.

Table 3: Prescribing indicators that are addressed by the Tools/Criteria involved in assessing quality of medication prescribing in older people

Components that measure prescribing appropriateness	**Assessment criteria**									
	Addressed by Beers criteria[32]				**McLeod Criteria[33]**	**STOPP and START[35]**	**IMU & PIT[36]**	**MAI[38]**	**A 10-step Conceptual Framework[3] [9]**	**Good Palliative-Geriatric Practice Algorithm[40]**
	1991	**1997**	**2003**	**2012**						
	Medication and disease related factors									
Drugs	✓	✓	✓	✓					✓	✓
Dose	✓	✓	✓	✓		✓	✓	✓	✓	✓
Duration	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Under prescribing						✓	✓			
Drug-drug interactions					✓	✓	✓	✓		✓
Drug-disease interactions		✓	✓	✓	✓	✓	✓	✓	✓	✓
Effectiveness				✓			✓	✓	✓	
Drug indication						✓	✓	✓	✓	✓
Drug duplication						✓	✓	✓	✓	
Medication cost								✓		
	Patient related factors									
Frailty (Cognition, mood and behaviour, functional status (ADL), continence, etc.)							✓*		✓*	✓*
Falls, fatigue						✓	✓			
Life expectancy									✓	

***Studies that included some surrogates of frailty.**

STOPP: Screening Tool of Older Person's Prescriptions; **START:** Screening Tool to Alert Doctors to Right Treatment; **IMU & PIT:** Inappropriate Medication Use and Prescribing Indicators Tool; **MAI:** Medication Appropriateness Index.

McLeod Criteria: These criteria for identifying inappropriate prescribing in older patient were developed by a 32 member national board of experts in 1997 in Canada.(118) They developed a list of 71 indicators in prescribing for older patients and ranked the clinical implication of each on a scale of 1 (not significant) to 4 (highly significant). IP was initially classified into three types: i) medications that are contraindicated for older people because of an unacceptable risk-benefit ratio. ii) medications that are prone to cause drug-drug interactions and iii) medications that are prone to cause drug-disease interaction.(118) Unfortunately, these criteria have a limited applicability to geriatric clinical practice.(119) The major limitation for application of this criteria was the need for patient-specific information such as indication for the medication, its intended duration of use and detecting co-morbidities.(120)

Improved Prescribing in the Elderly Tool (IPET): Naugler *et al.* published the IPET criteria in 2000, updating McLeod's criteria of assessing IP.(121)IPET contains a list of 14 situations where IP could be avoided. Although the IPET criteria are brief and concise, they have a number of limitations. They had a strong focus on cardiovascular and psychotropic drugs as well as NSAIDs and other drug categories are under-represented.(107)Moreover, the recommendation to avoid beta-blockers in heart failure and avoidance of benzodiazepines with long half-lives under any circumstances makes IPET even more difficult to use in contemporary clinical practice.(122)

Zhan's Criteria: The Zhan criteria were developed in 2001 in North America by a group of seven experts in geriatric medicine, pharmacy and pharmaco-epidemiology.(123)They used a modified Delphi technique to identify a total of 33 inappropriate medications that are based on the 1997 version of the Beers criteria. Zhan divided inappropriate medications into three groups: i) those medications to be avoided always ii) those medications that are rarely appropriate; and iii) those medications that have some indications but are frequently misused. Like Beers, Zhan's criteria contain medications that are not available or prescribed outside of the US.(123)

A 10-step Conceptual Framework: To minimize inappropriate medications in older population, a quality use of medicine framework was developed by a panel of researchers in Australia.(124) This framework comprises 10 steps that aim to decrease IP in older patients to the minimum number of essential drugs. The systematic and individualized approach of this framework identifies the medications that are of little or no benefit in

individual older patients with assistance on discontinuing them. Unlike other tools and criteria, it focuses on both medication related and medication management related aspects of appropriate prescribing which ultimately addresses the gap observed in other tools. However, further studies are needed to validate this framework as a practical approach for clinical decision making for appropriate prescribing in vulnerable older patients.(124)

1.4.1.2 Implicit Criteria: Implicit tools and criteria of identifying IP usually focus on the individual patient and rely on professional judgment of clinicians to assess every medication the patient receives. This makes implicit criteria more time consuming and impractical in busy clinical settings and the result depends upon the clinical knowledge and skills of the person using them.(14)Unlike explicit approaches that focus predominantly on medication or disease, implicit criteria address patient preferences and certain aspects of patient's vulnerability.(74) Moreover, implicit criteria are independent of national drug formularies that make them easily transferable across countries.(106)

Some commonly used implicit criteria are:

Medication Appropriateness Index (MAI): The Medication Appropriateness Index (MAI) was developed in the US in 1991;it evaluates each drug with 10 elements of prescribing: indication, effectiveness, dose, correct directions, practical directions, drug–drug and drug–disease interactions, duplication, duration and cost.(125) The evaluator rates the medication as 'appropriate', 'marginally appropriate', or 'inappropriate' for each criterion. Whilst the method can be applied to older populations, it has several limitations. The MAI does not identify under-prescribing and whilst it has a good reliability in ambulatory settings, but there is no clear evidence of its effectiveness in the community setting and the generalizability of the instrument as used by other clinicians is unknown.(126, 127)

Lipton Criteria: In 1990, Lipton *et al.* developed and validated these criteria in the US using a panel of experts assessing patient cases.(128, 129)To assess the appropriateness of each prescription, these criteria were grouped into six categories: dosage, frequency, drug allergy, appropriate choice of drug therapy, duplication and drug-drug interactions (DDIs). An advantage of the Lipton's criteria is its use of explicit categories and definitions, together with the ability of the prescriber to apply implicit judgment. However these criteria were tested in a small patient population and therefore warrant further reliability and validity testing among larger geriatric populations.(130)

Assessment of Underutilization of Medication (AOU) Tool: This tool was developed to address under-prescribing, an important aspect of inappropriate prescribing, which was lacking in the MAI.(131) It identifies the omission of indicated medications by comparing the list of chronic conditions with prescribed medicines.

1.4.1.3 Combined explicit and implicit criteria: A few researchers have combined explicit and implicit criteria to assess inappropriate prescribing. Examples are:

Australian Prescribing Indicators Tool: A list of prescribing indicators for older people (aged >65 years) based on the most frequent medications prescribed to Australians, and the most frequent medical conditions for which elderly Australians consult medical practitioners was developed in Australia in 2008. These criteria involve 48 prescribing indicators: 45 are explicit and 3 implicit with explanatory footnotes and associated tables to address the common problem of adverse medication-related events in the older Australian population. Unlike other IP criteria, the Australian Prescribing Indicators Tool was derived from Australian clinical guidelines and prescribing databases rather than from a consensus panel. In addition to addressing the medication related indicators, they also address medication management factors.(132) Unlike other tools to assess IP, the presence of important health interventions such as ‘smoking cessation’ and ‘seasonal vaccination’ make this tool unique. In addition, this tool has been validated using consensus methods.(133) However, since the reference is specific to Australian sources, their usability in other countries might be limited.(107)

Swedish Criteria for Prescribing Indicators: The Swedish National Board of Health and Welfare developed a set of indicators to assess the quality of pharmacotherapy in older people.(134) These indicators were based on the international literature and included 9 drug-specific and 11 disease-specific indicators (134, 135) representing the mix of explicit and implicit criteria.

1.4.1.4 Other approaches: A number of additional methods and approaches of detection as well as prevention of IP have been reported. One method includes comprehensive geriatric assessment (CGA) that comprises a multidisciplinary team of physician, pharmacist, nurse and other health care workers who evaluate the older patient’s overall health status as well as functional, physical, cognitive and nutritional abilities. This type of

assessment helps support the informed decision making for prescribers with a more appropriate use of services and resources.(67)The proven benefit of CGA has been supported by several studies.(136-138) Despite the widespread advantage of CGA for managing older people, a further multidimensional approach is needed to optimize medication in older people. A standardized comprehensive assessment linked to a coordinated and integrated plan for treatment and follow-up ideally should improve the healthcare of older people.

An expert pharmacist review providing pharmaceutical care that involves the process through which a pharmacist collaborates with other health professionals and patients in designing, implementing, and monitoring a therapeutic plan to produce specific therapeutic outcomes for the patient is another approach that has been reported to minimize the inappropriate medication prescribing in older patients.(24) Pharmacists conduct a standardized pharmaceutical assessment of prescription medications and provide feedback to the patients and their physicians. A recent study by Spinewine reported that pharmacotherapy in older people is improved when pharmacists conduct an comprehensive medication review and active educational interventions for other healthcare team.(139)However in several instances, they found mixed outcomes of the pharmacist intervention in terms of cost effectiveness and patients' quality of life.

Educational interventions targeting specifically those involved in prescribing for older patients help to minimize inappropriate medication prescribing. Some studies reported that most medical practitioners do not receive sufficient training in geriatric pharmacotherapy and this impact negatively on prescribing appropriateness.(140, 141)

Computer-based prescribing approaches are effective in minimizing prescribing errors and improving appropriateness. They have a significant role at the time of prescribing particularly on drug dose, drug-drug interactions, monitoring and cost.(142, 143)However, these approaches are costly and are limited to general adult population while the concern of older people with multiple comorbidities remains unaddressed.(117)

1.4.2 Prevalence of inappropriate prescribing in older people

In older people, IP has become an area of major worldwide concern. It is generally acknowledged that certain drugs should be used cautiously or avoided completely in this age group, if a safer alternative is available.(144) Because of the pharmacokinetic and

pharmacodynamics changes associated with ageing, this older population is more susceptible to adverse effects.(145, 146) ADRs are the most frequently occurring medical error in the United States(147) a study found that two-thirds of nursing facility residents experience at least one ADR in any 4-year period and one in seven of these ADRs lead to hospitalisation.(148) In Australia, older people living in care facilities are prescribed significantly more medications than older people living in their own homes with the consequent increased risk of ADRs.(149) Bates *et al.* reported that 28% of ADRs, and 42% of life-threatening and serious events in hospitals, were preventable.(150) These findings are comparable with the prevalence reported by Gurwitz, who found that 28% of ADRs in an ambulatory setting and 51% in nursing homes were preventable.(151, 152)

Prevalence of IP in the UK: Older people in the UK can receive long term care in 'care homes' which include nursing homes (for those requiring assistance with activities of daily living), residential homes (for people who are more independent) and those with both nursing and residential care. Parsons *et al*. studied residents in six residential care homes in England using the STOPP criteria. Of the study population, 46.2% were prescribed at least one or more PIM with 9.2% on two or more and 1.7% on three.(153) A similar study was conducted by Ryan and colleagues in an older population in primary care using Beers and STOPP criteria to assess IP and START criteria to assess potential prescribing omissions (PPOs). Beers criteria identified 286 PIPs in 18.3% (243) of patients whereas STOPP criteria identified 21.4% (284) IP with 346 potentially inappropriate prescriptions. On the other hand, START criteria identified a total of 333 PPOs in 22.7% (302) of patients.(115) Cahir and colleagues investigated the prevalence as well as the total cost associated with PIP in the national Irish population aged ≥ 70 years using STOPP criteria. The overall PIP prevalence was 36% with polypharmacy being the main issue. Total PIP costs in the year 2007 were 9% of the overall pharmaceutical expenditure in those populations.(154)

Prevalence of IP in the rest of Europe: A study by Berger *et al.* from Germany investigated the extent of potentially inappropriate prescribing (PIP) in patients 65 years and older with anxiety disorder; 40% of patients were receiving potentially inappropriate medications based on Beers criteria of inappropriateness.(155) Gallagher *et al.* assessed the use of PIP in older patients admitted to six university teaching hospitals in Switzerland, Spain, Belgium, Italy Czech Republic and Ireland. The overall prevalence of PIP using STOPP criteria was 51.3%, varying from 34.7% in Czech Republic to 77.3% in

Switzerland. By contrast, the overall prevalence using the Beers criteria was 30.4%, with 22.7% in Czech Republic to 43.3% in Switzerland. They also investigated the overall prescribing omissions using START criteria; they found the overall prevalence was 59.4%, ranging from 51.3% in Ireland to 72.7% in Italy.(156) Another European study found a 20% prevalence of prescribing at least one PIM for the older patients with substantial differences among European countries because of varied clinical practices, regulatory measures and differences in socioeconomic status.(157) A systematic review to estimate the extent of IP in older population in the primary care setting by Opondo *et al.* reported that approximately one in five prescriptions to the older population is inappropriate in this setting.(158)

Prevalence of IP in the USA: Lund *et al*. conducted a study to determine whether implicit criteria such as Medication Appropriateness Index (MAI) can predict the risk of ADE. IP at baseline was identified by Beers criteria (2003), an explicit measure and MAI, an implicit measure. Of 236 patients, 34(14.4%) had an ADE. Beers criteria identified 48.7% of patients with IP while MAI identified 98.7% patients with at least one inappropriate prescription. Only the modified MAI was associated with the risk of a subsequent ADE.(159) Pyszka *et al.* studied the incidence of PIMs in older patients aged over 70 in a teaching hospital in Wisconsin using the STOPP/START measure of IP. Based on the list of patients' medication, commissions and omission of medications were documented. PIMs were prescribed to 22% of patients. The authors suggested that an assessment by a clinical pharmacist might help identify patients at risk and minimize PIMS.(160) Zuckerman and colleagues used Beers criteria (2003) to assess inappropriateness in nursing homes and investigated the association among inappropriate medication use in a community-dwelling older population and their subsequent admission in nursing home. The prevalence of IP was 41.9% that implied the use of PIMs as the cause of increased nursing home admission.(161)

Prevalence of IP in Australia: According to Stafford *et al.,* IP is relatively common in Australian nursing homes and the prevalence and factors influencing IP are consistent with other countries. They investigated the prevalence of IP in older residents of residential aged care facilities (RACFs) in Australia using the Beers and McLeod criteria. They found 43.8% of patients received at least one PIM; Beers criteria identified more patients with PIMs (35.3%) than the McLeod criteria (18.7%).(162)In older hospitalized inpatients, Wahab and colleagues, using the STOPP criteria identified 60% of patients on PIMs.(163)

In 2008, Basger *et al.* developed a prescribing indicator tool that addresses drug related problems (DRPs) in older Australians.(132)Later in 2012, using this tool to identify potential DRPs in a group of older Australian subjects, they found high incidence of under-treatment, and utilization of PIMs.(164) A prospective cohort study by Beer *et al*. from Western Australia evaluated the prevalence and adverse outcomes of PIM use in 4260 community-dwelling older men. Under-utilisation of medicines, polypharmacy and PIMs were observed in respectively 56.7%, 35.8% and 48.7% of the study population. A total of 82.3% of participants reported at least one type of PIM use, which was associated with hospitalization.(165) Castelino *et al.* investigated the effect of home medication review (HMR) services by pharmacists, focusing on utilization of medications in 372 community-dwelling, older people and the associated drug burden index (DBI). Beside other aims, one of the objectives of study was to identify the prevalence of PIM use among the study population. They found that 60.5% of medications contributed to the DBI, while PIMs were observed in 39.8% of population. The authors observed that pharmacist recommendations could reduce patients' drug burden as well as minimize PIMs.(166)

1.4.3 Published Paper: A systematic review of prescribing criteria to evaluate appropriateness of medications in frail older people

Poudel A, Peel NM, Mitchell C, Nissen LM and Hubbard RE. Reviews in Clinical Gerontology 2014; 24(04):304-318.

This paper is reproduced in full in Appendix A.

1.4.3.1 Abstract

This study systematically reviews the published literature regarding inappropriate prescribing in frail individuals aged at least 65 years. Twenty-five of 466 identified studies met the inclusion criteria. All papers measured some surrogate indicators of frailty, such as *performance based tests, cognitive function and functional dependency*. Beers criteria were used in 20 (74%) studies to evaluate inappropriate medication use and 36% (9/25) studies used more than one criterion. The prevalence of inappropriate medications ranged widely from 11% to 92%. Only a few studies reported the relationship between PIMs use and surrogate measures of frailty. These diverse findings indicate the need for a standardized measure for assessing appropriateness' of medication in frail older individuals. Prescribing tools should address both *medication* and *patient* related factors such as life expectancy and functional status to minimize inappropriate prescribing in frail individuals.

1.4.3.2 Introduction

The number of drug prescriptions for older people has risen progressively and has drawn increasing attention worldwide.(167) While older people are the principal drug consumers, benefits from the drug therapy can only be achieved if prescribing is appropriate.(168) Inappropriate prescribing (IP), defined as a situation where pharmacotherapy does not meet the established medical standards, is associated with negative health outcomes such as adverse drug events, hospitalization, redundant healthcare utilization and untimely death.(8) IP is more likely to have its adverse influence on frail older people who often have multiple co-morbidities with signs of impairment in activities of daily living. In frail individuals, their ability to tolerate medications becomes less due to age related changes in pharmacokinetics and pharmacodynamics, thereby making prescribing a more difficult task.(169) Furthermore, the increasing prevalence of chronic illness in frail individuals leads to an increase in the number of total prescriptions.

Several criteria have been developed to identify potentially inappropriate medications (PIMs) in older patients, particularly certain aspects of prescribing such as indication, drug-drug interactions, drug-disease interaction, drug duplication and under prescribing. PIMs can be detected using explicit (criterion-based) or implicit (judgment-based) prescribing criteria.(170) Explicit criteria are derived from expert reports or published reviews. They have high reliability and reproducibility but focus mainly on specific drugs and disease states. In contrast, implicit criteria are person specific and explore patient preferences rather than disease and medications, they rely on evaluator judgment and may have low reliability and low practical utility.(9) Yet, these guides and criteria are applicable only to robust, healthy older adults and cannot be generalized to frail patients.(74) Consequently, optimising prescribing warrants measuring the frailty level of individual patients using clinically validated tools and prescribing criteria that consider a patient's quality of life, functional status, life expectancy and goals of care for optimal choice of drug with the paramount risk-benefit ratio.

We conducted a systematic review to identify studies that measured the prevalence of potentially inappropriate prescribing in older people assessed as 'frail', based on the presence of deficits defined as symptoms, signs, disabilities and diseases contributing to frailty.

1.4.3.3 Methods

Types of Studies

Original studies measuring inappropriate prescribing using well validated tools in a population assessed as frail using at least two indices of frailty were included in the review.

Types of Participants

Studies involved individuals aged 65 and older with an indication of frailty or disability. Patients were included in the study if they met two or more of the following criteria of frailty (46); disability in activities of daily living (ADL) and instrumental activities of daily living (IADL), impairments in general cognition and mobility, history of falls, malnutrition, low level of physical activity, incontinence and depression.

Information Sources

The search was conducted using PubMed and EMBASE. Articles published in English between January 1990 and December 2013 were retrieved for analysis.

Search Strategies

Keyword searches and MeSH headings were used that included the following terms: frail elderly, inappropriate prescribing, suboptimal prescribing, potentially inappropriate medication, and inappropriate medication.

Study Selection

Initial eligibility assessment was performed by a single investigator (A.P.) who reviewed abstracts based on the inclusion criteria and was confirmed by a second reviewer (N.P.). Full articles were reviewed for final inclusion. This systematic review is reported according to the PRISMA guidelines.(171)

Data Abstraction and Risk of Bias assessment

For each paper, data extracted included study design, study setting, sample size, participant age, frailty measures, implicit/explicit criteria used and the prevalence of PIM use. An association between PIM use and patient characteristics was also recorded in a specially designed data abstraction tool.

1.4.3.4 Results

Study Selection

The initial search found 466 citations (Figure 2). Of these, 135 were excluded because of duplication and 284 excluded after reviewing the abstracts, as they failed to meet the inclusion criteria. After abstract review, full text was sought for 47 articles, from which 28 articles were excluded that did not meet the following criteria: not an original study (*n*=1), prescribing criteria not well defined (*n*=1), age less than 65 years (*n*=1), frailty measurement not well defined (*n*=9), studies focusing on particular drug or disease condition (*n*= 13), studies on the same population (*n*=3). Finally, 25 studies met the inclusion criteria including six additional studies from manual search in bibliographies.

Study Characteristics

Table 4 summarizes detailed description of reviewed studies. The majority of studies were conducted in the inpatient hospital settings (*n* = 8), nursing homes or assisted living settings (*n* = 8) and in community-dwellers (*n* = 8) with one study in home care. The studies were conducted in Europe (*n*=12), USA (*n*= 9) and Oceania & Asia (*n*= 4).

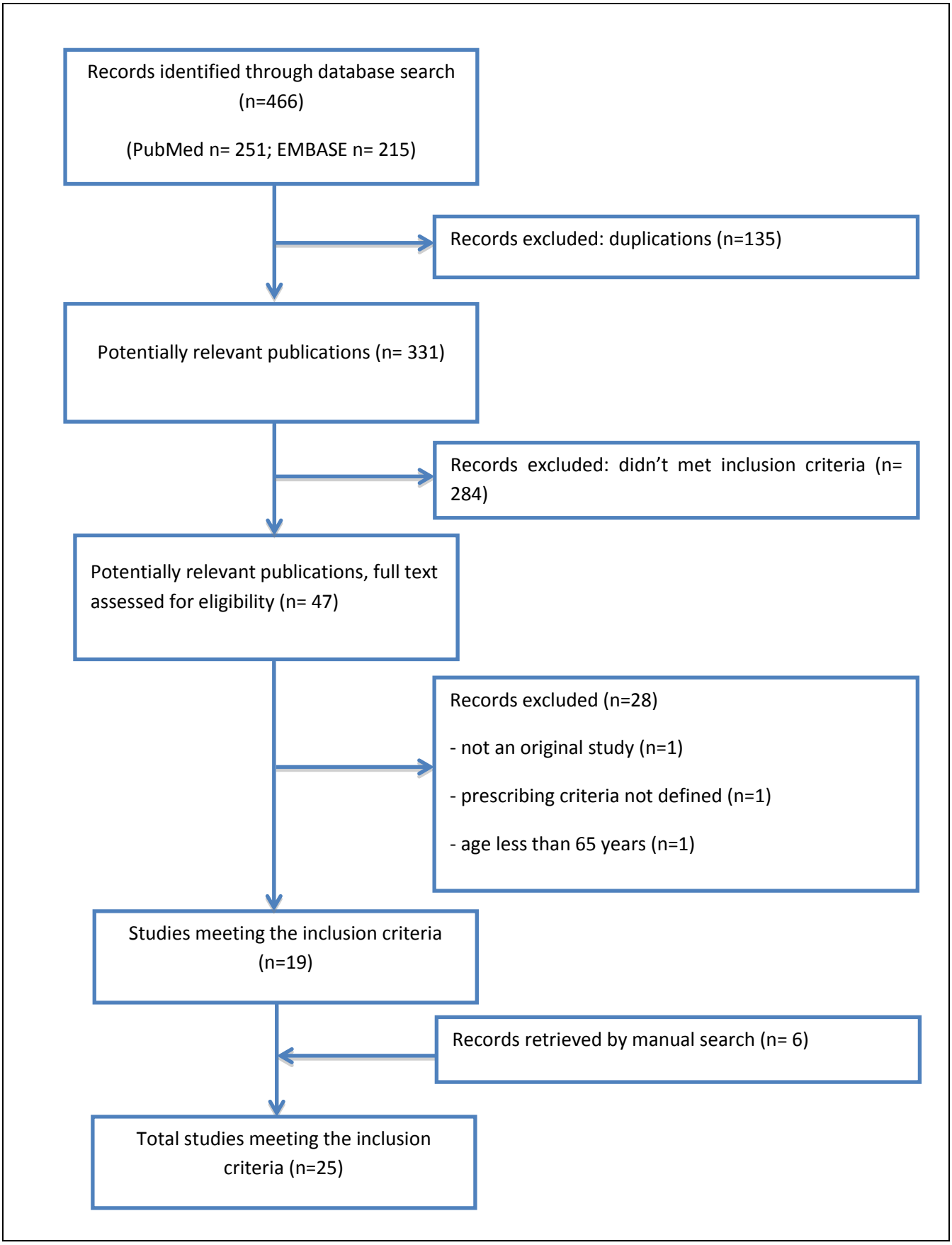


Figure 2: Flowchart of systematic review

Table 4: Studies evaluating frailty status and describing the criteria for evaluating inappropriate prescribing in frail older individuals

Reference/ Year/ Country	**Study design/setting**	**Sample (N); Age(Years)**	**Assessment of frailty**	**Criteria used**	**Results** **-** prevalence of PIMs - population characteristics associated with PIM use
Dosa *et al*., 2013, USA(172)	Retrospective, cross-sectional study in Veteran Affairs nursing homes	N= 176,168, Age ≥75 (75%)	Minimum Data Set (MDS) includes - CPS - ADL	HEDIS potentially inappropriate medications	Between 2004 and 2009, 16.4 (± 9.5%) veterans admitted to VA nursing homes received at least one HEDIS listed high-risk medications while in the facility the rate decreased from 23.9 (± 10%) in 2004 to 10.0 (± 6.6%) in 2009. High-risk medication use was associated with being female, age 75 and older and better cognitive and ADL functional status
Fromm *et al*., 2013, Germany(173)	Retrospective cohort study at discharge from 44 geriatric units	N= 45809, Median Age = 82 (IQR 78-86)	Geriatric assessment including: - Barthel score - Timed Up-and-Go (TUG) test	German PRISCUS list	25.9% received at least one PIM. Use of at least one PIM was independently associated with - being female

			- MMSE - GDS		- slightly higher Barthel score - inability to walk independently
Koyama *et al*., 2013, USA(174)	Longitudinal cohort study in community-dwelling elderly women	N= 1484, Mean Age 78 (±3)	- GDS - Goldberg Anxiety Scale - MMSE	2003 Beers	At baseline, 24.3% of women were PIM users and 23.9% at 10 years follow-up was associated with: - high GDS - poor sleep quality - lower scores on MMSE - increased anxiety - urinary incontinence Over 10 years PIM use increased in those who later developed dementia.
Dalleur *et al*., 2012, Belgium(175)	Cross-sectional study in teaching hospital	N= 302, Median Age 84 (IQR 81-88)	A positive frailty profile was defined as having two or more of the six Identification of Seniors At Risk (ISAR) items including: - Need for help in	STOPP and START	Prevalence of PIMs and PPOs was 48% and 63% respectively. Overall inappropriate prescribing contributed to hospital admission and a history of previous falls,

			activities of daily living. - Increase in need related to the current illness. - Memory problems - Altered vision - Hospitalization in last 6 months. - Daily use of ≥3 medications at home. - History of recent multiple falls		
Ubeda *et al*., 2012, Spain(176)	Descriptive study in a nursing home	N= 81, Mean Age 84 (±8)	- Barthel index - MMSE	- 2003 Beers -STOPP/START	The prevalence of PIMs was 25% according to Beers criteria while STOPP identified 48% of patients using at least 1 inappropriate medication. START detected 58 potential prescribing omissions in 44% of patients.

					Negative correlation between number of PIMs (STOPP criteria) with Barthel index and MMSE scores was noted.
Chang *et al*., 2011, Taiwan(177)	Comparative study in teaching hospital	N= 193, Mean Age 76 (±6)	- Nagi Index - IADLs - MMSE - GDS-15 items - Fall - Comorbidities (including urinary incontinence)	- 2003 Beers - Rancourt - Laroche - STOPP - Winit-Watjana - NORGEP	The prevalence of PIMs varied from 24% (the NORGEP criteria) to 73% (the Winit-Watjana criteria) Depending on criteria prevalence of PIMs are associated with - higher number of chronic conditions - higher number of chronic medications - history of falls - higher IADL score - higher physical performance - higher GDS score
Pozzi *et al*., 2010, Italy(178)	Longitudinal study in community dwellers	N= 1022, Mean Age 73 (±7)	- BADL - IADL	1991 Beers	Of the 776 participants receiving at least one medication at baseline, prevalence of at least one PIM was 9%.
Berdot *et al*.,	Multicentre	N = 6343, Age	- CES-D scale	- 1997 Beers	31.6% of subjects reported

2009, France(179)	prospective cohort study in community dwellers	<75 (64%)	- MMSE - Impaired mobility was assessed by three items of the Rosow and Breslau scale: - Doing heavy housework, walking half a mile and - Going up and down to the second floor	- Fick - Laroche	inappropriate medication use at baseline. Use of PIMs is associated with increased risk of falling mainly due to long acting benzodiazepines and other inappropriate psychotropics.
Gnjidic *et al*., 2009, Australia(180)	A cross-sectional survey on community-dwelling older men	N= 1705, Mean Age 77 (±6)	- MMSE (score ≤ 26) - GDS (score ≥ 5) - IADL - 6 m walking speed - 20 cm narrow 6 m walking speed - Chair stand - Balance score - Grip strength	DBI	Of 1527 medications 21% were exposed to anticholinergic and 13% to sedative drugs. Higher DBI was associated with poorer physical performance and functional status

			- History of falls		
Hosia-Randell *et al*., 2008, Finland(181)	Cross-sectional assessment of nursing home residents	N= 1987, Mean Age 84 (±8)	- RAI depression score - Mini Nutritional Assessment score - Dementia - Ability to move independently	2003 Beers	34.9% regularly used at least one PIM. Residents taking PIMs were less likely to have a diagnosis of dementia.
Landi et al., 2007, Italy(182)	Prospective cohort study in community	N= 364, Mean Age 86 (±5)	- Physical performance was assessed by the 4-m walking speed and the S SPPB score. - Muscle strength was assessed by hand grip strength measured by a dynamometer. - BADL - IADL - CPS	2003 Beers	At baseline prevalence of inappropriate drug use was 26%. Prevalence was associated with - cognitive impairment (higher CPS) - lower level of physical activity - higher number of medicines - lower score on SPPB Two or more PIMs was associated with - slower gait speed - lower ADL score

			- Physical activity level - Fall history		
Spinewine *et al*., 2007, Belgium(24)	Randomized, controlled trial in GEM unit	N= 203, Mean Age 82 (±6)	- Cognitive impairment - Falls - ADL - Self rated health	- 2003 Beers - MAI - ACOVE	Almost 60% of prescriptions for all patients included in the study had at least one inappropriate rating at baseline (MAI). Approximately 30% of all patients included in the study were taking at least one drug to avoid at admission. (Drugs to avoid in older people) Seventy-eight percent of patients were eligible for at least one indicator. (ACOVE criteria of underuse)
Niwata *et al*., 2006, Japan(183)	Cross-sectional study in long-term care facilities	N= 1669, Mean Age 84.5	MDS assessment - ADL - CPS - Depression Rating Scale	2003 Beers	A total of 21.1% of the patients were treated with PIMs. Increase in number of medications and older age increased risk of PIMs.

Fialova *et al*., 2005, Europe(157)	Retrospective cross sectional study of elderly patients receiving home care	N= 2707, Mean Age 82 (±7)	The inter- RAI MDS-HC instrument - IADL - ADL - Cognition - Depression	- 2003 Beers - McLeod	19.8% of patients in the total sample used at least 1 inappropriate medication combining all 3 sets of criteria. Substantial differences across Europe (5.8% in Denmark to 41.1% in Czech Republic). PIM use is associated with polypharmacy, depression and younger age (< 85 years).
Hajjar *et al*., 2005, USA(184)	Cross sectional study in VA Medical Centres.	N= 384, Age ≥75 (46%)	Patients were defined as frail if they meet at least two of the following 10 criteria: - Limitations in at least one activity of daily living (ADL), - Cerebrovascular accident within previous 30 days - History of falls,	MAI	44% of patients had at least one unnecessary drug, with the most common reason being lack of indication. PIM use is associated with polypharmacy.

			- Documented difficulty in ambulating - Malnutrition - Dementia - Depression		
Lau *et al*., 2005, USA(185)	Longitudinal study in nursing home	N= 3372, Age ≥85 (50%)	MDS assessment - ADL - Mental status	-1997 Beers - 2003 Beers	50% of all residents with an Nursing home stay of three months or longer received at least one PIMs A non-dementia mental disorder was associated with greater odds of PIMs as was having communication problems and less impairment in ADL. Having dementia was associated with less likelihood of PIM use.
Lechevallier-Michel *et al*., 2005, France(186)	Retrospective, cross-sectional study in community-dwelling	N= 9,294, Mean Age 74 (±6)	- Lawton's IADL - MMSE - CES-D	French criteria adapted from 2003 Beers	Nearly 40% of the participants used at least one PIM. This use was significantly more frequent among women, older

	elderly				subjects and poorly educated subjects.
Onder *et al*., 2005, Italy(187)	Retrospective cohort study in 81 hospitals	N= 5152, Mean Age 79 (±9)	- ADL - Hodkinson Abbreviated Mental Test	- 2003 Beers	During hospital stay, 28.6% patients received one or more inappropriate drugs. Lower prevalence of PIMs was observed in those more impaired in ADL and cognition. Higher PIM use was associated with polypharmacy.
Saltvedt *et al*., 2005, Norway(188)	Randomized study in geriatric unit	N= 127 in each unit (GEM and MW), Age 82 (±5)	Winograd targeting criteria : - Acute impairment of a single ADL, - Impaired mobility, - Falls, - Confusion, - Depression, - Dementia, - Malnutrition,	1997 Beers	10% of patients in geriatric evaluation and management unit (GEMU) had at least one PIMs and 9% of patients in general medical wards (MW) had at least one PIMs.

			- Vision or hearing impairment, - Urinary incontinence, - Polypharmacy		
Mamun *et al*., 2004, Singapore(189)	Cross-sectional study in 3 randomly selected nursing homes.	N= 454, Mean Age 80	Resident Assessment Form that measures functional category as I-IV	1997 Beers	Inappropriate medication use was seen in 70% of residents with a significant association between polypharmacy and inappropriate medication use.
Gray *et al*., 2003, USA(190)	A cohort study in community residential care facilities	N= 282, Mean Age 83 (±8)	- ADL - Global Health Status - Cognitive Status	- 1997 Beers	22% of residents took potentially inappropriate medications. Potentially inappropriate use was related to self-reported fair or poor health and number of prescription drugs
Raji *et al*., 2003, USA(191)	Cross-sectional study of community-	N= 3050, Age <75 (65%)	- MMSE - CES-D	- 1997 Beers - Zhan	Approximately 12% of the patients had at least one PIMs

	dwelling elderly				Those with ≥1 chronic diseases and with high depressive symptoms were more likely to have used at least one PIMs.
Hanlon *et al*., 2002, USA(192)	Cohort study in community-dwelling elderly	N= 3234, Age <75 (49%)	- SPMSQ - ADL	1997 Beers	At baseline 21.0% of the population were using one or more inappropriate medications according to the Drug Utilization Review (DUR) criteria. The drugs-to-avoid criteria identified no significant associations between use of these drugs and decline in functional status. With DUR criteria, however, the association was observed between use of inappropriate drugs and basic self-care
Sloane *et al*., 2002, USA(147)	Cross-sectional study in long term care facilities	N= 2,078, Age ≥85 (52%)	- ADL - MMSE	- 1997 Beers	About 16.0% of these patients were receiving PIMs. PIM use is associated with absence of dementia

Chin *et al*., 1999, USA(193)	Prospective cohort study in an emergency department (ED)	N= 898, Mean Age 76 (±8)	- ADL - MMSE	- 1997 Beers	A total of 10.6% of the patients were taking a PIM. PIMS and adverse drug-disease interactions in the ED were correlated with worse physical function and pain.

ACOVE: Assessing Care of Vulnerable Elders; ADL: Activity of Daily Living; ADR: Adverse Drug Reactions; BADL: Basic Activities of Daily Living; CES-D: Centre for Epidemiologic Studies Depression; CPS: Cognitive Performance Scale; DBI: Drug Burden Index; GDS: Geriatric Depression Scale; GEM: Geriatric Evaluation and Management; HEDIS: Healthcare Effectiveness Data and Information Set; IADL: Instrumental Activities of Daily Living; ISAR: Identification of Seniors At Risk; MAI: Medication Appropriateness Index; MDS-HC: Minimum Data Set for Home Care; MMSE: Mini-Mental State Examination; MW: Medical Ward; NORGEP: Norwegian General Practice; SPMSQ : Short Portable Mental Status Questionnaire; SPPB: Short Physical Performance Battery; STOPP: Screen Tool of Older Person's Prescription; START: Screening Tool to Alert doctors to Right Treatment; VA: Veterans Affairs

Synthesis of results

A total of 15 explicit and implicit criteria were used in the 25 studies. Of these, 14 were explicit (Beers, HEDIS, German PRISCUS list, STOPP/START, Rancourt, Laroche, Winit-Watjana, NORGEP, Fick, DBI, ACOVE, McLeod, French criteria adapted from 2003 Beers, Zhan) and only one was implicit (Medication Appropriate Index). The most commonly used criteria were one of the three versions of Beers criteria (1991, 1997, and 2003) which were used in 20 (74%) studies. Beers criteria are one of the best known and widely used explicit list of medications for evaluating inappropriate medication use.(194) Three studies used Screening Tool of Older Person's Prescriptions (STOPP)/Screening Tool to Alert doctors to Right Treatment (START) criteria to identify inappropriate medications. These latter tools identify respectively overuse of inappropriate medications and underuse of potentially appropriate medications. This differentiates them from Beers criteria.(195) Two studies used Laroche approach developed by a French consensus panel that proposed 36 criteria applicable to older people to assess inappropriate medications.(196) More than one criteria was used in 34% (9/27) of the studies to evaluate combined inappropriate medication use. Clear variation among the prevalence of inappropriate medications use was observed that ranged from 10.6% up to almost 92%.

Frailty in patients was measured using different scales. ADLs were assessed in 15 studies, mental status in 14, depression and cognitive status each in 10 studies, falls in eight studies, IADL and physical performance in six studies. Less frequently, malnutrition was reported in three studies, walking speed in three studies, incontinence and grip strength in two studies. None of these studies used established frailty measures.

1.4.3.5 Discussion

In this overview, we compiled studies that measured the prevalence of inappropriate prescribing in older people assessed as frail based on presence of geriatric syndromes. Large variation was observed in the prevalence of inappropriate medications. The study settings, population characteristics and the inter country differences on availability of some of the listed drugs(183) might account for this variations. These study settings does not fully explain the differences in the prevalence of PIMs. In NH/institutionalised settings where the population would be expected to be frail the prevalence ranged from 9.5% to

70%.While the maximum prevalence was lower in community settings where the participants would be expected to be less frail, the prevalence still ranged from 9% to 40%.The age of the population under study might have been a factor in determining prevalence of PIMs. Since polypharmacy increases with frailty and frailty increases with age (197) it might be expected that younger population has lower prevalence of PIMs. For example the prevalence of PIMs was 9% in community based study of Pozzi *et al*.(178) with the mean age of 73 years while in the study of Landi*et al*.(182) where the mean age was 86, the prevalence of PIMs was 26%.

The criteria used for assessing PIMs might also have a significant role in this variation as some of the studies compared different criteria for prevalence of PIMs in the one population. For example a study in geriatric outpatients using six sets of published explicit criteria reported the variation of PIMs from 24% (the NORGEP criteria) to 73% (the Winit-Watjana criteria).(177) The majority of criteria used for identifying inappropriate medications specifically focus on the clinical appropriateness of prescribed drugs. The MAI is the only criteria that go beyond the pharmacological appropriateness of a drug and explore other aspects of the medication management process.(125) The MAI questions whether the dose is correct. The MAI is also the only criterion that includes drug costs.(125) Most of these criteria are aimed at a healthy or robust population aged 65 years and older and are probably not appropriate in the frail older population.

Objective measures of physical, cognitive and mental functioning are significant for older people as they predict subsequent adverse health outcomes such as disability, hospitalization, nursing home admission, and death.(180) Here, frailty in older individuals was measured using different clinical features that included functional status, physical performance, mental status and vulnerability or a combination of these. Generating a composite measure that would meet all the criteria is difficult. Although few studies reported the association between PIMs with the surrogate measures of frailty or the geriatric syndromes, they had diverse findings. Dosa *et al*.(172) reported the prevalence of PIM was associated with better cognitive and ADL functional status, however Landi *et al*.(182) reported lower level of physical activities and worsening results on ADL score associated with the prevalence of PIMs. Similarly, a study by Fialova *et al*.(157) suggested

that PIM use was associated with younger age (<85 years) while a study by Niwata *et al*.(183) found that older age was associated with increased risk of PIMs. Hence, the measures of frailty used in these studies cannot be considered as a gold standard.

Frailty can now be measured objectively, rather than by using surrogate markers. While several different measures have been validated,(101) the Frailty index derived from Comprehensive Geriatric Assessment has high potential utility for older inpatients since it does not rely on performance based tests and, as a continuous variable, has greater granularity for those at the "frail" end of the health spectrum.(198) Assessment of frailty may inform decision making on medication, based on the health status and risk profile of an individual patient.(170) Utilisation of a clinically validated tool is of utmost importance in identifying frail patients in clinical practice so that their management can be more appropriately determined. Ultimately, such a tool combined with the optimal choice of drug and patients' preferences should result in better and more cost effective care.

1.4.3.6 Limitations

There were limitations to our study. The literature search was limited to articles published in English, so criteria published in other languages might have been missed. We acknowledge that the search term may not be sufficient, although the most-relevant criteria are likely to be included. Although we had a broad definition of frailty we might have missed other criteria of assessing frailty in some studies.

1.4.3.7 Conclusion

Most of the criteria used for assessing inappropriate medications are explicit, which are applicable only to the robust older population. While surrogate measures of frailty were included in the studies, frailty was poorly defined. Populations were considered frail based on age (such as >75) or setting (such as nursing homes).For appropriate prescribing in frail populations, implementing a clinically validated tool (such as frailty index) for assessing frailty as well as a specific tool to assess the appropriateness of therapy that considers patient factors such as quality of life, functional status, goal of care, and remaining life expectancy is warranted.

1.5 Summary

Inappropriate prescribing in older populations has attracted significant attention worldwide as a major public health concern due to its direct correlation with morbidity, mortality and wastage of health resources. Frail older persons often have multiple comorbidities with signs of impairment in activities of daily living. Prescribing drugs for these vulnerable individuals is complex and potentially unsafe. Factors such as polypharmacy, multiple comorbidities, age-related changes in pharmacokinetics and pharmacodynamics and functional impairment in frail older people make pharmacotherapy a complex issue. Several criteria have been developed to identify the presence of inappropriate prescribing in older patients. They address certain aspects of medication prescribing such as indication, drug-drug interactions, drug-disease interaction, drug duplication, under prescribing.

Unfortunately, there appear to be no specific criteria for assessing appropriateness of therapy in frail older patients. Complying with evidence-based clinical guidelines is usually acceptable for patients with few if any comorbidities, but as the patients' clinical and functional states deteriorate leading towards frailty and disability, the goals of care and treatment targets need to be readjusted. This discrepancy should be addressed either by developing new criteria or by refining the existing tools so they are applicable in frail older people. These tools should support prescribing practices and improve the overall well-being of such patients. The first and foremost step is to identify frail patients in clinical practice by developing a clinically validated, practical tool. Once frail patients are identified, there is a need for specific measures to assess appropriateness of therapy that considers each patient's quality of life and the goals of care such that drugs are chosen with the most appropriate risk-benefit ratio.

With these issues in mind, the overall aim of this thesis was to optimise medication prescribing in frail older people. The following chapters of this thesis will describe four connected phases of research that address this aim.

The second chapter of this thesis concentrates on polypharmacy and frailty. It describes the derivation of the frailty index (FI) from an acute care dataset and relates frailty to

prescribing. The aim of this chapter is to evaluate the impact of polypharmacy on adverse outcomes in older inpatients, stratified according to their frailty status.

The third chapter focuses on the prevalence of potentially inappropriate prescribing (PIP). As patients who are frail are often discharged to residential aged care facilities (RACFs), this chapter aims to identify the prevalence and nature of potentially inappropriate medications (PIM) using the 2012 version of the American Geriatrics Society (AGS) Beers Criteria in patients discharged from acute care to RACFs and explores the association of risk factors and PIM.

Chapter 4 explores the impact of a geriatrician intervention on patients in RACFs. As chapter 3 reported a high prevalence of PIMs in patients in RACFs, the objective here is to examine whether geriatric assessment by a geriatric medicine specialist resulted in changes to prescribing patterns, and reduced the prevalence of PIM use in RACFs. We also aimed to review prospectively the medication charts in RACF to determine if medication changes recommended by geriatricians are implemented and sustained.

Chapter 5 focuses on the development of best practice guidelines for prescribing in frail older people. Even after the involvement of specialist geriatrician, a moderate prevalence of potentially inappropriate medications was observed as noted in chapter four. Hence, the aim in chapter five was to develop a pragmatic, easily applied algorithm for medication review to help clinicians identify potentially inappropriate medications that predispose older patients to develop various geriatrics syndromes so that they may be discontinued.

Finally, chapter six summarizes the main findings of our studies and discusses various methodological and theoretical aspects, followed by limitations, overall conclusions and implications for future research and practice.

Chapter 2: Adverse outcomes, polypharmacy and frailty in older inpatients

2.1 Chapter Introduction

The literature outlined in Chapter 1highlighted the prevalence of inappropriate prescribing practices in frail older people. Evidence suggests that these vulnerable populations often have multiple comorbidities, for each of which clinicians, using evidence-based guidelines may prescribe the recommended therapy such that these patients are then at risk of polypharmacy. Several studies outlined in Chapter 1reported an association between polypharmacy and adverse outcomes in older people in both in-patient and community settings. Therefore, understanding the relationship between polypharmacy and frailty and their consequences in older people is a key challenge from both a clinical and a public health perspective.(199)As such, it could be anticipated that the identification of frail older patients who are at risk of adverse outcomes would assist in improving their clinical management.

The aim of this chapter was therefore to determine the prevalence of polypharmacy and its association with adverse outcomes among older hospitalised patients and to assess the additional role of frailty status of patient.

2.2 Submitted Paper: Adverse outcomes in relation to polypharmacy in robust and frail older inpatients

This paper has been submitted to Journal of the American Geriatrics Society.

2.2.1 Abstract

Background: The association of polypharmacy with adverse outcomes is motivating programmes of medication de-prescribing for older people.

Objective: To explore the relationship between polypharmacy and adverse outcomes among older hospital inpatients stratified according to their frailty status.

Design and setting: A prospective study of 1418 patients, aged 70 and older, admitted to 11 hospitals across Australia.

Methods: The interRAI Acute Care (AC) assessment tool was used for all data collection, including the derivation of a frailty index calculated using the deficit accumulation method. Polypharmacy was categorised into three groups based on the number of regular drugs prescribed. Recorded adverse health outcomes were falls, delirium, functional and cognitive decline, discharge to a higher level of care and in-hospital mortality.

Results: Patients had a mean age(SD) of 81 (6.8) years and 55% were female. Polypharmacy (5-9 drugs per day) was observed in 48.2% (n= 684) and hyper-polypharmacy (≥10 drugs) in 35.0% (n= 497). Severe cognitive impairment was significantly associated with non-polypharmacy compared with polypharmacy and hyper-polypharmacy groups combined (p= 0.004). In total, 591 (42.5%) patients experienced at least one adverse outcome. The only adverse outcome associated with polypharmacy was delirium. Within each polypharmacy category, frailty was associated with adverse outcomes and the lowest overall incidence was among robust patients prescribed 10 or more drugs.

Conclusions: While polypharmacy may be a useful signal for medication review, in this study it was not an independent predictor of adverse outcomes for older inpatients. A measure of frailty status better predicts risk of adverse outcomes in older patients. Extensive de-prescribing in all older inpatients may not be an intervention that directly improves outcomes.

Keywords: *adverse outcomes, frailty, older inpatients, polypharmacy*

2.2.2 Introduction

Ageing is associated with the development of chronic illness and the implementation of guidelines for the management of these conditions has resulted in an increase in the cost and number of prescribed medications. Global spending on prescription medications is growing and is likely to reach $1 trillion by 2017.(200) In Australia, for example, medications account for over 14% of the annual $140.2 billion health care expenditure.(201) Older people are the major recipients of medications(96) with those aged over 65 contributing to over half of all Pharmaceutical Benefits Scheme expenditure (202).

There is increasing concern that the prescription of multiple drugs for older people can cause significant harm.(203) Pharmacokinetic and pharmacodynamics changes with chronological age increase the risk of adverse drug events.(204) In community-dwellers, polypharmacy (defined as the use of 5 or more medications per day) is associated with falls, functional decline and mortality.(205) Among older inpatients, polypharmacy is widely cited as a risk factor for falls(206) and delirium(207), geriatric syndromes which independently predict nursing home admission.(208)

On the other hand, medication can be of considerable value to older people, improving quality of life through symptom control, preventing cerebrovascular morbidity and reducing cardiovascular mortality. The absolute benefits of primary and secondary prevention are greatest in the oldest old (209) and the systematic under-prescription of potentially beneficial medicines has been implicated in adverse outcomes.(210) Definitive evidence to support de-prescribing is currently lacking. Recent Cochrane reviews conclude that

interventions to reduce polypharmacy improve prescribing practice with no clinically significant improvement in outcomes(211) and that medication review in hospital may reduce emergency department contacts but with no effect on mortality or hospital readmissions.(212)

The relationship between polypharmacy and adverse outcomes is likely to be complex rather than linear. Comorbidity is a clear mediating factor, i.e. patients taking multiple drugs may be at greater risk because of the disease conditions triggering prescribing. The frailty status of patients may be another important confounder. A recent study suggested that frail older people are more vulnerable to the impact of fall-risk-increasing drugs than their more robust (fit) peers.(213) Hence, in this study we aim to determine the prevalence of polypharmacy and its association with adverse outcomes in hospitalised older patients and to assess the additional role of frailty.

2.2.3 Methods

Study sample and setting

This was a secondary analysis of three cohorts of older patients (n=1418), aged 70 and older, admitted to 11 acute care hospitals in Queensland and Victoria, Australia between 2005 and 2010, for whom data were collected prospectively. The majority (N = 1220) were admitted to general medical units, with 71 in orthopaedic wards and 127 in surgical wards. The study sites were diverse, from small secondary care centres with 120-160 beds to major tertiary referral centres with more than 650 beds. Patient recruitment has been described in detail elsewhere. (214-216) Patients were excluded if they were admitted to coronary or intensive care units, for terminal care only or transferred within 24 hours of admission to the ward.

Data collection and measurement tools

The interRAI Acute Care (AC) assessment tool was used for data collection. This instrument has been specifically developed for use in the acute setting to support Comprehensive Geriatric Assessment (CGA) of older inpatients.(217, 218) It collates information across a large number of domains including sociodemographic data, physical, cognitive and psycho-social functioning, medications, medical diagnoses, advance

directives, and discharge destination. Nurse assessors who were trained to use the interRAI AC instrument gathered data at admission (within 24 hours in the ward) and at discharge. To obtain information for each item in the interRAI instrument, patient and family interviews, direct observations, staff interview and medical records were used. A number of scales embedded in the interRAI instruments combine single items belonging to domains such as activities of daily living (ADL), instrumental activities of daily living (IADL) and cognition; these are used to describe the presence and extent of deficits in these domains.(217) For each patient, all prescribed medication was recorded on admission and at discharge. Data were entered by pharmacists or pharmacy students and verified by a second pharmacist or geriatrician.

Polypharmacy: Polypharmacy at admission was categorised into three groups based on the number of regular drugs prescribed. Hyper-polypharmacy was defined as concurrent prescription of 10 or more drugs per day; polypharmacy was defined as prescription of five to nine drugs and non-polypharmacy represented patients prescribed four or fewer drugs concomitantly. These cut-off points were based on previous studies.(33, 34)

Adverse outcomes

Fall in hospital: In-hospital fall was defined as having at least one fall during the period of hospitalisation. This data were collected prospectively by the research nurses using all available sources of information (interviewing the patient and medical staff, daily ward visits to review medical records, and checking the forms or systems for recording adverse events).

Delirium in hospital: As part of the interRAI AC, varying mental function and acute changes in mental status from baseline were evaluated by the nurse assessors at admission and discharge. The two items were combined to screen for delirium. This screener has been validated in a prospective observational study with good positive predictive value of delirium.(219) Delirium in hospital was recorded if the interRAI delirium screen was positive at the admission or discharge assessments or if delirium and/or any acute change in cognitive function was noted in the hospital records on daily ward visits by the nurse assessor.

In hospital ADL function decline: This was assessed using change in the ADL short form scale that consists of four items (personal hygiene, walking, toilet use, and eating). Scores on the ADL scale range from 0 to 16, with higher scores indicating greater impairment.(215) In hospital functional decline was defined as having a worse (higher) ADL score on discharge compared to admission.

In-hospital cognitive function decline: The Cognitive Performance Scale (CPS) was used to measure cognitive impairment.(215) Scores range from '0' to '6' with higher scores indicating greater impairment. In hospital cognitive decline was defined as having a higher CPS score on discharge compared to admission.

Discharged to a higher level of care: The residential status on admission was classified on an ordinal scale as community (independent), community (supported), institutional care (hospice, low or high level Residential Aged Care). Discharge to a higher level of care was defined as change to higher score on the ordinal scale at discharge, for example change in permanent living arrangement from a community to an institutional setting, and within the institutional environment from a low care to a high care setting. Those who died in hospital were excluded.

In-hospital mortality: In-hospital mortality was recorded for those patients who died during the hospital episode.

Composite adverse outcome

To explore the association of polypharmacy with adverse outcomes, a composite adverse outcome (CAO) was derived as the presence of at least one adverse outcome.

Frailty measurement

A Frailty Index (FI) at admission was calculated using a well-defined methodology.(220) Data collected using the interRAI assessment tool was coded as deficits. Each individual's deficit points were summed and divided by the total number of deficits considered (here = 52). For example, an individual with 12 deficits out of 52 counted had an FI of 0.23. In

order to tease out the impacts of frailty and polypharmacy on adverse outcomes, the number of medications used was excluded as a deficit in calculating the FI in these analyses.

The FI has a potential range of 0 to 1, where 0= absence of all deficits and 1= all deficits present.(58) Patients were categorised into three FI groups: low (0 - 0.25), medium (0.26 - 0.39) and high (≥0.4). Although the FI can be considered as a continuum with higher values representing greater frailty, a score of 0.25 has been proposed as the cut-off between 'fit' and 'frail' in community-dwelling older people (221) and scores of 0.4 and above describe older people who are dependent on others for activities of daily living and have a significantly higher risk of death.(65) These cut-points have also been validated in the inpatient setting.(222)

Statistical analysis

Data were analysed using Statistical Package for the Social Sciences 22.0 (IBM SPSS Statistics 22.Inc). Frequency distributions were used to describe the data and proportions were calculated as percent of available data. To describe characteristics across polypharmacy groups, comparison of means (Analysis of Variance) or medians (Kruskal-Wallis Test) for continuous variables was used, depending on distribution of the data. For categorical variables, the Chi-square test was performed. Multivariate logistic regression analysis was used to explore the independent effects of polypharmacy on adverse outcomes (odds of fall in hospital, delirium in hospital, functional decline, cognitive function decline, discharge destination, in-patient mortality), adjusting for age and gender. A p-value of less than 0.05 was considered statistically significant. Polypharmacy groups were stratified by frailty status to investigate the combined effects of polypharmacy and frailty on having at least one adverse outcome. Dummy variables were created to compare the risk of composite adverse outcome across polypharmacy/frailty groups in a logistic regression model. The most robust group with 10 or more medications was coded as 0 for all combinations as being the reference group.(223)

Ethics

Ethical approval was obtained from the human research and ethics committee of each participating hospital and University of Queensland Medical Research Ethics Committee. All patients or their substitute decision-maker gave informed consent for participation.

2.2.4 Results

Patients' mean age was 81 (6.8) years, and 55% were female. Prior to admission 86% were living independently in the community and 36% were living alone. Sociodemographic and clinical characteristics of the study population by polypharmacy categories are shown in Table 5. Polypharmacy was observed in almost half of the study population (n=684, 48.2%) and hyper-polypharmacy in 497 (35.0%) patients. Patients with severe cognitive impairment were significantly more likely to be in the non-polypharmacy group compared with polypharmacy and hyper-polypharmacy groups combined (p= 0.004). The mean (SD) Frailty index was 0.32 (0.15) and the association between FI and polypharmacy categories was significant (p=0.003).

Polypharmacy categories in relation to adverse outcomes are shown in Table 6. In total, 591 (42.5%) patients experienced at least one adverse outcome. The univariate analysis showed no association between polypharmacy categories and adverse outcomes studied except that those on 5 or more medications were less likely to have delirium compared with the non-polypharmacy group. In multivariate analysis, when adjusted for age and gender, a significant relationship was observed between hyper-polypharmacy group and composite adverse outcomes as shown in Table 7. However, the relationship between polypharmacy categories and delirium was not significant when cognitive status was added to the model.

The relationship between polypharmacy, frailty and (at least one) adverse outcome is illustrated in Figure 3.There was a significant association of polypharmacy and frailty with having at least one adverse outcome (see Appendix F). Within polypharmacy categories, frailer patients were more likely to have an adverse outcome. The most robust patients taking 10 or more drugs had the lowest incidence of adverse events.

Table 5: Characteristics of study population (N=1418)

	All N = 1418	**Non Polypharmacy <5 drugs n = 237 (16.7%)**	**Polypharmacy 5 – 9 drugs n = 684 (48.2%)**	**Hyper-polypharmacy ≥10 drugs n = 497 (35.0%)**	**p value**
Age mean ± SD	81.0 ± 6.8	81.0 ± 7.0	81.5 ± 7.0	80.4 ± 6.3	**0.017**
Female	780 (55.0)	117 (49.4)	390 (57.0)	273 (54.9)	0.125
Median Length of Stay (IQR)	6 (4-11)	6 (4-13)	7 (4-11)	6 (4-10)	0.640
Cognitive status [a]					
Intact Mild to moderate Severe	1016 (71.9) 289 (20.5) 108 (7.6)	153 (64.6) 55 (23.2) 29 (12.2)	467 (68.7) 157 (23.1) 56 (8.2)	396 (79.8) 77 (15.5) 23 (4.6)	**<0.001**
FI Low FI (0-0.25)= 503 Intermediate FI (0.26-0.39)= 530 High FI (0.40-1)= 922	0.32 ± 0.15	0.30 ± 0.17	0.32 ± 0.15	0.34 ± 0.13	**0.003**

Notes: Unless otherwise stated columns represent n (%), SD Standard Deviation, [a] Based on the Cognitive Performance Scale (CPS), which ranges from 0 to 6 categorised as Intact (0-1); Mild to moderate (2-4); Severe (5-6)

Table 6: Medication prescribing in relation to adverse outcomes

Adverse outcomes	**Total** **n=1418**	**Non-Polypharmacy (<5 drugs) n=237 (16.7%)**	**Polypharmacy (5-9 drugs)** **n=684 (48.2%)**	**Hyper Polypharmacy (≥10 drugs) n=497 (35.0%)**	**p value**
Fall in hospital -no -yes	 1334 (94.1%) 83 (5.9%)	 224 (94.9%) 12 (5.1%)	 641 (93.7%) 43 (6.3%)	 469 (94.4%) 28 (5.6%)	0.768
Delirium in hospital -no -yes	 1071 (76.9%) 322 (23.1%)	 158 (69.0%) 71 (31.0%)	 522 (77.6%) 151 (22.4%)	 391 (79.6%) 100 (20.4%)	**0.006**
In hospital ADL function decline [a] -no -yes	 1249 (92.3%) 104 (7.7%)	 209 (92.5%) 17 (7.5%)	 601 (91.1%) 59 (8.9%)	 439 (94.0%) 28 (6.0%)	0.187
In-hospital cognitive function decline [a] -no -yes	 1287 (95.4%) 62 (4.6%)	 214 (94.7%) 12 (5.3%)	 623 (95.1%) 32 (4.9%)	 450 (96.2%) 18 (3.8%)	0.610
Discharged to a higher level of care [a] -no -yes	 1069 (78.6%) 291 (21.4%)	 172 (76.1%) 54 (23.9%)	 510 (76.9%) 153 (23.1%)	 387 (82.2%) 84 (17.8%)	0.064
In-hospital mortality -no -yes	 1360 (96.0%) 57 (4.0%)	 226 (95.4%) 11 (4.6%)	 663 (97.1%) 20 (2.9%)	 471 (94.8) 26 (5.2%)	0.120
At least one adverse outcome -no -yes	 801 (57.5%) 591 (42.5%)	 122 (52.6%) 110 (47.4%)	 379 (56.4%) 293 (43.6%)	 300 (61.5%) 188 (38.5%)	0.056

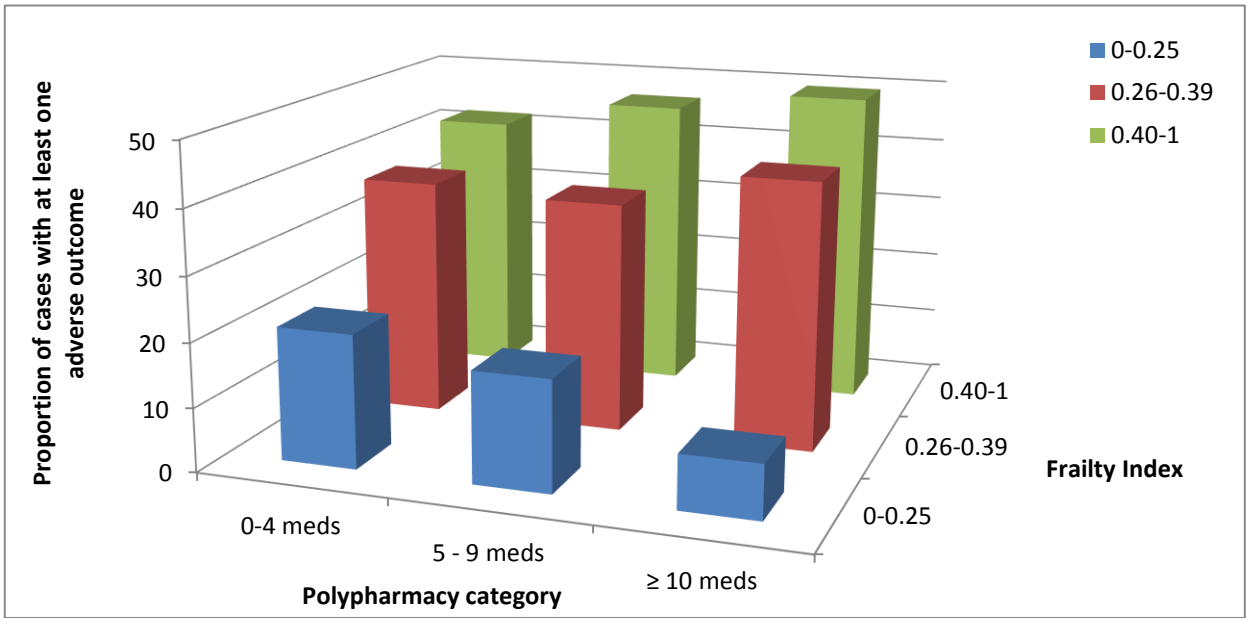
Notes: Unless otherwise stated columns represent n (%),[a] Excluding deaths in hospital

Table 7: Odds ratios relating individual adverse outcomes to polypharmacy categories (adjusted for age and gender)

Adverse outcomes	**Polypharmacy**		
	4 or fewer meds*	5-9 meds	10 or more meds
Fall in hospital	1.00	1.30 (0.67, 2.51) (p= 0.433)	1.15(0.57, 2.31) (p= 0.687)
Delirium in hospital	1.00	0.63 (0.45, 0.89) (p= 0.007)	0.60 (0.41, 0.85) (p= 0.005)
In hospital ADL function decline	1.00	1.22 (0.70, 2.14) (p= 0.495)	0.80 (0.43,1.50) (p= 0.477)
In-hospital cognitive function decline	1.00	0.89 (0.45, 1.78) (p= 0.749)	0.77 (0.36, 1.65) (p= 0.507)
Discharged to a higher level of care	1.00	0.93 (0.65, 1.33) (p= 0.688)	0.73 (0.50, 1.08) (p= 0.115)
In-hospital mortality	1.00	0.65 (0.31, 1.38) (p= 0.263)	1.22 (0.59, 2.53) (p= 0.591)
Composite adverse outcome	1.00	0.83 (0.61, 1.14) (p= 0.250)	0.72 (0.52, 0.99) (p= 0.046)

*Reference group

Figure 3: Relationship between polypharmacy, frailty and (at least one) adverse outcome



Note: percentage of adverse outcomes refers to % within each polypharmacy category.

2.2.5 Discussion

In this large and well-characterised cohort of older inpatients, we found no significant association between polypharmacy and a range of clinically relevant adverse outcomes. The association of polypharmacy and frailty with having at least one adverse outcome was significant. Within each polypharmacy category, the incidence of adverse outcomes increased with increasing frailty, and the most robust patients taking 10 or more drugs had the lowest incidence compared with other polypharmacy/frailty categories.

Here, the only significant association between polypharmacy and an adverse outcome was an unexpected one: patients prescribed 5 or more medications were less likely to experience delirium compared with the non-polypharmacy group. This contrasts with previous studies linking incident delirium with higher numbers of prescribed drugs.(207, 224) A possible explanation for this finding is that delirium is more frequent in those with dementia (225) and in this cohort, patients with dementia were prescribed fewer drugs. Prescribers may already be taking account of frailty status and prescribing fewer medications to the most vulnerable patients especially those with severe cognitive impairment. The association between polypharmacy and delirium was no longer significant when cognitive status was added to the model.

Our results are consistent with previous studies reporting no association between polypharmacy and falls. In an Italian nursing home, polypharmacy was not found to be a risk factor for fall-related injuries. The association was observed only when an injurious fall risk-increasing drug such as anti-arrhythmic or anti-parkinsonian drugs were part of patient's therapeutic regimen.(226) A similar study in an Australian residential aged care facility (RACF) also reported that polypharmacy was not significantly associated with falls.(227) Other studies of community-dwellers have found no association between polypharmacy and ADL impairment in older adults.(228, 229) A randomized trial of interdisciplinary medication review reported no change in cognition and physical function even though polypharmacy was reduced.(229) Polypharmacy was not associated with discharge destination in our study. A similar finding was reported by a study from a tertiary care hospital in Australia where polypharmacy (defined as patients with 9 or more medications) had no association with discharge destination.(230) The lack of association

between polypharmacy and in-hospital mortality observed in our study was also reported by a study conducted in 38 hospitals in Italy.(231)

This study has certain strengths. The study population is a large cohort of patients recruited from secondary and tertiary care settings with detailed assessment of patients' functional and cognitive status and of medications prescribed. Data collection was comprehensive and complete with less than two percent missing data in the final analysis models. We also acknowledge methodological weaknesses. We investigated older hospitalised patients and results may not be generalizable to populations in different settings. Furthermore, our methodology for collection of medication data (documentation from patients' prescription charts) is not the current gold standard. As an observational study, we can make inferences about the associations found but interventional studies would be needed to determine the optimal number of medications for patients according to their frailty status.

Despite these limitations, this study provides a new insight into the relationship between polypharmacy and adverse outcomes. While polypharmacy stands as a valuable indicator for medication review, it might not be an independent marker of the quality use of medicines. More robust patients might tolerate a greater (but appropriate) number of medications regardless of their chronological age.(232) However, our results do support a link between polypharmacy and adverse events in older inpatients who are frail. Individualisation of medication prescribing, based on patients' own goals of care as well as their frailty status, has considerable potential to improve outcomes and this is the focus of further enquiries by our group.

2.3 Next Steps

The above article described the relationship between polypharmacy and a range of clinically relevant adverse outcomes and outlined the clinical usefulness of the measurement of frailty in older inpatients. Most studies use polypharmacy as a marker of risk, which may in fact mean the most vulnerable group of patients i.e. those with cognitive impairment is missed because they may be taking less medications. Frailty status of a patient has the potential to be used in a clinically useful paradigm in predicting adverse outcomes in older patients.

The findings from this article could serve as a reference point to commence a rational discussion around medication optimisation in this patient population. However, withdrawal of medications particularly needs to be carefully considered in the broader context of all of the relevant patient factors. Wholesale medication withdrawal in all older inpatients may not be an intervention that directly improves outcomes. Therefore, taking into account a frailty status of the patient may underpin a more robust approach to these types of interventions.

A key observation from this study was that the most frail, older subjects were discharged into residential aged care facilities from hospitals. Hence, in Chapter 3, we aimed to determine the prevalence of potentially inappropriate prescribing at discharge from acute care hospitals to residential aged care facility and the independent risk factors for such prescribing.

Chapter 3: Potentially Inappropriate Prescribing in Frail Older Patients Discharged to Residential Aged Care Facilities

3.1 Chapter Introduction

Many people who live beyond the age of 75 become frail at some point, and over 40% will spend time in a residential aged care facility (RACF).(233) In Australia, approximately 6% of people aged 65 and over live in RACF, and this proportion rises to 26% for those aged 85 and over.(234) Those discharged from hospital to RACFs had a higher frailty status (n= 206; FI = 0.42±0.15) than those discharged to the community (n= 919; FI = 0.28±0.12) in our dataset.

For older people requiring nursing home care, admission to hospital is an opportunity to review and rationalise medication after weighing up the benefits and significant risks of polypharmacy and inappropriate prescribing. The main aim of this chapter was to determine the prevalence of potentially inappropriate prescribing in older hospitalised people returning to, or newly discharged to, RACF from the acute sector. The published paper also aims to identify the independent risk factors for inappropriate medication use.

3.2 Published Paper: Potentially Inappropriate Prescribing in Older Patients Discharged from Acute Care Hospitals to Residential Aged Care Facilities

Poudel A, Peel NM, Nissen L, Mitchell C, Gray LC, Hubbard RE. Potentially Inappropriate Prescribing in Older Patients Discharged From Acute Care Hospitals to Residential Aged Care Facilities. Annals of Pharmacotherapy. 2014; 48(11):1425-1433.

This paper is reproduced in full in Appendix B.

3.2.1 Abstract

Background: The frequency of prescribing potentially inappropriate medications (PIMs) in older patients remains high despite evidence of adverse outcomes from their use. Little is known about whether admission to hospital has any effect on appropriateness of prescribing.

Objectives: This study aimed to identify the prevalence and nature of PIMs and explore the association of risk factors for receiving a PIM.

Methods: This was a prospective study of 206 patients discharged to residential aged care facilities (RACFs) from acute care. All patients were aged at least 70 years and were admitted between July 2005 and May 2010; their admission and discharge medications were evaluated.

Results: Mean patient age was 84.8 ± 6.7 years; the majority (57%) were older than 85 years and mean (SD) Frailty Index was 0.42 (0.15). At least one PIM was identified in 112 (54.4%) patients on admission and 102 (49.5%) patients on discharge. Of all medications prescribed at admission (1728), 10.8% were PIMs and at discharge of 1759 medications, 9.6% were PIMs. Of total 187 PIMs on admission, 56 (30%) were stopped and 131 were continued; 32 new PIMs were introduced. Of the potential risk factors considered, in-hospital cognitive decline and frailty status were the only significant predictors of PIMs.

Conclusion: Although, admission to hospital is an opportunity to review the indications for specific medications, a high prevalence of inappropriate drug use was observed. The only

associations with PIM use were the frailty status and in-hospital cognitive decline. Additional studies are needed to further evaluate this association.

Keywords: Beers criteria, frailty, inappropriate prescribing, older patients, residential aged care facilities

3.2.2 Introduction

Our aging population, while a consequence of societal success, does present a challenge to the health care system. Older people are prescribed multiple medications and are more prone to adverse drug events (ADEs) that lead to increased mortality and morbidity and higher health care cost.(169, 199, 235)Advancing age is associated with substantial pharmacokinetic (PK) and pharmacodynamics (PD) changes, impaired homeostasis and increased risk of ADEs as the physiologic changes that occur with aging make the body more sensitive to the effects of medications.(236) Renal function declines in older age and body composition changes with advancing age (relative lipid content increases; total body water and lean body mass decreases) which can affect drug distribution and often will result in drug retention and a prolonged half-life.(237)

Age-related changes in PK and PD will occur with several drugs and the action of drugs can be altered due to age related up and down regulation of target receptors, transmitters and signalling pathways. Hence, the appropriate use of available pharmacotherapy requires consideration of both the benefits and risks of the medications. Drugs are classified as potentially inappropriate when the risks of treatment outweigh the benefits(25); they are prescribed for longer periods than clinically indicated or without any clear indication; they are not prescribed when indicated(163); and when they are likely to interact with other drugs and diseases.(8)

Inappropriate prescribing in older patients can be detected using either explicit (criterion-based) or implicit (judgment-based) screening tools.(106, 238, 239)Explicit criteria are derived from expert reports or published reviews. They have high reliability and reproducibility but focus mainly on specific drugs and disease states. By contrast, implicit criteria are person-specific and explore patient preferences, rather than the disease and

medications; they rely on evaluator judgment and tend to have low reliability and poor clinical utility.(74) Although these criteria address some aspects of prescribing in older patients, they seldom consider the frailty of such patients. The omission of health status from established prescribing tools may help to explain the lack of clinical benefit from algorithm-based medication reviews.(169)

The Beers criteria are commonly used and they do measure some surrogates of frailty. They were originally developed in 1991(109) for use in the older nursing home population and have been subsequently updated in 1997, 2002 and 2012 so as to be applicable to all persons over 65 years of age, regardless of their place of residence.(111) The recently updated Beers criteria divide medications into three main categories according to major therapeutic classes and organ systems: 34 medications are considered potentially inappropriate, independent of diagnosis, 14 are to be avoided in older adults with certain diseases and syndromes that can be exacerbated by the listed drug , while another 14 are to be used with caution in older adults.(111) Although many medications on the Beers list are not available in Australia, use of these criteria for evaluation of prescribing has the advantage of enabling international comparison.

Admission to hospital is an opportune time to review and rationalize prescribing, weighing up the benefits of pharmacotherapy against significant risks of polypharmacy and inappropriate prescribing in older adults, particularly those who are frail. Pharmacists in hospital can play a significant role in the initiation of changes to patient's therapy and management. In Australia, all major government funded hospitals provide inpatient clinical pharmacy services.(240) These services encompass medication management reviews during inpatient episodes, clinical reviews, medication reconciliation, ADE monitoring, patient medication counselling and provision of drug information.(241)However, little is known about whether admission to hospital has any effect on appropriateness of prescribing.

Potentially inappropriate prescribing (PIP) is particularly common in long-term residents of aged care facilities; indeed institutionalization itself is an established independent risk factor for PIP.(242) Studies that have compared prevalence of potentially inappropriate

medications (PIMs) at admission to hospital and discharge have reported inconsistent results. A prospective drug surveillance in an acute medical geriatric unit in France reported a decreased prevalence of PIMs from 66% at admission to 43.6% at discharge.(243) A retrospective, non-randomised study in the Specialist Health and Ageing Unit in England, UK found a decreased prevalence from 26.7% at admission to 22.6% at discharge.(244) By contrast a similar study in Norway showed the increased prevalence of PIMs from 24% at admission to 35% at discharge.(245)

Similar reports from Australian health care settings are limited and we cannot assume identical prevalence rates and PIM types in Australia due to the variations in health care systems and prescribing practices across countries. Therefore the main objective of this study was to determine the prevalence of PIP using the 2012 version of the American Geriatrics Society (AGS) Beers Criteria in patients discharged from acute care to residential aged care facilities (RACFs). We also aimed to identify whether polypharmacy, age, gender, in-hospital falls, delirium, functional and cognitive decline and the frailty status of patients were independent risk factors for receiving an inappropriate medication.

3.2.3 Methods

Study population: In this study, we undertook secondary data analyses of patients recruited as three separate prospective cohorts in studies originally designed to investigate prevalence of geriatric syndromes and quality of care in acute care settings.(214, 215, 246) This is a prospective study of patients, aged 70 and older, who were discharged to RACFs (206 out of total 1418 patients) following admission to 11 acute care hospitals in Queensland and Victoria, Australia. The sites ranged from small secondary care centres (with 120 – 160 beds, n = 2), through rural hospitals (250 – 280 beds, n = 2) to metropolitan teaching facilities (300 – 450 beds, n = 4) and major tertiary referral centres (>650 beds; n = 3). All patients were admitted to the acute care hospitals between July 2005 and May 2010. Patient recruitment has been described in detail elsewhere.(214, 215) Patients were excluded if they were admitted to coronary or intensive care units, for terminal care only or were discharged from hospital within 24 hours. Only those patients entering RACFs at discharge were included in the study.

Data collection and measurement tools: The interRAI Acute Care assessment tool was used for data collection.(247) interRAI is a not-for-profit research consortium with international collaboration from over 30 countries. It aims to improve the quality of life of vulnerable persons through a unified comprehensive assessment system. The interRAI suite consists of tools to support assessment and care planning of persons with chronic illness, frailty, disability, or mental health problems across care settings.(217) One of these tools is the interRAI Acute Care (interRAI AC) instrument that has been specifically developed for use in the acute setting, to support Comprehensive Geriatric Assessment (CGA) for older inpatients.(218) This instrument screens a large number of domains around socio-demographic information, physical, cognitive and psycho-social functioning, medications, medical diagnoses, advance directives, and discharge destination.(218)

A number of scales are embedded within the interRAI instruments combine single items belonging to domains such as activities of daily living (ADL), instrumental activities of daily living (IADL) and cognition, which are used to describe the presence and extent of deficits in these domains.(217)Trained nurse assessors gathered data at admission (within 24 hours in the ward) and at discharge. In completing the interRAI assessment, all available sources of information, including the patient, carers and medical/ nursing/ allied health staff were utilized, either directly as verbal reports or from written entries in hospital records. For each patient, all prescribed medication, including Anatomical Therapeutic Classification (ATC) codes, was recorded on admission and at discharge. Data were entered by pharmacists or pharmacy students and verified by a second pharmacist or geriatrician.

Measures of inappropriate prescribing: The prevalence of PIP was determined using the 2012 version of AGS Beers criteria. The inappropriate medications found by the study were classified as ‘PIMs independent of medical condition’, ‘PIMs in the presence of certain pathologies’ and ‘PIMs to be used with caution’, as proposed by the AGS.

Deriving a Frailty Index: A Frailty index (FI), an index of accumulated deficits, was calculated for each individual at admission using a well-defined methodology.(46) Data collected using the interRAI assessment tool was coded as deficits. For example, in the

domain of cognition, an acute change in mental status is recorded as a dichotomous, yes/ no response and this was coded as deficit present (1 point) or absent (0 points). Other data were recorded on an ordinal scale with cut-offs for 0/ 0.5/1 deficit coded according to the distribution of the data. For example, the domain of vision classified into four categories (0: adequate, 1: minimal difficulty, 2: moderate difficulty, 3: severe difficulty, 4: no vision) is coded with cut-offs of 0/0.5/1 (i.e. 0 = 0, 1 = 0.5, 2-4 = 1).

Deficits crossed the domains of function, cognition, mood and behaviour, disease diagnoses and sensory impairments. Medication use was excluded from the FI. Each individual's deficit points were then summed and divided by the total number of deficits considered (here, 52). For example, someone with 6 deficits out of 40 counted has a FI of 0.15. The FI has a potential score of 0-1, where 0= absence of all deficits, and 1= all deficits present.(58) Although the FI can be considered as a continuous variable with higher values representing greater frailty, 0.25 has been proposed as the cut-off between 'fit' and 'frail' individuals.(221)

Polypharmacy: Polypharmacy was categorised into three groups based on the number of drugs documented by the interRAI assessors who transcribed the patients' drug charts. All prescribed medications were recorded approximately 24 hours after admission to hospital and again at discharge from hospital. These lists may have included medications used for a finite period in hospital to manage the patients' acute medical conditions. Hyper polypharmacy was defined as concurrent use of ten or more drugs; polypharmacy was defined as use of five to nine drugs and non-polypharmacy represented patients using four or less drugs concomitantly. These cut-off points have been selected based on previous studies relating the risk of adverse outcomes in older people to numbers of prescribed medication.(248, 249)

Covariates

Fall in hospital: In-hospital fall was defined as having at least one fall during the period of hospitalization. These data were collected prospectively by daily chart reviews and ward visits by the research nurses using all available sources of information (interviewing the patient and medical staff, reviewing the medical records, and checking the forms or

systems for recording adverse events).(250) The process of data collection was based on the detailed instructions provided in the tool manual.(247)

Delirium in hospital: As part of the interRAI AC, varying mental function and acute changes in mental status from baseline was assessed by nurse assessor at admission and discharge. The two items were combined to screen for delirium.(219) Delirium in hospital was recorded if delirium screened positive at the admission or discharge assessments or if noted in the hospital records on daily ward visits by the nurse assessor.

Failure to improve in ADL: Failure in improvement of ADL was recorded as a change in the ADL short form scale that consists of four items (personal hygiene, walking, toilet use, and eating). Scores on the ADL scale range from 0 to 16, with higher scores indicating greater impairment.(215) Failure to improve in ADL was defined as those with some ADL impairment on admission who had the same or worse (higher) ADL score on discharge compared to admission or who developed a new ADL impairment in hospital.

In-hospital cognitive function decline: The Cognitive Performance Scale (CPS) was used to measure cognitive impairment.(215) Score ranges from ‘0’ to ‘6’with higher scores indicating greater impairment. In-hospital cognitive decline was defined as having a worse CPS score on discharge compared to admission.

Statistical analysis: Data were analysed using the Statistical Package for the Social Sciences 21.0 (IBM SPSS Statistics 21.Inc). A paired sample t-test was used to observe the relationship between admission and discharge medications. Two multiple logistic regression models were used to detect risk factors for PIMs at both admission and discharge. The number of PIMs was dichotomised into presence or absence of a PIM. Age, gender, number of admission and discharge medications, in-hospital falls, delirium, functional and cognitive decline and frailty index of patients were used as predictive variables for PIMs. A p-value of 0.05 was considered statistically significant.

Ethics: Ethics approval was obtained from the human research and ethics committee of each participating hospitals and The University of Queensland Medical Research Ethics

Committee. All patients or their substitute decision-maker gave informed consent for participation.

3.2.4 Results

Patient characteristics: Of the 206 patients discharged to RACFs, 142 (69%) were female. The principal characteristics of the study population are described in Table 8. They had a mean (SD) age of 84.8 (6.8) years; the majority (57%) were older than 85 years and mean (SD) Frailty Index was 0.42 (0.15).A total of 35%were admitted from the community and 65% from RACFs. The median length of stay in hospital was eight days. Of those discharged to RACFs, approximately 60% were discharged to high care (a high level care setting for older people with 24-hour nursing care) and remaining 40% discharged to low care (residents require accommodation and personal care type services, but not 24-hour nursing care).

General prescribing pattern: The number of medications prescribed on admission and discharge is shown in Table 9. Patients were prescribed a mean of 7.2 (±3.81) regular medications at admission and 8.1 (±3.95) on discharge to RACF. Comparing medication regimen at admission and discharge, the prevalence of polypharmacy was stable [106 (51.5%) vs 102 (49.5%) respectively] but with an increase in hyper-polypharmacy [from 50 patients (24.3%) to 67 (32.5%)].

At admission, two patients were prescribed 23 medications with 10 patients receiving at least 20 medications. On discharge one (different to admission) patient was prescribed 23 medications and four patients had at least 20 medications. At discharge, aspirin and anti-platelet agents were the most frequently prescribed medications (109, 54%), followed by anti-ulcer drugs in 105 (52%) patients. Other prevalent medication included antidepressants (28.2%), benzodiazepines (19.3%), antipsychotics (16.3%) and opioids (16.3%). Of the potential risk factors, frailty status and in-hospital cognitive decline were the only significant predictors of PIMs at both admission (p= 0.047) and discharge (p = 0.032). However, no association was observed between PIM use, polypharmacy categories, age, gender, in-hospital falls, delirium and functional decline.

Potentially inappropriate medications at admission: On admission, 112 (54.4%) patients were on at least one PIM; 5 patients were on 4 PIMs. Of the 1460 regular medications prescribed at admission 187 (12.8%) were PIMs. Of these, 149 (80%) were classified as PIMs for older people independent of diagnosis and 38 (20%) PIMs contraindicated in older people with certain diseases or syndromes (Table 10). PIMs to be used with caution accounted for 3.8% of total medications prescribed. Commonly prescribed PIM categories were central nervous, cardiovascular and gastrointestinal system drugs, and analgesics. Multiple regression analysis revealed that frailty status[($p<0.05$ OR= 0.92 (0.76, 1.12)] and in-hospital cognitive decline were significantly associated to PIMs at admission [($p<0.05$ OR= 0.82 (0.62, 0.99)] (see Appendix G).

Table 8: Characteristics of the study population

Characteristics	**Number of patients (%) n= 206**		
	Value	**At least one PIM at admission**	**No PIM at admission**
Age distribution			
Mean age (SD)	84.8 (6.8)		
65-74 years	20 (10)	13 (11.6)	7 (7.5)
75-84 years	69 (33)	41 (36.6)	28 (29.8)
>85 years	117 (57)	58 (51.8)	59 (62.7)
Sex (n [%])			
Female	142 (69)	78 (55)	64 (45)
Male	64 (31)	34 (53.2)	30 (46.8)
Admitted from (n [%])			
Community	73 (35.4)	35 (48)	38 (52)
RACF low care	64 (31.1)	37 (57.8)	27 (42.2)
RACF high care	69 (33.5)	40 (58)	29 (42)
Discharged to(n [%])			
RACF low care	81 (39.3)	48 (59.2)	33 (40.8)
RACF high care	125 (60.7)	64 (51.2)	61 (48.8)
Length of stay: Median length of stay (days [IQR])	8 [4-16]		
Frailty Index: Mean (SD)	0.42 (0.15)		
Fall in hospital	27 (13.1)	16 (59.3)	11 (40.7)
Delirium in hospital	47 (22.8)	22 (46.8)	25 (53.2)
Failure to improve in ADL	110 (53.4)	64 (58.1)	46 (41.9)
In-hospital cognitive function decline	37 (18.0)	11 (29.7)	26 (70.3)

IQR: Interquartile range; SD: Standard Deviation; RACF: Residential Aged Care Facility

Potentially inappropriate medications at discharge: At discharge, 102 (49.5%) patients were on at least one PIM; one patient was discharged on seven PIMs, five patients on four PIMs and eight patients on three. Of all the 1652 regular medications prescribed at discharge, 168 (10.1%) were PIMs. Of these 168, 129 (77%) were classified as PIMs for older people independent of diagnosis and 39 (23%) of PIMs contraindicated in older

people with certain diseases or syndromes (Table 10). PIMs to be used with caution accounted for 3.7% of total medications prescribed. Commonly prescribed PIMs categories were Central Nervous system (CNS) drugs, cardiovascular, gastrointestinal, respiratory medications, analgesics and antimuscarinics. Multiple regression analysis showed that frailty status [($p<0.05$, OR= 0.93 (0.77, 1.13)] and in-hospital cognitive decline [($p<0.05$, OR= 0.85 (0.65, 0.96)] were significantly associated with PIMs at discharge. (see Appendix G)

Changes in potentially inappropriate medication between admission and discharge: Table 9 shows the number of patients with total PIMs at admission and discharge. Of the 187 PIMs prescribed at admission, 56 (30%) were stopped and 131 (70%) were continued while 32 new PIMs were started. PIMs introduced included CNS drugs [benzodiazepines (14/32), antipsychotics (8/32), and antidepressants (1/32)], respiratory medications (3/32), antiarrhythmic (2/32), gastrointestinal (2/32) and analgesics (2/32).

Table 9: Polypharmacy categories and potentially inappropriate medication (PIM) distribution at admission and discharge

Variables	**Number of patients (%) n= 206**	
	Admission	**Discharge**
Medication category		
0 - 4 medications (non-polypharmacy)	47 (22.8)	35 (17.0)
5-9 medications (polypharmacy)	106 (51.5)	102 (49.5)
≥10 medications (excessive polypharmacy)	50 (24.3)	67 (32.5)
Missing	3 (1.5)	2 (1.0)
Total number of medications	**1460**	**1652**
Number of PIMs		
No PIMs	94 (45.6)	104 (50.5)
One PIM	60 (29.1)	59 (28.6)
Two PIMs	34 (16.5)	29 (14.1)
Three PIMs	13 (6.3)	8 (3.9)
Four or more PIMs	5 (2.4)	6 (2.9)
Total number of patients with at least one PIM	**112 (54.4)**	**102 (49.5)**

Table 10: Potentially inappropriate medications on admission and discharge as determined by 2012 Beers criteria (n= 206)

PIMs independent of medical condition					**PIMs in the presence of certain pathologies**					**PIMs to be used with caution**				
	Admission		**Discharge**			**Admission**		**Discharge**			**Admission**		**Discharge**	
System/ therapeutic category/drugs	**N**	**%**	**N**	**%**	**System/ therapeutic category/drugs**	**N**	**%**	**N**	**%**	**System/ therapeutic category/drugs**	**N**	**%**	**N**	**%**
Central Nervous System	**106**	**71.1**	**102**	**79**	**Central Nervous System**	**11**	**29.9**	**10**	**25.6**	**Antipsychotics**	**14**	**25.5**	**15**	**24.6**
Antidepressants	9	6	8	6.2	Antidepressants	2	5.3	2	5.1	**SNRIs**	**3**	**5.5**	**4**	**6.5**
Antipsychotics	50	33.6	40	31	Antipsychotics	9	23.7	8	20.5	**SSRIs**	**31**	**56.3**	**35**	**57.4**
Cardiovascular	**47**	**31.5**	**54**	**41.8**	**Cardiovascular**	**12**	**31.5**	**9**	**23**	**TCAs**	**7**	**12.7**	**7**	**11.5**
Alpha blockers	4	2.7	4	3.1	**Gastrointestinal**	**8**	**21**	**10**	**25.6**					
Antiarrhythmic	14	9.4	7	5.4	**Respiratory**	**5**	**13.1**	**8**	**20.5**					
Gastrointestinal	**23**	**15.5**	**12**	**9.3**	**Antimuscarinics**	**2**	**5.2**	**2**	**5.1**					
Analgesics	**2**	**1.4**	**4**	**3.1**										
Total	**149**	**100**	**129**	**100**		**38**	**100**	**39**	**100**		**55**	**100**	**61**	**100**

PIMs: Potentially Inappropriate Medications; TCAs: Tricyclic antidepressants; SNRIs: Selective Norepinephrine Reuptake Inhibitors; SSRIs Selective Serotonin Reuptake Inhibitors

3.2.5 Discussion

The present study demonstrated frequent use of inappropriate medications in older people discharged from acute care hospitals to RACFs. 54.4% of patients were on at least one PIM at admission to hospital with a non-significant trend to fewer PIMs on discharge (49.5%). The frailty status of patients and in-hospital cognitive decline were the only significant predictors for receiving PIMs at both admission and discharge. To our knowledge, this is the first study to identify this association.

The prevalence of PIMs observed in this study population differ from those of previous studies using the recent updated 2012 Beers criteria. A higher prevalence (82.6%) was observed in a Brazilian long term care home study (251) and around 66% was observed in an Argentinian geriatric hospital.(252) Yet, a very low prevalence (16% and 25.5%) was noticed in tertiary health care setting in India and Nigeria respectively.(253, 254) Inpatient studies using the prior versions (1997, 2003) of Beers criteria reported lower prevalence than that observed in our study. The 1997 Beers criteria was used for retrospective analyses of ED visits in US hospitals that reported 12.6% (255) and 10.6% of patients with PIMs (193) and 10% prevalence of PIMs were observed in a Norwegian hospital.(188) Using the 2003 Beers criteria, the prevalence of PIMs ranged from 12% to 37% in inpatient settings (255-257), was reported as 14.7% in Taiwan (258), and 30% in a study conducted in Belgium.(24) Commonly prescribed PIM categories at both admission and discharge were CNS, cardiovascular, gastrointestinal and respiratory drugs, and analgesics which are similar to those reported in other studies.(156, 162, 168, 259) Medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and anticholinergic are routinely prescribed to treat many common conditions in older people. Although the efficacy of NSAIDs for the treatment of inflammation and pain of various origins is well established, prescribing these drugs in older patients is a challenge because of a great variety of gastrointestinal and cardiovascular safety factors that need to be considered.(260) Medications with anticholinergic effects are associated with several adverse effects such as sedation, cognitive decline, delirium and falls.(245)

Of note, 30% of PIMs were stopped and other new PIMs were introduced at discharge. Although our study show that number of PIMs at discharge was lower than on admission,

the reduction was not significant. The proportion of those on PIMs at discharge remained high (49.5%). Australian studies have reported that an average of five to seven changes are made during hospitalisation, with cessation of two to three drugs and initiation of three to four.[43] Over-prescribing (benzodiazepines, antipsychotics, acid suppressants) and inappropriate drug selection (metformin in renal impairment, long-acting oral hypoglycaemic) is common in Australian hospitals.(261) This contributes to increased risk of drug-related problems and higher incidence of PIMs during and immediately following hospitalisation. Although pharmacists play an important role in medication reconciliation review, it was outside the scope of this study to investigate the appropriateness of medication prescribed. The role of the pharmacist in optimising medications in older hospitalized patients has been established by several studies.(139, 262) Studies suggest that strategies to revaluate drug treatment and reduce PIM use during hospitalisation of patients should be undertaken by collaborative efforts of physicians and pharmacists.(263, 264)

We found a clear association between the use of PIMs, frailty status and cognitive decline of patients at admission and discharge. However, no association was observed between PIM use, age and gender, which is consistent with previous reports.(265, 266) Also, no association of PIM use with in-hospital falls, delirium and functional decline was observed. Furthermore, in contrast to other studies,(181, 267, 268) we found no association between polypharmacy and PIM use. There might be several reasons behind this which needs to be explored further. The goals of care in this vulnerable group are likely to be an improvement in quality of life rather than focusing on survival.(269) This could result in a higher prevalence of drugs for the prevention of symptoms such as analgesics for pain, and laxatives or antiulcer drugs for gastrointestinal symptoms. Subsequently, although multiple drugs are used, the probability of having a PIM might be lower. Prolonged length of hospital stay (≥10 days) has been shown to have a significant association with polypharmacy and incidence of PIMs use.(270) The median length of hospital stay in this study was only 8 days which may have minimised the risk of a PIM being prescribed.

There are a number of limitations to this study. The appropriateness of prescribing at the level of individual patients based on clinical indications and contraindications were outside

the scope of this study. Although patients were recruited from multiple hospital sites, the sample size is relatively small .The recently updated Beers criteria contain medications which are either not available in Australia (e.g. carisoprodol and trimethobenzamide) or which have been withdrawn from use here (chlorpropamide, reserpine and phenylbutazone). Thus, the relevance of the tool within Australia could be questioned.(163) Moreover, these criteria also fail to address other factors such as drug duplication, under-prescribing, and drug-drug interaction.(111, 116, 119) Hence, the prevalence of PIMs may be higher than those reported in this study. However, this study demonstrated the prevalence of PIMs in frail older patients on admission and discharge and adds to existing research by identifying patient's frailty status as a unique risk factor associated with the use of PIMs.

These discrepancies in Beers and other established criteria should be addressed either by developing new criteria or by refining the existing tools to make them more applicable to frail older people. The first and foremost step is to identify the frail patient in clinical practice by applying clinically validated tools (e.g. frailty index). Once the frail patient has been identified, there is a need for specific measures or criteria to assess appropriateness of therapy that consider such factors as quality of life, functional status and remaining life expectancy and thus modified goals of care.(170)

3.2.6 Conclusion

A high prevalence of potentially inappropriate drug prescribing was observed in older patients on admission to acute care hospitals and on discharge to RACFs. Frailty status and in-hospital cognitive decline of patients were risk factors for the use of PIMs. The findings of this study provide a basis for designing interventions to rationalize prescribing in older patients. Further studies in different settings with larger population are warranted to evaluate the prevalence of potentially inappropriate medications and deviations in prescribing practices.

3.3 Next Steps

This chapter provides evidence that patients discharged to RACF from hospital continue to be exposed to PIMs. Although an admission to hospital is an opportunity to rationalise medications, this was not seen in this study population. There was an increase in number of patients with >10 meds at discharge compared to medication regimen at admission. However, the results showed no association between polypharmacy and PIM use but identified that frailty status of a patient is a unique risk factor for receiving a PIM. This correlates with the results from Chapter 2 suggesting that polypharmacy might not always be harmful.

The findings of this study suggest the need of more effective interventions in RACFs to rationalise prescribing. Therefore in Chapter 4, we aimed to identify if comprehensive geriatric assessment undertaken by a geriatric medicine specialist results in changes to prescribing patterns, and therefore reduces the prevalence of potentially inappropriate medication use in RACF populations.

Chapter 4: Geriatrician Interventions in Residential Aged Care Facilities

4.1 Chapter Introduction

The proven benefits of comprehensive geriatric assessment in the management of the clinical complexity in older population were discussed in Chapter 1.

Very few studies have evaluated the impact of a geriatrician-led intervention in aged care facilities. The project, '**An Outcomes Oriented Study Identifying Contributions of Geriatric Consultation via Video Conferencing'**, based at the Princess Alexandra Hospital aimed to identify the contributions made by a geriatrician to the care planning of residents at RACFs. An important part of the consultation is the recommendation the geriatrician makes about patients' medications, perhaps advising that some medications are stopped or others commenced. The aim of this phase (section 4.2) of research was to examine geriatrician reviews of RACF residents to assess advice given on medications.

In the next section (section 4.3) of this chapter, we undertook a prospective review of medication charts in RACFs where those reviews had been undertaken to determine if the geriatrician recommendations are implemented and sustained in the clinical setting.

4.2 Published Paper: Geriatrician interventions on medication prescribing for frail older people in residential aged care facilities

Poudel A,Peel NM, Mitchell CA, Gray LC, Nissen LM, Hubbard RE. Geriatrician interventions on medication prescribing for frail older people in residential aged care facilities. Clinical Interventions in Aging. 2015.10

This paper is reproduced in full in Appendix C.

4.2.1 Abstract

Objective: In Australian residential aged care facilities (RACFs), the use of certain classes of potentially inappropriate medication such as antipsychotics, potent analgesics, and sedatives is high. Here, we examined the medications prescribed and subsequent changes recommended by geriatricians during comprehensive geriatric consultations provided to residents of RACFs via video-conference.

Design: Prospective observational study.
Setting: Four residential aged care facilities in Queensland, Australia.
Participants: A total of 153 residents referred by *General Practitioners (GPs)* for comprehensive assessment by geriatricians delivered by video-consultation.

Results: Residents' mean (SD) age was 83.0(8.1) years and 64.1% were female. They had multiple co-morbidities (mean 6), high levels of dependency and were prescribed a mean (SD) of 9.6 (4.2) regular medications. Ninety-one percent of patients were taking five or more medications daily. Of total medications prescribed (n= 1469), geriatricians recommended withdrawal of 9.8% (n= 145) and dose alteration of 3.5% (n= 51) medications prescribed. New medications were initiated in 47.7% (n= 73) patients. Of the 10.3% (n= 151) medications considered as potentially inappropriate, 17.2% were stopped and dose altered in 2.6%.

Conclusion: There was a moderate prevalence of potentially inappropriate medications. However, geriatricians made relatively few changes, suggesting either that, on balance,

prescription of these medications was appropriate or, because of other factors, there was a reluctance to adjust medications. A structured medication review using an algorithm for withdrawing medications of high disutility might help optimise medications in frail patients. Further research, including a broader survey, is required to understand these dynamics.

Keywords: frail older, geriatrician intervention, potentially inappropriate medications, residential aged care facilities

4.2.2 Introduction

Many frail older people spend their final years of life in aged care facilities. In Australia, the proportion of older people living in care accommodation increases with age from 2% of people aged 65–74 years to 6% of people aged 75–84 years and 26% of people aged 85 years and over.(271) Those living in care homes often take more medications than non-institutionalised elderly and the risk of morbidity as a result of medication is high.(272) Also, the incidence of adverse drug events increases with the number of medications prescribed.(205) Residential aged care facilities (RACFs) in Australia are institutions in which prescribing of potentially inappropriate medication such as antipsychotics, potent analgesics, and sedatives is high, with between 25% and 30% of patients receiving such medication.(149, 162, 273) Ensuring high-quality care and appropriate medication use for these residents is challenging given their frailty, complex disabilities and multiple chronic conditions.(274)

Despite the growing body of literature indicating that medication errors and potentially inappropriate medications are important causes of morbidity and mortality, evidence for effective interventions and strategies to improve the pharmacological management of patients is still limited.(275)Well-organized approaches are needed to provide specialist advice in nursing homes to ensure quality medical care. Practice models that include a pharmacist as part of the multidisciplinary team represent best practice in inpatient, ambulatory and community settings, and in care transitions between settings.(276) Geriatrician-led case conference reviews and comprehensive geriatric assessments (CGA) have been shown to be effective in reducing potentially inappropriate medications use and

improved suboptimal prescribing.(274, 277) Although access to geriatric services in Australian RACFs is limited, expert advice is increasingly provided by videoconferencing.

In the model offered in relation to this study, a specialist geriatrician provides a comprehensive assessment of the patient and input into care plans via video conferencing (VC). Geriatricians make recommendation about patients' medications, perhaps advising that some medications are stopped or others commenced. We designed this study to examine whether VC mediated geriatric assessment resulted in changes to medications prescribed, and reduced the prevalence of potentially inappropriate medication use. We also aimed to identify if clinical and demographic characteristics of patients influence the use of potentially inappropriate medications.

4.2.3 Methods

Study population and setting: We conducted a prospective observational cohort study of four RACFs in Queensland, Australia that currently have regular access to geriatric consultations via video-conferencing (VC). The participating facilities were the first four to be supported by the geriatrician service operating out of the Centre for Research in Geriatric Medicine. We were able to record the information for 153 patients assessed by four geriatricians over the research timeframe.

Data collection and Intervention: At participating facilities, geriatrician-supported CGA is encouraged within 4 to 12 weeks of admission. All residents are offered CGA at entry into the participating RACF. However, uptake is determined by referral from the treating general practitioners. The CGA is conducted using a structured protocol based on the interRAI (Resident Assessment Instrument) Long Term Facility assessment system, administered by a senior registered nurse. The assessment includes a comprehensive diagnosis list, justification of all medications documented, functional profile, cognitive assessment confirming the presence or absence of cognitive and mood disorders, recommendations for prevention and management and advanced care planning. Observations made by the nurse are entered into a clinical decision support system (CDSS) which generates a draft resident health care profile and care plan. The CDSS is

mounted on a web based platform to permit review and comment by a specialist geriatrician. interRAI is a not-for-profit research consortium with international collaboration from more than 30 countries that aims to improve the quality of life of vulnerable persons through a unified comprehensive assessment system.

Ideally, one to four weeks following admission to the facility, residents who have been referred to a geriatrician by the GP are assessed via VC consultation by the specialist. The geriatrician is able to speak with the resident as well as attending RACF staff and resident's family members if present. Recommendations to the GP and RACF are made, as necessary, regarding the resident's care plan following the consultation. CGA is also offered to existing residents on an 'as needs' basis. A formal functional profile is prepared, and a report is generated recording recommendations made by the geriatrician. Data for this study were retrieved from these sources over an 18 month period from January 2013 to August 2014.

Ethics: Ethics approval was obtained from the University of Queensland Medical Research Ethics Committee. All patients or their substitute decision-maker gave informed consent for participation.

Key measures: The primary outcome measure was the appropriateness of prescribing. A potentially inappropriate medications list was created based on those recognised by the American Geriatric Society (AGS) 2012 Beers Criteria (194), the McLeod criteria (118), the Laroche criteria (196), the PRISCUS criteria(278), and the Norwegian General Practice (NORGEP) criteria (279) (Table 11). These criteria consider a medication as potentially inappropriate when it has a tendency to cause adverse drug events and drug toxicity in older adults due to its pharmacological properties and the physiologic changes of aging. For our study, we defined potentially inappropriate medications as those that are listed on any one of these criteria. We excluded medications not available in Australia. Polypharmacy status was categorized into three groups based on the number of medications prescribed: non-polypharmacy (0–4 medications), polypharmacy (5–9 medications) and hyper-polypharmacy (≥10 medications) (280). Complementary and as-

required medications were excluded. Three levels of change on current prescription were defined as: drug stopped, dose altered, and new drug started.

Statistical analysis: The Statistical Package for Social Science 21.0 (IBM SPSS Statistics 21. Inc) was used for statistical analysis. Categorical variables were summarised using proportions and continuous variables using mean, standard deviation (SD) and range. In univariate analysis, the differences in the distribution of variables between patients with or without potentially inappropriate medications were compared using the chi-squared test for categorical variables, and non-parametric or parametric comparison of means for continuous variables, depending on the distribution of the data. Tests of significance were two-tailed, using a significance level of $p \leq 0.05$.

Table 11: Potentially inappropriate medications list

Medication	**ATC Codes**	**Main concerns**	**References**
Analgesics, anti-inflammatory			
NSAID			
Aspirin >325mg/day	N02BA01	– very high risk of gastrointestinal hemorrhage, ulceration, or perforation, which may be fatal - risk of renal toxicity especially in patients with pre-existing chronic kidney disease - risk of fluid retention and fluid overload leading to decompensated heart failure in pati8ents with underlying cardiac dysfunction - indomethacin may also have CNS side effects	(194)
Diclofenac	M01AB05		(194)
Ketoprofen	M01AE03		(194, 278)
Ketorolac	M01AB15		(118, 194)
Mefenamic acid	M01AG01		(118, 194)
Meloxicam	M01AC06		(194, 278)
Naproxen	M01AE02		(194)
Piroxicam	M01AC01		(118, 194, 278)
Indometacin	M01AB01		(118, 194, 196, 278)
Etoricoxib	M01AH05		(278)
Ibuprofen	M01AE01		(194)
Opioid analgesics			
Pethidine	N02AB02	– elevated risk of delirium and falls - risk of neurotoxicity	(118, 194, 278)
Antiarrhythmic			
Amiodarone	C01BD01	- predisposition to bradycardia and heart block	(194)
Flecainide	C01BC04	- pro-arrhythmic effects	(194, 278)
Sotalol	C07AA07	- pro-arrhythmic effects	(194, 278, 279)

Disopyramide	C01BA03	- potent negative inotropic effects predisposing to heart failure - anticholinergic activity	(118, 194, 196)
Digoxin > 0.125 mg/d	C01AA05	- risk of toxicity especially in presence of renal insufficiency	(194, 196, 278)
Nifedipine	C08CA05	- potential for postural hypotension - short-acting formulations associated with increased mortality in elderly	(194, 196, 278)
Spironolactone > 25 mg/d	C03DA01	- risk of hyperkalemia	(194)
Diltiazem	C08DB01	- potential to promote fluid retention and exacerbate heart failure	(194)
Verapamil	C08DA01		(194)
Antibiotics			
Nitrofurantoin	J01XE01	long-term use associated with pulmonary side effects, renal impairment, liver damage	(194, 196, 278)
Anticholinergics			
Antihistamines			
Chlorpheniramine	R06AB02	- risk of anticholinergic effect: constipation, dry mouth, visual disturbance, bladder dysfunction - clearance reduced with advanced age, - increased risk of confusion and sedation, impaired cognitive performance	(194, 278)
Cyproheptadine	R06AX02		(194, 196)
Dexchlorpheniramine	R06AB02		(194, 196, 279)
Diphenhydramine	R06AA02		(194, 196, 278)
Doxylamine	R06AA09		(194, 196, 278)
Promethazine	R06AD02		(194, 196, 279)
Antiparkinson agents			
Benztropine	N04AC01	- risk of anticholinergic side effects - not recommended for prevention of extrapyramidal symptoms due to antipsychotics	(194)
Antispasmodics			
Propantheline	A03AB05	- highly anticholinergic, uncertain effectiveness	(194)
Oxybutynin	G04BD04	– anticholinergic side effects – ECG changes (prolonged QT)	(194, 196, 278)
Solifenacin	G04BD08		(194, 196, 278)
Tolterodine (non-sustained release)	G04BD07		(194, 196, 278)
Antithrombotics			
Dipyridamole (short-acting)	B01AC07	- risk of orthostatic hypotension	(118, 194, 196)
Warfarin	B01AA03	- increased risk of bleeding	(194, 278)
Prasugrel	B01AC22		(194, 278)
Ticlopidine	B01AC05		(194, 278)
Antidepressants			
TCA			
Amitriptyline	N06AA09	– peripheral anticholinergic side effects (e.g., constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia)	(118, 194, 196, 278, 279)
Clomipramine	N06AA04	– central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium)	(194, 196, 278, 279)

Doxepin (>6mg)	N06AA12	– cognitive impairment – increased risk of falls	(194, 196, 278, 279)
Imipramine	N06AA02		(118, 194, 196, 278)
Nortriptyline	N06AA10		(194)
SSRI			
Fluoxetine (daily use)	N06AB03	– central nervous side effects (nausea, insomnia, dizziness, confusion) – hyponatremia	(194, 278, 279)
Paroxetine	N06AB05	- confusion and other types of delirium – cognitive impairment	[11]
MAO inhibitors			
Tranylcypromine	N06AF04	- hypertensive crises - cerebral hemorrhage - malignant hyperthermia	(194, 278)
Antiemetic drugs			
Trimethobenzamide	NA	- can cause extrapyramidal adverse effects	(194)
Antiepileptic drugs (AED)			
Phenobarbitone	N03AA02	– sedation – paradoxical excitation - highly addictive	(194, 278)
Antihypertensive agents			
Clonidine	C02AC01	- hypotension (orthostatic), bradycardia, syncope	(194, 196, 278)
Methyldopa	C01AB01	- CNS side effects: sedation, cognitive impairment	(194, 196, 278)
Moxonidine	C02AC05	- hypotension (orthostatic) – bradycardia – sedation	(196)
Nifedipine	C08CA05	– short-acting nifedipine: increased risk of myocardial infarction, increased mortality in elderly patients	(194, 196)
Prazosin	C02CA01	- hypotension	(194, 196, 278)
Terazosin	G04CA03	- dry mouth - urinary incontinence/impaired micturition - increased risk of cerebrovascular and cardiovascular disease	(194, 278)
Antipsychotics (Neuroleptic drugs)			
First-Generation (Conventional) Agents			
Chlorpromazine	N05AA01	– anticholinergic and extrapyramidal side effects – parkinsonism	(118, 194, 196, 279)
Fluphenazine	N05AB02	– hypotonia	(194, 196, 278)
Haloperidol (>2mg)	N05AD01	– sedation and risk of falls	(194, 278)
Promazine	N05AA03	– increased mortality in patients with dementia	(194, 196)
Trifluoperazine	N05AB06		(194)
Prochlorperazine	N05AB04		(194, 196, 278, 279)
Second-Generation (Atypical) Agents			

Aripiprazole	N05AX12	– fewer extrapyramidal side effects – clozapine: increased risk of agranulocytosis and myocarditis	(194)
Asenapine	N05AH05		(194)
Clozapine	N05AH02		(194, 196, 278)
Olanzapine (>10mg)	N05AH03		(194, 196, 278, 279)
Muscle relaxants			
Baclofen	M03BX01	– CNS effects: amnesia, confusion, falls	(196, 278)
Solifenacin	G04BD08	- anticholinergic side effects: constipation, dry mouth, CNS side effects	(194, 196, 278)
Orphenadrine	N04AB02	- more sedation and anticholinergic side effects than safer alternatives	(194)
Sedative and hypnotics			
Long acting benzodiazepines			
Clonazepam	N03AE01	in general, all benzodiazepines increase risk ofcognitive impairment, delirium, falls (muscle-relaxing effect, prolonged sedation) with risk of hip fracture, depression, psychiatric reactions (can cause paradoxical reactions, e.g., agitation, irritability,hallucinations, psychosis)and motor vehicle accidents in older adults	(194)
Diazepam	N05BA01		(118, 194, 196, 278, 279)
Bromazepam	N05BA08		(196, 278)
Clobazam	N05BA09		(196)
Nitrazepam	N05CD02		(196, 278, 279)
Flunitrazepam	N05CD03		(196, 278, 279)
Short- and intermediate acting benzodiazepines			
Alprazolam	N05BA12		(194, 196, 278)
Lorazepam	N05BA06		(194, 196, 278)
Oxazepam	N05BA04		(194, 196, 278, 279)
Temazepam	N05CD07		(194, 196, 278)
Triazolam	N05CD05		(118, 194, 196, 278)
Non benzodiazepine hypnotics			(118, 194, 196, 278)
Zolpidem	N05CF02		(194, 196, 278)
Zopiclone	N05CF01		(196, 278, 279)
Chloral hydrate	N05CC01		(194, 278)
Others			
Theophylline	R03DA02	- risk of arrhythmias - no proof of efficacy in COPD	(194, 279)
Glipizide	A10BB07	- long half-life leading to possible prolonged hypoglycemia	(196)
Cimetidine	A02BA01	- confusion - more interactions than other H2 antagonists	(118, 194, 196)
Diphenoxylate	A07DA01	- no proof of efficacy - blocks the muscarinic receptors	(118, 196)

ATC: Anatomical therapeutic chemical, COPD: Chronic obstructive pulmonary disease, CNS: Central nervous system, ECG: Electrocardiogram, MAO: Monoamine oxidase inhibitors, NSAID: Non- steroidal anti-inflammatory drugs, SSRI: Selective serotonin reuptake inhibitors, TCA: Tricyclic antidepressants.

4.2.4 Results

Over the course of the study, 153 patients were assessed by the four participating geriatricians across four facilities. Demographics and clinical characteristics of the study population are presented in Table 12. The mean (± SD) patient age was 83.0 (± 8.1) years and 64.1% were female. The median length of stay in the facility at the time of assessment was 488 days (Range 6 – 3213 days). Twenty-four percent of patients were assessed within 12 weeks of admission to the facility. Patients had multiple co-morbidities (mean 6), including dementia diagnosed in 67.3%, depression in 46.4% and delirium in 11.7%. Other prevalent comorbidities were hypertension (35.9%); diabetes (20.9%); heart diseases (13.7%); and respiratory diseases (11.1%). Patients were prescribed a mean (± SD) of 9.6 (4.2) regular medications. Polypharmacy (≥5 medications) was seen in 91% (n= 139) residents, half of whom (n=69) were exposed to hyper-polypharmacy (≥ 10 medications).

Of all medications prescribed (n= 1469), the geriatrician recommended withdrawal of 9.8% (n= 145) and dose alteration for 3.5% (n= 51) medications. Medications were stopped because of: adverse effects (n= 66), no clear indication/medication burden (n= 63) and disease cured (n= 16). Similarly, the medication dose was altered because of: adverse effects and other factors (n= 36), changed to ‘as required’ (n= 5), and ineffective dose (n= 10). New medications were initiated in 47.7% (n= 73) patients (see Table 13). Potentially inappropriate medications prescribed (10.3%; n=151) and intervention by geriatrician are listed by drug classes in Table 14. At least one potentially inappropriate medication was prescribed to 58.2% (n= 89) patients. The univariate analysis showed that the length of stay was the only variable significantly associated with patients having at least one potentially inappropriate medication (see Table 15). Of the potentially inappropriate medications, the geriatrician ceased 17.2% (n= 26) medications and altered the dose in 2.6% (n= 4). Potentially inappropriate medications stopped were: analgesics (n= 6), antispasmodics (n= 5), sedative and hypnotics (n= 5), antipsychotics (n= 3), antiarrhythmic (n= 3), antihypertensive (n= 2), gastrointestinal medications (n= 1), and antibiotics (n=1). The dose was altered for: antiarrhythmic (n= 2), antidepressants (n= 1) and sedative and hypnotics (n= 1).

Table 12: Demographic and clinical characteristics of study population

Characteristics	**Total N=153**
Age, y	
Mean ± SD	83.0 ± 8.1
Median	83
Females, n (%)	98 (64.1)
Length of stay at the time of assessment : median length of stay, days [IQR]	488 [6- 3213]
Marital status (%)	
Married	50 (32.6)
Widowed	73 (47.7)
Separated/Divorced	19 (12.4)
Never married	11 (7.1)
Comorbidities (%)	
Dementia	103 (67.3)
Delirium	18 (11.7)
Depression	71 (46.4)
Under nutrition	49 (32.0)
COPD*/Asthma	17 (11.1)
Hypertension	55 (35.9)
Diabetes	32 (20.9)
Ischemic Heart Disease	21 (13.7)
Prescription medications	
Total number of prescribed medications	1469
Mean ± SD	9.6 ± 4.2
Polypharmacy categories (%)	
0-4 medications (non-polypharmacy)	14 (9.2)
5-9 medications (polypharmacy)	70 (45.8)
≥ 10 medications (hyper-polypharmacy)	69 (45.1)

*COPD: Chronic obstructive pulmonary disease; RACF: Residential aged care facility

Table 13: Outcomes of geriatrician intervention

Interventions	**No of Medications**	**Reasons**
Drug stopped [145 (9.8%)]	66	adverse effects
	63	no clear indication/medication burden
	16	disease cured or quiescent
Dose altered [51 (3.5%)]	36	dose reduced (because of adverse effects and other factors)
	10	dose increased (because of ineffective dose)
	5	changed to "as required'
New drug started [102 (6.9%)]	58	untreated morbidity
	23	better alternative to present therapy
	21	symptom relief

Total medication prescribed: 1469; **Total potentially inappropriate medications prescribed:** 151(10.3%)

Table 14: Potentially inappropriate medication prescribed and geriatrician intervention

System/therapeutic category/medications	**Potentially inappropriatemedications prescribed n(%)**	**Result of geriatrician intervention**
Central nervous system medications	**80 (52.9)**	
Antidepressants	10 (6.6)	DA - 1
Antipsychotics	21 (13.9)	DS - 3
		NDS - 1
Sedative and hypnotics	49 (32.4)	DS - 5
		DA - 1
		NDS - 2
Cardiovascular system medications	**21 (13.9)**	
Antiarrhythmic	12 (7.9)	DS - 3
		DA - 2
		NDS - 1
Antihypertensive	9 (5.9)	DS - 2
Gastrointestinal	**6 (3.9)**	DS - 1
Antihistamines	**5 (3.3)**	
Antithrombotic	**22 (14.5)**	
Antiparkinson agents	**1 (0.6)**	
Antispasmodics	**5 (3.3)**	DS - 5
Analgesics	**9 (5.9)**	DS - 6
Antibiotics	**2 (1.3)**	DS - 1
Total	**151 (100)**	**DA – 4**
		DS – 26
		NDS – 4

DA: Dose altered; DS: Drug stopped; NDS: New drug started

Table 15: Univariate analysis of variables influencing the use of potentially inappropriate medications

Characteristics	**Patients**		**p-value**
	Without PIMs (n= 64)	With at least one PIM (n= 89)	
Socio-demographic			
Age	83.55 ± 8.5	82.67 ± 7.8	0.513
Sex(Female)	44 (68.8)	54 (60.7)	0.304
Clinical			
Length of Stay	303 [70.75 – 780.50]	630 [100- 1022.50]	0.044
Assessment status (within 12 weeks of admission)	18 (28.1)	19 (21.3)	0.334
Polypharmacy (>4medications)	57 (89.1)	82 (92.1)	0.516
Comorbid conditions			
Delirium	7 (10.9)	11 (12.4)	0.788
Dementia	44 (68.8)	59 (66.3)	0.749
Depression	27 (42.2)	44 (49.4)	0.375
Undernutrition	24 (37.5)	25 (28.1)	0.218

PIM: Potentially inappropriate medication, Values represent frequency (% of n).

4.2.5 Discussion

To our knowledge, this is the first study of a geriatrician intervention where the medication advice for residents at long term residential care facilities was specifically assessed via video consultation. We found moderate levels of potentially inappropriate medications prescribed to residents in RACFs. Geriatricians made relatively few changes. This

suggests that either the prescription of these medications was appropriate or other factors influenced the decision not to adjust medications.

The aim of defining potentially inappropriate medication use is to focus on a group of medications for which there is common consensus about potential inappropriateness. In principle, the potentially inappropriate medications prescribed to RACF residents in our study should not have been started or continued except under certain conditions ; for example, amiodarone, a potentially inappropriate medication used in older people, is a therapy that may be indicated to treat supraventricular arrhythmias effectively in patients with heart failure(281); and benzodiazepines, that may increase the risk of mental decline, delirium, falls and fractures in older adults, may be appropriate for treating seizures, certain sleep disorders and anxiety disorders.(194) The reluctance on the part of the geriatrician in adjusting/stopping many of these potentially inappropriate medications might suggest that prescription of some of these medications was appropriate. It is also possible that patients' (or primary care medical practitioners') strong belief in their medications might impact on an otherwise appropriate reduction in the number of medications taken, but this was not specifically explored in our study. Despite the GPs' recognition that use of multiple medication is hazardous in their older patient population and the fact that GPs perceive it as their role in addressing the problem; they experience obstacles at different levels such as difficulties in keeping an overview of the exact medication intake caused by polypharmacy and patients' strong belief in their medication.(282) Patients are not always inclined to stop medication that they have been using chronically.(283) In addition to these patient-related factors, there might be some prescriber-related factors that hinder medication adjustment, such as involvement of several prescribers, use of preventive medication and evidence based medicine guidelines that often induce polypharmacy, uncertainties of precipitating disease relapse or drug withdrawal syndromes, and lack of risk/benefit information for the frail older residents.(203)

Interventions for appropriate prescribing in older people such as education, medication reviews, computerised support systems and interdisciplinary team review have a positive impact on prescribing.(277) Yet, evidence for effective interventions to improve care in residential care settings is limited. A study by Crotty *et al.* suggested that case

conferences help an outreach geriatrician team to optimise medication management.(274) They describe the use of multidisciplinary case conference meetings to review medication in RACFs with significant improvement in medication appropriateness in the intervention group. There is conflicting evidence, however, concerning the efficacy of case conference medication reviews. One study using case conferencing to review the prescription and use of medications for community-dwelling older adults was unsuccessful in demonstrating change in inappropriate use of medications.(284) A similar study in residential care facilities was unsuccessful in establishing changes in the number of medications.(285) Other approaches to optimise prescribing in frail older people might be the integration of a pharmacist in a team to make a collaborative approach on the quality of prescribing. Studies from inpatient settings suggest that the addition of a pharmacist to health care teams could lead to major reductions in morbidity and improved patient outcomes.(24, 286) Another study on older patients transferring from hospital to a long-term care facility showed that adding a pharmacist transition coordinator on evidence-based medication management and health outcomes could improve aspects of inappropriate use of medications.(287)

Optimising prescribing requires appropriate ways to taper or withdraw potentially inappropriate medications in older adults. Available explicit and implicit criteria for appropriate prescribing encompass medications that have been validated in, and applied to, robust, healthy populations aged 65 and older. Therefore, these approaches may not be applicable to the more frail and multi-morbid oldest old who reside in RACFs.(169) Most attention has been paid to the development of guidelines on how to initiate medications but there are limited studies on the most effective way to cease medications.(288, 289) Barriers to ceasing medications include time constraints on medical practitioners. This had led some to advocate that there should be some systematic approaches to follow in ceasing medications.(290, 291) In responding to polypharmacy and minimising potentially inappropriate medications, there appears a need for a practical algorithm that helps clinicians identify and discontinue potentially inappropriate medications using a systematic approach. This algorithm should signify a range of different clinical scenarios in relation to potentially inappropriate medications and offer an evidence-based approach to identifying

and, if appropriate, discontinuing such medications and/or suggesting alternative treatments when required.

Our study has several limitations. Although, combining five different explicit criteria gives us an opportunity to extract a comprehensive list of potentially inappropriate medications, this list is not meant to regulate practice in a manner that surpasses the clinical judgement and the assessment of a prescriber. Also, because of our definition of potentially inappropriate medications as a list of drugs, the further domains of inappropriate prescribing such as underuse of medications and drug-drug interaction might be missed. Any adverse health events occurring among the residents using potentially inappropriate medications were also not investigated in our study.

4.2.6 Conclusion

In this study of 153 residents in four RACFs, we found a moderate prevalence of potentially inappropriate medications. However, geriatricians made relatively few changes, suggesting either that, on balance, prescription of these medications was appropriate or, because of other factors, there was a reluctance to adjust medications. Further research, including a broader survey, is required to understand these dynamics. Medication review algorithms for withdrawing medications of high disutility might help optimise medication prescribing in frail older people.

4.3 A Prospective Review to Evaluate the Impact of Medication Changes Recommended by Consultant Geriatricians

4.3.1 Introduction

A study to identify contributions of geriatric consultation via video conferencing (VC) for residents at long term Residential Aged Care Facilities (RACF) was started in 2012 at The Centre for Research in Geriatric Medicines (CRGM), Princess Alexandra Hospital (PAH). Geriatricians made recommendations on patients' medication (stopped medication, altered dose or commenced a new medication). Following up on such recommendations at the VC consultation is important for patient outcomes and safety.

One of the important aspects of transition care is a follow up on recommendations made at the time of hospital discharge. Although data on transition of patients to nursing home is lacking, it has been postulated that errors in transitional care may result in adverse patient outcomes.(292) Similarly in our study, once the geriatrician's consultation has been completed there is currently no follow-up on the recommendations that have been made.

The aim of this study was to review the impact of these recommendations on patient medications **3 months after the initial VC consultation** to determine the extent to which the medication changes recommended by the consultant geriatricians have been implemented in clinical practice.

4.3.2 Methods

This study was designed to review **medication charts** and **care plans** of patients in one RACF three months after they have been seen by a consultant geriatrician via VC where 89 subjects were assessed between January 2013 and August 2014. This RACF was the first among others to use this service. From the 89 subjects, 50 were randomly selected for review using a random number generator program.

To appropriately assess the impact of the geriatricians review on medication, the medication chart and patient medical record were reviewed. Each patient was assigned a unique identification number which eliminated the requirement to collect identifiable data at the RACF site, thus protecting the anonymity of patient specific data. Data collection included information on demographic characteristics of the subject, recommendations made by the geriatrician during initial consultation, and whether or not these recommendations had been implemented.

4.3.3 Results

Sixty records were reviewed to obtain the required sample of 50 subjects. 10 subjects' medical record could not be accessed because they had passed away. The baseline characteristics of study sample are presented in Table 16.The mean age was 82.7 ± 8.1 (range 62-103) and 57% were female. The median length of stay in the RACF at the time of assessment was 475 days (range 25-3000 days).

Table 16: Baseline characteristics of study population (N=50)

Characteristics	**Total N=153**
Age, y	
Mean ± SD	82.7 ± 8.1
Median	83
Females, n (%)	57 (64.0)
Length of stay at the time of assessment : median length of stay, days [IQR]	475 (25- 3000)

Table 17 lists the categories of 126medication recommendations made for the 50 subjects made by the geriatricians. The most common recommendation was to stop medication (n=55; 43.6%), start a new medication (n=44; 35%) and alter dose (n=27; 21.4%).Table 18 lists the categories of recommendation that were not followed within 90 days of geriatrician assessment. Of those 126 recommendations, only 17 (13.5%) were not followed.

Table 17: Categories of medication recommendations made by geriatrician

Recommendations	**Frequency (%)**
Stop current medication	55 (43.6)
Alter dose	27 (21.4)
Start new medication	44 (35.0)
Total	**126**

Table 18: Categories of recommendations not followed

Recommendations	**Total number of recommendations not followed (% of categories of medication recommended)**
Stop current medication	7 (12.7)
Alter dose	6 (22.2)
Start new medication	4 (9.0)
Total	**17**

4.3.4 Discussion

Three months after the initial consultation, we reviewed the recommendations made by geriatricians for patients in RACF. Almost 14% of recommendations made during consultations were not followed by the patients' usual prescriber – the local GP).

The reason behind the variation between the recommendation and what had been implemented was not determined in this study. For example, stopping a sedative may have resulted in increased patient agitation leading the local general practitioner (GP) to restart the medication. Another reason might be that sometime after the geriatrician assessment, the patient's health might have declined which favoured changes in goals of care so the GP returned back to the previous treatment plan. Other reasons might be the personal views of the treating GP, costs to the patient and availability of various interventions. The potential reasons why some recommendations were not followed were

not directly investigated during the chart review. This requires further investigation that could include semi-structured interviews or other direct feedback from the patients'' usual prescriber.

This study has limitations. This was a single site study with a relatively small sample size. Only 60 medical records were selected and 50 reviewed because of restricted time and resources.

4.3.5 Conclusion

While most of the recommendations made by the geriatrician were acted upon by the local GP, approximately one in seven recommendations were not followed. This discrepancy needs further evaluation in order to best understand potential barriers to achieving optimal pharmacotherapy for this group of patients. It is hoped that the outcomes of this project will provide a clearer picture of the value of the geriatricians' recommendations regarding RACF patient medication management.

4.4 Next Steps

Given that in this group of RACF patients, geriatricians made relatively few recommendations to reduce the frequency of PIM use, a pragmatic and easily applied approach is needed to assist clinicians in identifying potentially inappropriate medications in order they might consider their cessation. Also, the availability and feasibility of non-drug alternatives needs to be better addressed. The outcomes of the research we have undertaken so far suggests the need for an algorithm of medication review that focuses on minimisation of potentially inappropriate medications in frail older people. Such an approach is described in Chapter 5.

Chapter 5: Best Practice Guidelines for Prescribing in Frail Older People

5.1 Chapter Introduction

The findings from Chapter 4 suggested that geriatrician intervention in aged care facilities led to relatively few changes in patients' potentially inappropriate medication. One of the tools that might assist is nursing home/aged care facility specific prescribing practice guidelines.

The well-documented prevalence and harm from potentially inappropriate medications in this setting should prompt clinicians to identify and stop, or reduce the dose of, inappropriate medications as a matter of priority. Clinical research, guidelines and models of care seldom support the complex and difficult decisions about when to stop existing drugs or withhold new ones in frail older patients. Although tools have been developed to assess the appropriateness of prescribing in older people, these tools and instruments are often used to audit current practice and provide feedback in regard to specific patient cohorts. They are rarely used by clinicians in making prescribing decisions for individual patients in routine practice.

We therefore developed a practical algorithm to help clinicians identify and discontinue potentially inappropriate medications that predispose older patients to develop various geriatrics syndromes.

5.2 Accepted Paper: An Algorithm of Medication Review in Frail Older People: Focus on Minimizing Use of Potentially Inappropriate Medications

This paper has been accepted for publication in Geriatrics & Gerontology International.

5.2.1 Abstract

Aim: Frail older people typically suffer several chronic diseases, receive multiple medications and are more likely to be institutionalized in residential aged care facilities (RACFs). In such patients, optimising prescribing and avoiding use of potentially inappropriate medications might prevent adverse events. This study aimed to develop a pragmatic, easily applied algorithm for medication review to help clinicians identify and discontinue potentially inappropriate medications.

Methods: The literature was searched for robust evidence of association of adverse effects related to potentially inappropriate medications (PIMs) in older patients to identify potentially inappropriate medications. Prior research into the cessation of PIMs in older patients in different settings was synthesised into a 4-step algorithm for incorporation into clinical assessment protocols for patients, particularly those in RACFs.

Results: The algorithm comprises several steps leading to individualised prescribing recommendations: 1) identify a potentially inappropriate medication; 2) ascertain the current indications for the medication and assess their validity; 3) assess if the drug is providing ongoing symptomatic benefit; 4) consider withdrawing, altering, or continuing medications. Decision support resources were developed to complement the algorithm in ensuring a systematic and patient-centred approach to medication discontinuation. These include a comprehensive list of potentially inappropriate medications and the reasons for inappropriateness, lists of alternative treatments, and suggested medication withdrawal protocols.

Conclusions: The algorithm captures a range of different clinical scenarios in relation to PIMs and offers an evidence-based approach to identifying and, if appropriate,

discontinuing such medications. Studies are required to evaluate algorithm effects on prescribing decisions and patient outcomes.

Keywords: algorithm, potentially inappropriate medications, medication review, medication withdrawal, residential aged care facilities.

5.2.2 Introduction

While many older people remain robust and independent, others become frail, suffer chronic diseases, receive multiple medications, and are susceptible to adverse drug events (ADEs).(124) In addition, age-related changes in drug pharmacokinetics and pharmacodynamics complicate medication prescribing.(293) Identifying ways for optimising prescribing and minimizing harm in this vulnerable population is increasingly a priority for health care providers and policy makers. This is of particular importance for patients in residential aged care facilities (RACFs). Frail older people are more likely to be institutionalized in RACFs with approximately 40% of people aged greater than 75 years requiring long-term residential care: this proportion is predicted to increase further as family and work patterns change(294). Age-specific death rates are higher among institutionalized versus community-living older people as a result of a higher burden of co-morbidity and frailty.(295)

Higher risks of ADEs result from medication errors, adverse drug reactions and drug-drug and drug-disease interactions.(296, 297) Risk factors for medication-related harm include polypharmacy (defined as 5 or more regularly prescribed drugs)(249) and use of potentially inappropriate medications (PIMs) such as selective serotonin reuptake inhibitors (SSRIs), hypnotics, antipsychotics, analgesics (opiates), anxiolytics and anticholinergic drugs which are regularly prescribed to 25% to 30% of patients in Australian RACFs.(149, 162, 273) Many of these drugs predispose to falls which occur in more than 50% of RACF residents each year (at a rate of 1.5 falls per bed per year) some with serious consequences such as hip fracture, hospitalization, depression and a mobility-limiting morbid fear of falling.(273) About 40% of all hip fractures occur in RACF populations.(298) Delirium occurs in between 22% and 70% of patients (299), with

medications the sole precipitant in 12% to 39% of cases (300). Urinary incontinence occurs in more than 50% of RACF patients, often exacerbated by diuretics, while malnutrition affects about half of RACF residents secondary to reduced appetite, nausea or lack of attention to eating, with analgesics, sedatives and metformin being contributory agents.(301)

Polypharmacy is seen in over 80% of residents in RACFs (302) with between 40% and 50% being prescribed one or more potentially inappropriate medications (PIMs) associated with incidence rates of adverse drug reactions ranging from 1 to 7 per 100 residents per month, depending upon the method of detection.(303) This high rate of polypharmacy in frail older people is driven by the high prevalence of diseases and the perceived need, on the part of prescribers, for more medications, reinforced by disease specific guidelines that invariably advocate multidrug regimens.(304) Although data on factors that predict individual risk of adverse consequences related to inappropriate prescribing are limited, it is likely that frail patients who are more likely to develop geriatric syndromes constitute a high risk group.(175)

A number of explicit and implicit criteria for identifying instances of potentially inappropriate under- or over-prescribing in older people have been assessed. Some widely used and validated criteria include The Beers Criteria (194), the Medication Appropriateness Index (MAI) (125), the Screening Tool of Older Person's Prescriptions/Screening Tool to Alert Doctors to the Right Treatment (STOPP/START) (305) and the Inappropriate Prescribing in the Elderly Tool (IPET) (121). The majority of these tools are aimed at general populations aged 65 and older that include healthy, robust, older adults. Hence, they may be less useful in identifying drugs associated with considerable risk of harm among the more frail and multi-morbid oldest old who reside in RACFs.(106) Moreover, there is little guidance on recognizing geriatric syndromes strongly associated with specific PIMs and how to safely taper or withdraw PIMs in such adults.

Hence, we sought to develop a practical algorithm to help clinicians identify and discontinue PIMs that predispose older patients to develop various geriatrics syndromes. The algorithm aims to provide step-by-step instructions to taper and withdraw

inappropriate medications. It differs from the generic ‘drugs-to-avoid’ list in that it targets drugs of highest risk, suggests alternative therapies (which can include non-pharmacological approaches), and informs the discontinuation process by highlighting risk of withdrawal or disease recurrence syndromes while recommending appropriate tapering regimens. In particular, this algorithm might be easier to apply by prescribers to individual patients and exert more impact than generic ‘drugs-to-avoid’ lists in reducing medication-related adverse effects in long term care facilities.

5.2.3 Methods

First, we created a provisional list of PIMs based on those recognized by the American Geriatric Society (AGS) 2012 Beers Criteria (194), the McLeod criteria (118), the Laroche list (196), the PRISCUS list (278), and the Norwegian General Practice (NORGEP) criteria (279). These criteria consider a medication as potentially inappropriate when it has a well-documented tendency to cause adverse drug events and drug toxicity in older adults due to its pharmacological properties and the physiologic changes of aging. For our study, we defined PIMs as those that are listed on any one of these criteria. We excluded drugs that are not frequently used or unavailable in Australia.

Second, while not intending to perform a systematic review, we undertook a structured PubMed literature search of each drug and its association with adverse effects using search terms including ‘falls’, ‘delirium’, ‘depression’, ‘cognitive impairment’, ‘activities of daily living’, ‘adverse health outcomes’, ‘adverse effects’ and ‘geriatric syndromes’. This was followed by a citation search of relevant articles. For each of these relevant articles, a cited reference search was conducted using Web of Science. The final list of drugs and their most prevalent side effects are listed in Table 11.

Third, to gather information about safe discontinuation of PIMs in older patients, a literature search using PubMed was made using the final list of PIMs and terms such as “withdrawal”, “cessation” and “discontinuation”, “stopping” and “deprescribing”. A comprehensive table of clinical manifestations of withdrawal or disease recurrence syndromes, suggested withdrawal regimen, and specific facts or recommendations concerning discontinuation, where applicable, was developed (Table 19). This search

revealed several recently published systematic reviews of strategies for minimizing use of potentially inappropriate medications in older patients,(211, 212, 306-310) including use of algorithms, which informed the design of the present algorithm, and which obviated the need for us to perform a more formal systematic review. While several deprescribing algorithms have been proposed,(1, 103, 311) no randomized controlled trials have been performed to date to evaluate their effectiveness in routine care.

Finally, we constructed a 4 step algorithm that guided clinicians in assessing medication lists of patients in RACFs, identifying medications potentially eligible for discontinuation, and formulating withdrawal regimens. This algorithm is a condensed form of an earlier version of a 10-step conceptual framework developed by Scott and colleagues that has been shown to have face validity in observational studies.(124) This condensed algorithm is targeted to a specific frail population and is expected to have easy application in busy clinical settings.

Table 19: Withdrawal regimens for commonly used medications in older people

GROUP OF MEDICATIONS	SUGGESTED WITHDRAWAL REGIMENT	FACTORS INFLUENCING RATE OF WITHDRAWAL	TYPE OF SYNDROME	CLINICAL MANIFESTATION	REFERENCES
CNS ACTING DRUGS					
Opioid analgesics					
	• **Slow approach:** 10% dose reduction per week • **Rapid approach:** 25-50% dose reduction every few days	**Factors influencing the reduction rate** **Slow:** - High starting dose - Occurrence of withdrawal syndrome **Rapid:** - Reason of discontinuation – adverse effects of the drug - Presence of psychiatric comorbidities - Lower starting dose	D, W	Restlessness Irritability Tremor Nausea Vomiting Diarrhea Increased blood pressure Watery eyes, runny nose, yawning, sweating Cramps and muscles aches	(312) (313)
Anxiolytics/hypnotics					
Benzodiazepines Z-drugs	**Dosage tapering:** • Slow withdrawal schedules, usually effective in long half-life benzodiazepines • Low dose tapering with cognitively-behavioral therapy is recommended depending on the indication of the drug (anxiety/insomnia) **Switching to diazepam:** • When using short half-life benzodiazepines	- Short and intermediate half-life W symptoms 24-36 hr. after interruption, W symptoms can be more acute and intense - Long half-life = W symptoms up to 1 week after interruption - W symptoms duration = 6-8 hr after cessation - Peak intensity = second and third	D,W	**Most frequent:** Tremor, confusion, anxiety, insomnia, nightmares, sweating, tachycardia, irritability **Severe:** Convulsions, psychotic reactions, substantial increase in blood pressure, increased risk of myocardial ischemia	(314) (315)

	• Might be beneficial just when patient experiences a severe withdrawal syndrome, and those who should be under supervision for adverse effects (e.g. fall, cognitive impairment, delirium)	weeks			
Antidepressants					
Amitriptyline, Clomipramine, Doxepin, Imipramine	Taper slowly with caution		W	Anxiety, nausea, vomiting, headache, dizziness, dyskinesia, insomnia, restlessness	(316)
H1- antihistaminics					
Dexchlorpheniramine, Doxylamine, Promethazine	Taper slowly with caution		W	Anxiety, nausea, vomiting, headache, dizziness, dyskinesia, insomnia, restlessness	(316)
Antiepileptic					
Carbamazepine	Taper slowly with caution		W	Anxiety, nausea, vomiting, headache, dizziness, dyskinesia, insomnia, restlessness	(316)
Antipsychotics					
Chlorpromazine, Fluphenazine, Trifluoperazine	Taper slowly with caution		W	Anxiety, nausea, vomiting, headache, dizziness, dyskinesia, insomnia, restlessness	(316)
Antiparkinsonics					
Dopamine agonists	Taper slowly with caution – for doses tapering refer to medication information sheets of individual drugs	- Onset of W is variable - The rate of the taper does not appear to influence the risk of W – patients can experience W even with extremely low taper	D, W, R	DOPAMINE AGONIST WITHDRAWAL SYNDROME - Appears to be a class effect - Dopamine dysregulation syndrome – severe dyskinesia - Anxiety, panic attacks, social phobia,	(317)

		- Duration of W is variable (months to years) - Doesn't react to levodopa treatment – avoid overmedication - Levodopa treatment can be used for fixation of baseline non-motor and motor PD symptoms		agoraphobia, irritability, dysphonia, depression, suicidal ideation - Diaphoresis, fatigue, flushing, nausea, vomiting (these autonomic symptoms can be extremely severe) - Paradoxical orthostatic hypotension - Generalized pain, restless legs (even if there is no prior history)	
Levodopa	Taper slowly with caution	Additional risk factor leading to W: - Neuroleptic medication - Dehydration - Excessively hot weather - Wearing-off phenomenon	W, D, R	PARKINSONISM-HYPERPYREXIA SYNDROME (also called NEUROLEPTIC MALIGNANT-LIKE SYNDROME, LEVODOPA-WITHDRAWAL HYPERTERMIA): - Typically develop in 18 hours to 7 days after trigger – patient becomes rigid, sometimes with tremor, and progresses to immobile status - Within 72-96 hours most patients develop pyrexia (>38 °C) and a reduced conscious level ranging from conscious to coma - After that autonomic dysfunction with tachycardia, labile blood pressure and diaphoresis follows - Laboratory leukocytosis, elevated creatinine kinase	(318)
Drugs for Alzheimer's disease					
Anticholinesterases	Taper slowly with caution		W, D	Delirium	(319)

CARDIOVASCULAR DRUGS					
Antihypertensives					
Alpha-blockers	Taper slowly with caution		W, R	Agitation, headache, hypertension, palpitations	(316)
Central-acting drugs	Taper slowly with caution		W, D, R	Hypertension	(320)
Beta-blockers	Taper slowly with caution		W, D, R	Angina, anxiety, hypertension, acute coronary syndrome, tachycardia	(316)
ACEI	Taper slowly with caution		D	Heart failure, hypertension	(316)
Sartans	Taper slowly with caution		D	Heart failure, hypertension	(316)
Calcium channel blockers	Taper slowly with caution		D	Hypertension	
Diuretics	Taper slowly with caution		D	Heart failure, hypertension	(316)
Antiarrhythmics					
Amiodarone	Can be withdrawn without tapering	Drug has a very long half-life and therefore no need to taper			
Digoxin			D	Heart failure, palpitations	(316)
Other CVS medications					
Disopyramide	Taper slowly with caution		W	Anxiety, nausea, vomiting, headache, dizziness, dyskinesia, insomnia, restlessness	(316)
GASTROINTESTINAL TRACT DRUGS					
Antiulcerotics					
Proton pump inhibitors	Taper slowly	- R can occur after a second week of discontinuation and can last up to 2-3 months (probably depends on the previous length of treatment with PPI) - Evidence shows higher prevalence among patients not infected by *H. pylori*	D, R	REBOUND ACID HYPERSECRETION - Increase in gastric acid secretion above pre-treatment levels - Contribution to recurrence of gastroesophageal reflux disease (GERD)	(321) (322) (323)

H2 antagonists	Taper slowly	Evidence suggest short term, not severe rebound phenomena compared to PPI	D, R	**REBOUND ACID HYPERSECRETION** - Increase in gastric acid secretion above pre-treatment levels - Contribution to recurrence of GERD	(323)
Stimulant laxatives					
Bisacodyl, senna, sodium picosulfate	Taper slowly	- Usually need cognitively-behavioral therapy - Need for control of electrolyte and metabolic disturbances - Utilization of fiber/osmotic supplements to establish normal bowel movements	D, W	Obstipation, GIT disorders and discomfort	(324)
Spasmolytics with anticholinergic effect					
Dicyclomine, Hyoscyamine, Belladonna, Scopolamine, Diphenoxylate	Taper slowly with caution		W	Anxiety, nausea, vomiting, headache, dizziness, dyskinesia, insomnia, restlessness	(316)
OTHER DRUGS					
Genital-urinary antispasmodics					
Oxybutynin, Tolterodine	Taper slowly with caution		W	Anxiety, nausea, vomiting, headache, dizziness, dyskinesia, insomnia, restlessness	(316)
Antiasthmatics					
Ipratropium bromide	Taper slowly with caution		W	Anxiety, nausea, vomiting, headache, dizziness, dyskinesia, insomnia	(316)

ACEI: Angiotensin-converting enzyme inhibitors**, CNS:** Central Nervous System, **D**: Disease recurrence, **R**: Rebound, **W**: Withdrawal

5.2.4 Results

Proposed medication review algorithm

The 4-step algorithm is shown in Figure 4. Each step and the recommended process for withdrawing medications identified as inappropriate are described below with supporting evidence.

1) Identify a high risk PIM: Potentially inappropriate medications are those that tend to cause ADEs in older adults due to their pharmacological properties interacting with the physiologic changes of aging. The list of potentially inappropriate medications and their associated risk of adverse effects contained in Table 11 underscored this step. We do not claim this list is exhaustive, and the safety of other drugs not included here has to be considered depending on the patient's individual circumstances.

2) Ascertain and validate current indications for each PIM: Once PIMs are identified, their indications must be ascertained and validated, which involves 2 steps – verifying the diagnosis against formal diagnostic criteria and then verifying the indication according to evidence of benefit (or utility) of the drug gained from clinical studies whose participants resemble patients living in RACFs. In validating indications in this patient population with limited life expectancy, evidence of the effects of drugs on improving symptoms, function and quality of life should be considered no less important than that which relates to reduction in risk of future adverse clinical events.

In cases where there is no valid diagnosis or indication, medication withdrawal should be strongly considered, although the outcome of any previous trial of discontinuation needs to be taken into account. If a previously discontinued medication was recommenced because of withdrawal symptoms, disease relapse or for other reasons, then further assessment of the current or future level of benefit or harm which the drug confers on the patient should be considered in justifying another trial of discontinuation. If no previous attempt at discontinuation has been performed, then the medication should be ceased using an appropriate withdrawal regimen (Table 19). For those PIMs where a valid current diagnosis-specific indication appears to exist, further steps of the algorithm should be followed.

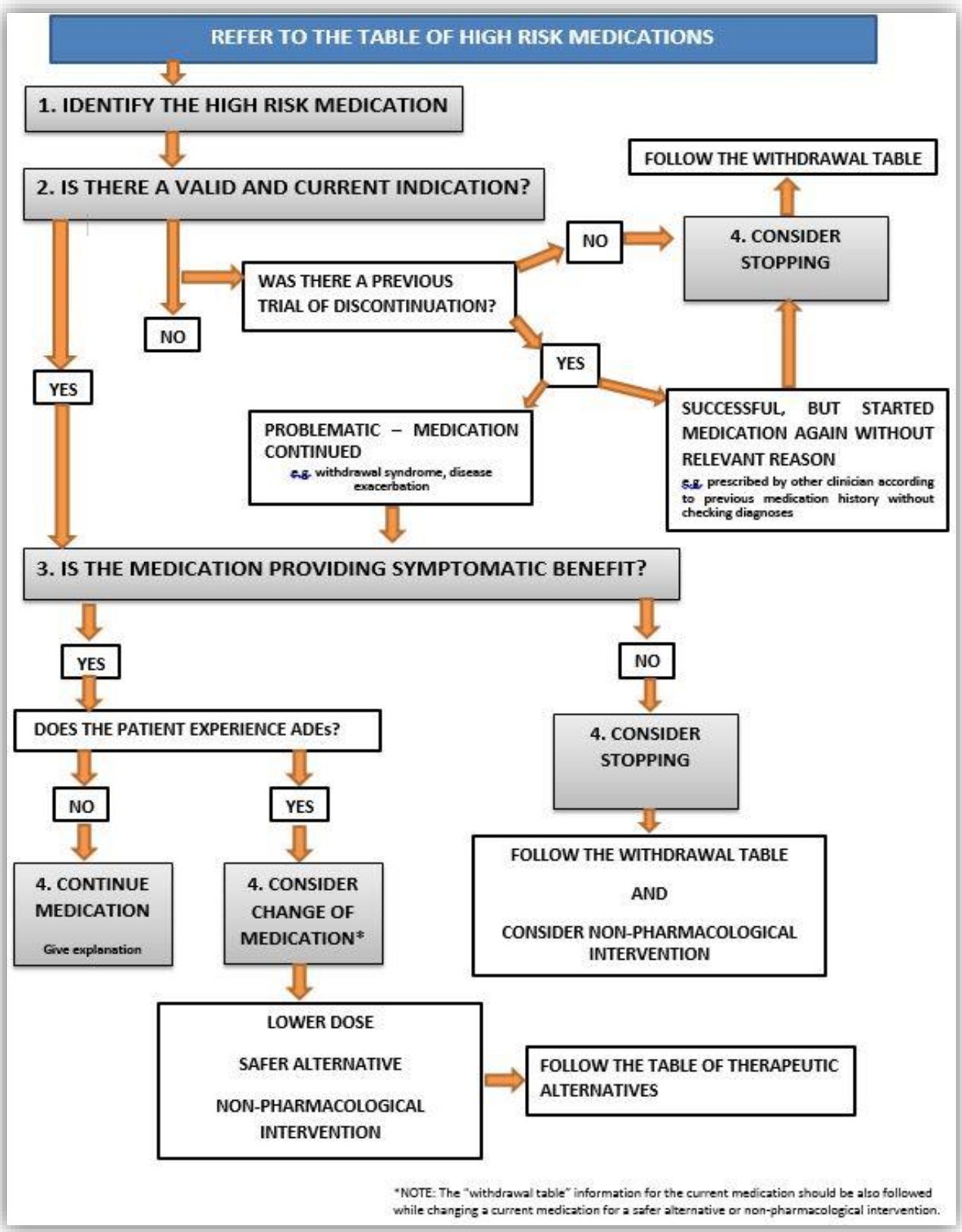


Figure 4: Algorithm of medication review process identifying potentially inappropriate medications, their indications, and protocols for modification

3) Determine if the drug is providing ongoing symptomatic benefit: Use of medications in frail patients should be prioritised according to their ability to suppress disabling or troubling symptoms of currently active disease as opposed to primary or secondary prevention of future disease events, especially those unlikely to occur within the patient's remaining lifespan.(325) According to this step, a medication can essentially belong to one of two categories: 1) drugs providing immediate symptomatic benefits (e.g. analgesics or thyroxine) or essential to preventing rapid symptomatic deterioration (e.g. diuretics and ACE inhibitors in severe systolic heart failure); 2) drugs having no effect on symptoms and primarily used to prevent disease complications in the medium to long-term future. Potentially inappropriate medications in the former category will need to be assessed for eligibility for discontinuation on a case by case basis, based on the balance between the magnitude of immediate symptomatic benefit and the magnitude of risk of short-term harm, and the availability of equally effective non-pharmacological treatment options. Potentially inappropriate medications in the second category should be considered for discontinuation in almost all cases, unless it is estimated that the risk of a catastrophic disease event is very high and likely to occur in the relatively near future (6 to 12 months).

4) Consider withdrawing, altering, or continuing medications: Randomized and observational trials involving patients over 65 years of age have demonstrated minimal harm and improved outcomes when certain classes of medications such as anti-hypertensives, benzodiazepines, and antipsychotics are withdrawn under supervision in appropriate cases.(326) Where a currently prescribed PIM is causing, or has caused, an ADE, a trial of discontinuation is definitely warranted. Review of the medication in the context of each patient's clinical status should seek to determine which of the following four steps should occur next:

- Adjustment of the medication dosage or frequency
- Change to a safer alternative from the same drug class or from another pharmacologically similar drug class which is generally considered to be safer (Table 20)
- Use of a non-pharmacological strategy when available and appropriate (Table 20)
- Withdrawal of the medication (Table 19)

Any decision regarding stopping, altering or starting medicines must be tailored to individual patient circumstances and take into account each patient's life expectancy, values and preferences, and the likely positive or negative impact of the drug on the patient's quality of life.

It is important to note that, in recognition of the complexity of a patient's clinical status and limitations in the available evidence of benefit of many drugs in older, frail, multi-morbid patients, the algorithm is not intended to be a normative tool but more a cognitive guide to help clinicians including pharmacists determine whether, in individual patients, medications pose inordinate risk of harm and, if so, to consider what can be done to reduce this risk.

Table 20: Alternative management strategies for commonly used PIMs in older people

Medication	**ATC Codes**	**ALTERNATIVE MANAGEMENT STRATEGIES** **Alternative medication/Non-pharmacological interventions**	**References**
Analgesics, anti-inflammatory			
NSAID			
Aspirin >325mg/day	N02BA01	ALTERNATIVE MEDICATION: - Paracetamol - Opioids – tramadol, codeine - NSAIDs in low dose for a limited period of time NON-PHARMACOLOGICAL INTERVENTIONS - Cognitive-behavioral therapy - Cold/heat application - Massage - Exercise - Immobilization	(278, 327)
Diclofenac	M01AB05		
Ketoprofen	M01AE03		
Ketorolac	M01AB15		
Mefenamic acid	M01AG01		
Meloxicam	M01AC06		
Naproxen	M01AE02		
Piroxicam	M01AC01		
Indomethacin	M01AB01		
Etoricoxib	M01AH05		
Ibuprofen	M01AE01		
Opioid analgesics			

Pethidine	N02AB02	- Relaxation techniques	
Antiarrhythmic			
Flecainide	C01BC04	ALTERNATIVE MEDICATION: - Beta blockers - Amiodarone	(278)
Sotalol	C07BA07	ALTERNATIVE MEDICATION: - Cardio selective beta blockers (metoprolol, bisoprolol, carvedilol) - Amiodarone, propafenon (depending on the type of arrhythmia)	(278)
Disopyramide	C01BA03	ALTERNATIVE MEDICATION: - Amiodarone, or other antiarrhythmic	(196)
Digoxin > 0.125 mg/d	C01AA05	ALTERNATIVE MEDICATION: - Digoxin 0.125mg/day with serum concentration between 0.5 – 1.2 ng/ml	(196)
Nifedipine	C08CA05	ALTERNATIVE MEDICATION: - Other antihypertensive, e.g. ACEI, AT1 blockers, thiazide diuretics, beta blockers - Long-acting calcium channel blockers with peripheral effect	(278)
Antibiotics			
Nitrofurantoin	J01XE01	ALTERNATIVE MEDICATION: - Antibiotics with renal elimination according to the antibiogram - Other antibiotics – cephalosporin, cotrimoxazole, trimethoprime - Use of the sensitivity and resistance test	(196, 278)
Anticholinergics			
Antihistamines			
Chlorpheniramine	R06AB02	ALTERNATIVE MEDICATION: - Cetirizine, desloratadin, loratadine	(196, 278)
Cyproheptadine	R06AX02		
Dexchlorpheniramine	R06AB02		
Diphenhydramine	R06AA02		
Doxylamine	R06AA09		
Promethazine	R06AD02		
Antiparkinson agents			

Benztropine	N04AC01	ALTERNATIVE MEDICATION: - Other antiparkinsonian drugs	(194)
Antispasmodics			
Oxybutynin	G04BD04	ALTERNATIVE MEDICATION: - Other drugs with lower anticholinergic activity NON-PHARMACOLOGICAL INTERVENTIONS - Exercise of pelvic floor - Physical and behavioral therapy	(196, 278)
Solifenacin	G04BD08		
Tolterodine (non-sustained release)	G04BD07		
Antithrombotics			
Dipyridamole (short-acting)	B01AC07	ALTERNATIVE MEDICATION: - Clopidogrel - Aspirin	(196, 278)
Warfarin	B01AA03		
Prasugrel	B01AC22		
Ticlopidine	B01AC05		
Antidepressants			
TCA			
Amitriptyline	N06AA09	ALTERNATIVE MEDICATION: - SSRI: citalopram, sertraline - Mirtazapine NON-PHARMACOLOGICAL INTERVENTIONS (328) - Behavioral therapy - Problem solving therapy - Interpersonal psychotherapy	(196, 278)
Clomipramine	N06AA04		
Doxepin (>6mg)	N06AA12		
Imipramine	N06AA02		
Nortriptyline	N06AA10		
Paroxetine	N06AB05		
SSRI			
Fluoxetine (daily use)	N06AB03		
MAO inhibitors			
Tranylcypromine	N06AF04		
Antiemetic drugs			
Trimethobenzamide	NA	ALTERNATIVE MEDICATION:	(278)

Diphenhydramine	R06AA02	- Domperidone	
Antiepileptic drugs (AED)			
Phenobarbitone	N03AA02	ALTERNATIVE MEDICATION: - Other antiepileptic: lamotrigine, valproic acid, levetiracetam, gabapentin	(278)
Antihypertensive agents and other cardiovascular drugs			
Clonidine	C02AC01	ALTERNATIVE MEDICATION: - Other antihypertensives except short-acting calcium channel blockers and reserpine - Other antihypertensives, e.g. ACEI, AT1 blockers, thiazide diuretics, long acting calcium channel blockers with peripheral effect	(196, 278)
Methyldopa	C01AB01		
Moxonidine	C02AC05		
Nifedipine	C08CA05		
Prazosin	C02CA01		
Terazosin	G04CA03		
Antipsychotics (Neuroleptic drugs)			
First-Generation (Conventional) Agents			
Chlorpromazine	N05AA01	ALTERNATIVE MEDICATION: - Neuroleptics with better risk/benefit ratio, e.g. risperidone, pipamperone, haloperidol (in acute psychosis, short term use less than 3 days) NON-PHARMACOLOGICAL INTERVENTIONS – DELIRIUM - Prevention - Avoid use of delirium related drugs - STOP DELIRIUM – multicomponent intervention - Identification of clinical changes during the prodromal phase NON-PHARMACOLOGICAL INTERVENTIONS - Psychological strategies tailored to patients: music, reminiscence therapy, exposure to pets, outdoor activities, bright light exposure - In agitation and aggression try to identify the cause of the problem – can be disease, pain, medication	(196, 278, 329, 330)
Fluphenazine	N05AB02		
Haloperidol (>2mg)	N05AD01		
Promazine	N05AA03		
Trifluoperazine	N05AB06		
Second-Generation (Atypical) Agents			
Aripiprazole	N05AX12		
Asenapine	N05AH05		
Clozapine	N05AH02		
Olanzapine (>10mg)	N05AH03		
Sedatives, hypnotic agents			
Long-acting benzodiazepines			
Clonazepam	N03AE01	ALTERNATIVE MEDICATION:	(196, 278,

Diazepam	N05BA01	➢ In anxiety indication: - Short-acting benzodiazepines –less than half of the dose usually given to adults - Mirtazapine, trazodone, mianserine ➢ In hypnotic indication: - Ise non benzodiazepine hypnotics: zolpidem, zopiclone - Valeriana NON-PHARMACOLOGICAL INTERVENTIONS – ANXIETY - Cognitive-behavioural therapy NON-PHARMACOLOGICAL INTERVENTIONS – INSOMNIA - Sleeping hygiene - Explore the cause of sleep disorder – can be disease, medication, environment - Light therapy	331-333)
Bromazepam	N05BA08		
Clobazam	N05BA09		
Nitrazepam	N05CD02		
Flunitrazepam	N05CD03		
Short- and intermediate acting benzodiazepines			
Alprazolam	N05BA12		
Lorazepam	N05BA06		
Oxazepam	N05BA04		
Temazepam	N05CD07		
Triazolam	N05CD05		
Others			
Cimetidine	A02BA01	ALTERNATIVE MEDICATION: - Proton pump inhibitors - Other H2 antagonists: ranitidine, famotidine,	(196)
Diphenoxylate	A07DA01	ALTERNATIVE MEDICATION: - Mebeverin, fluoroglucinol	(196)

ATC: Anatomical therapeutic chemical, COPD: Chronic obstructive pulmonary disease, CNS: Central nervous system, ECG: Electrocardiogram, MAO: Monoamine oxidase inhibitors, NSAID: Non- steroidal anti-inflammatory drugs, SSRI: Selective serotonin reuptake inhibitors, TCA: Tricyclic antidepressants.

5.2.5 Discussion

We have proposed a prescribing algorithm specifically designed to minimize prescribing of potentially inappropriate medications in frail older patients in residential care settings. This algorithm incorporates a systematic approach to identifying, evaluating and, if indicated, withdrawing such medications on an individual basis. However, we acknowledge that there will be potential practical difficulties in using this algorithm, for example, ascertaining the reasons why medications (which have been prescribed for a considerable period of time) were originally commenced. In some cases, even the past diagnosis, which served as the original indication for the drug, may be difficult to reconfirm using currently accepted diagnostic criteria. Both tasks can be difficult and time consuming in elderly individuals

with polypharmacy and multiple co-morbidities, and no algorithm will be able to reconcile the complexity of this task with the desire for simplicity and specificity in its application.

Although current national quality measures give us an opportunity to extract a comprehensive list of potentially inappropriate and potentially inappropriate medications, the further domains of inappropriate prescribing such as underuse of medications, drug-drug interaction, drug-disease interaction and medication duplication might be missed. Hence, we do not claim this list is exhaustive, and the safety of other drugs not included here has to be considered depending on the patients individual circumstances as research indicates medications other than PIMs also have the potential to cause adverse drug events.(334)

We acknowledge that the utility of the algorithm in routine clinical practice needs to be evaluated, especially in view of the mixed effects reported in some studies of various interventions designed to minimize the use of PIMs among patients in RACFs.(310) Barriers to its application need to be determined, with a particular focus on logistical constraints of busy clinical settings where there may be few financial reimbursements for the extra time spent applying the algorithm.

Studies involving a randomized controlled trial might validate the algorithm. Prescriber outcome measures that might be relevant in any controlled trial could be the number of medications identified as potential candidates for discontinuation (and the rationale for such decisions) and the specific actions enacted by prescribers in regards to drug withdrawal. Patient outcome measures could include incidence rates of ADEs (including geriatric syndromes) and medication-related hospitalizations. Process measures could include time taken to conduct medication reviews (does the algorithm speed up or prolong consultations?) and the ease of use of the algorithm (as determined by questionnaire and focus group discussions). In the meantime, current prescribers may find the algorithm of use and we welcome feedback as to their perceptions of its utility.

5.3 Next Steps

We believe that the algorithm described in this chapter covers a range of different clinical scenarios and offers an evidence-based approach to identifying and, if appropriate, discontinuing potentially inappropriate medication.

The lack of strong evidence to guide clinicians to avoid or discontinue treatment in frail older people might make this a particularly challenging and time-consuming process. Widespread adoption of this strategy might have its challenges but also has considerable potential to relieve suffering and minimise harm in vulnerable older persons. Although there are a few recent studies to support the feasibility and safety of discontinuing medication in the elderly,(335, 336) stronger evidence could be obtained if future trials incorporate a discontinuation arm or post discontinuation follow-up.

The next logical step would be to evaluate the usefulness of the algorithm in routine clinical practice, particularly identifying the enablers and barriers to its application. This has not been rigorously assessed as part of this thesis, but is discussed in Chapter 6 under ‘Future Research’.

Chapter 6: Discussion, Future Research, and Conclusions

6.1 Discussion

Older patients pose a complex challenge for the health care system, as they often present with multiple co-morbidities, polypharmacy, disability and frailty. The risk of adverse drug events is particularly high in this population. ADEs are associated with polypharmacy,(205) frailty,(64) use of potentially inappropriate medications,(159), and age-related changes that affect the pharmacodynamics and pharmacokinetics of drugs.(337) When compared with younger adults, ADEs are approximately twice as frequent in older adults, with a significant proportion considered preventable.(338) Optimization of appropriateness of prescribing in this vulnerable population should be a priority of health care providers.

The objective of this thesis was the optimization of medication prescribing in frail older people, with a focus on polypharmacy, frailty and potentially inappropriate medications, with a view to developing best practice guidelines for prescribing in frail older people. In this section, the findings of the studies reported in this thesis will be discussed from a broader perspective.

The thesis commenced with a literature review that provided a comprehensive background on ageing populations, appropriate and inappropriate prescribing, existing screening tools to assess inappropriate prescribing, the prevalence of inappropriate prescribing, frailty and its measurement and a systematic review of criteria that evaluated appropriateness of medications in frail older people (Chapter 1). This literature review indicated that older people are at increased risk of polypharmacy, inappropriate prescribing and adverse drug outcomes. The frailty status of patients is rarely considered overtly during prescribing and in identifying inappropriate prescribing in older people. This suggests the need for a standardized approach to assessing appropriateness of medication in frail older individuals considering both *patient* and *medication* related factors.

Chapter 2 explored issues around polypharmacy and adverse outcomes in older hospitalised patients and investigated the potential role of frailty status. Polypharmacy is generally associated with adverse outcomes but, in our study, we did not find any

association between polypharmacy and adverse outcomes studied except for delirium. This led us to explore further to see if the frailty status of patient adds another dimension to this relationship.

Our study showed that, within each polypharmacy category, the incidence of adverse outcome increased with increasing frailty, and the most robust patients taking 10 or more drugs had the lowest incidence of adverse events compared with other polypharmacy/frailty categories. This indicates that polypharmacy in the presence of frailty is much worse than polypharmacy in those who are not frail. Therefore, extensive medication withdrawal or de-prescribing in all older inpatients might not be the ideal intervention as many patients are likely to benefit from appropriate multiple medications if not frail. The assumption that polypharmacy is always hazardous and that it indicates suboptimal care needs to be reconsidered.

As such, this phase of our study suggested that polypharmacy is not always an independent risk factor for predicting an adverse outcome in older inpatients. By considering the frailty status of the patient, we may better appraise risk and lead to improved clinical care.

Patients who are frail are often discharged from hospitals to RACFs. Thus, in Chapter 3, we aimed to identify the prevalence of PIMs and explore the association of risk factors for receiving PIMs in a subset of patients who are discharged to RACFs from our initial larger cohort of 1418 inpatients. Among the widely used tools for detecting inappropriate prescribing such as Beers, STOPP/START and MAI, we used the latest 2012 version of the American Geriatrics Society Beers criteria for several reasons. Beers criteria were updated in 2012 providing a more comprehensive list more in line with current clinical practice. The quality of criteria has been improved using an evidence based approach that now includes a clear indication of the strength of the evidence and of the recommendation. The updated version excluded medications that are no longer available while newly marketed medications were added in the list.(194) The 2012 Beers criteria detected the highest number of PIMs in a comparative study of the STOPP, the 2003 Beers criteria, and the 2012 AGS update of the Beers criteria determining the prevalence of PIMs.(339) The

2012 update has also been shown to be the most sensitive tool despite concerns related to the applicability of the previous version of the Beers criteria in Europe. Despite these updates, the relevance of the tool for data collected outside the US could be questioned. For example this recent update contain medications that are either not available in Australia or that have been withdrawn from use.

In our study, the current Beers criteria demonstrated frequent use of PIMs in older people discharged from acute care hospitals to RACFs. However, the number of PIMs was lower on discharge than on admission although this reduction was not significant. During the hospital admission, few PIMs were stopped, and other new PIMs had been started. A clear association between the use of PIMs, frailty status, and cognitive decline of patients at admission and discharge was observed. Although an admission to hospital is an opportunity to rationalise medications according to their appropriateness, this did not occur in this study. Patients discharged to RACF from hospital continued to be exposed to extensive polypharmacy and medications with uncertain risk–benefit ratios. This suggests the need of interventions in hospitals and RACFs to rationalise prescribing in these frail older patients.

Following the identification of PIMs in patients discharged to RACF, Chapter 4 evaluated a prospective observational study to examine if geriatrician intervention during comprehensive video-conference geriatric consultations resulted in changes to prescribing patterns, and reduced the prevalence of PIMs use for residents of aged care facilities. Comprehensive geriatric assessments supported by a geriatric medicine specialist has been shown to be beneficial to older patients (66, 136), but many of these patients are unable to travel to seek such advice because they are physically impaired, or they live in remote areas. Telemedicine has been used to address this concern, whereby consultations are undertaken using video conferencing. An important part of the consultation is the recommendations the geriatrician makes about patients' medications.

A moderately high prevalence of potentially inappropriate medications was prescribed to residents in RACFs but geriatricians made relatively few changes. This suggests that either the prescription of these medications was appropriate or other factors (which may

include patients' beliefs in their medications, involvement of several prescribers, use of preventive medication and evidence based medicine guidelines that often lead to polypharmacy, and lack of risk/benefit information for the frail older residents) influenced the decision not to modify medications. Although specialist geriatrician involvement helps optimise medication in this age group, potentially inappropriate medications were still observed in our study. This suggests the need for an algorithm for withdrawing medications of high disutility which might help optimise medication prescribing in frail older people.

We also aimed to review prospectively the medication charts in a RACF to determine if medication changes recommended by geriatrician were implemented and sustained. A follow up study at 3 months after the initial consultation showed that most of the recommendations were followed by RACF staff or the GP overseeing the care of the patient. Occasionally, the recommendations were not followed but the reasons for this have not been established in this study. Although this was a single site study with a relatively small sample size, the outcome of this follow-up has implications for geriatricians' recommendations regarding patient medication management.

In Chapter 5, we have addressed polypharmacy and minimisation of potentially inappropriate medications by developing a practical algorithm that helps clinicians identify and discontinue potentially inappropriate medications using a logical and practical approach. We propose a 4-step algorithm that provides instructions when and how to taper and withdraw inappropriate medications. It adds to the previously available generic 'drugs-to-avoid' list in that it targets drugs of highest risk, suggests alternative therapies (which can include non-pharmacological approaches), and informs the discontinuation process by highlighting the risks of withdrawal on disease and syndrome recurrence and recommends appropriate tapering regimens.

Given the lack of evidence surrounding the topic, various logistical constraints, and the practical complexity of medication cessation in elderly individuals, this algorithm is not intended as a normative decision aid but more a conceptual framework that may prompt clinicians to more critically examine factors that influence their prescribing. Although,

widespread adoption of a medication withdrawing protocol in clinical care has its challenges, it also has significant potential to relieve unnecessary suffering and disability in older patients.(306) Ceasing medications might be complex and time consuming, yet, minimising the potential harm and waste of resources arising from inappropriate polypharmacy in frail older patients is a responsibility of prescribers.(316) The utility of the algorithm developed in this study needs to be evaluated in routine clinical practice. The enablers and barriers to its use need to be determined and studies involving randomised controlled trials are needed.

This study focused only on institutionalized elderly. Given the current long-term trend to deinstitutionalize health care, more frail elderly persons are now receiving care through public home care programs where supports for frail elderly patients are not as continuous or readily available as they are in an institution.

6.3 Conclusion

This thesis demonstrates that prescribing in frail older people remains a significant problem but that optimisation of prescribing should be attainable by accurate identification of frail patients in various clinical settings. By individualising prescribing based on each patient's own goal of care and frailty status, better outcomes could be achieved for the individual patient and the health system as a whole.

While polypharmacy stands as a valuable indicator for medication review, it might not be an independent marker of the quality use of medicines in the individual patient. Assessing the frailty status of patients better appraises risk. Frail older patients continue to be exposed to polypharmacy and potentially inappropriate medications. A medication review algorithm for withdrawing medications of high disutility, particularly in those who are frail, should assist clinicians to optimise medication prescribing in this vulnerable population.

Future research should focus on incorporating frailty assessment in various clinical settings to investigate the effectiveness of the proposed medication review algorithm for specific potentially inappropriate medications.

The findings of this thesis should stimulate further evaluation by researchers, policy makers and clinicians into the relationship between polypharmacy, frailty status and adverse outcomes.

6.2 Future Research Directions

Future research should include the impact of frailty measurement on clinical decisions in the elderly. Management of chronic disease and optimisation of prescribing will differ between frail and non-frail individuals. Identifying those at risk of developing frailty will be important when recruiting for clinical trials that evaluate interventions that target and prevent frailty.(340) Furthermore, unless frail individuals are included in clinical trials, the effectiveness of treatment and interventions cannot be established in this group.(341)Only in this way will clinical research lead to improvements in care of older adults.

Although a significant body of research has focused on the negative consequences of polypharmacy, it is now time that further research should focus on other dimensions to this phenomenon. Constantly assuming that polypharmacy inevitably leads to adverse outcomes needs to be reassessed because some patients would appear to benefit from receiving a greater number of drugs provided that they are not frail. Similarly, it should not be assumed that de-prescribing in all older patients will always improve outcomes.

Future research should validate the medication review algorithm developed in this study using a randomized controlled trial. Enablers and barriers to its application in routine clinical practice also need to be evaluated especially when there are few financial benefits for the extra time spent applying this algorithm in busy clinical settings.

Some studies have found that pharmacist involvement can lead to better medication management.(124, 342, 343). Pharmacists would be in a position to apply the medication management tools such as the algorithm developed in this study in real clinical settings and liaise with primary care providers and specialists in decision-making.(344)Pharmacists are usually not integrated into the care process as well as they could be. Hence, future research should evaluate the potential benefits of integrating pharmacists in to multidisciplinary teams to see if this can improve outcomes in a cost effective manner.

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Appendices

Appendix A: Published Paper: A systematic review of prescribing criteria to evaluate appropriateness of medications in frail older people

Reviews in Clinical Gerontology 2014 24; 304–318 First published online 3 November 2014
 doi:10.1017/S0959259814000161

A systematic review of prescribing criteria to evaluate appropriateness of medications in frail older people

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Summary

This study systematically reviews the published literature regarding inappropriate prescribing in frail individuals aged at least 65 years. Twenty-five of 466 identified studies met the inclusion criteria. All papers measured some surrogate indicators of frailty, such as performance-based tests, cognitive function and functional dependency. Beers criteria were used in 20 studies (74%) to evaluate inappropriate medication use and 36% (9/25) studies used more than one criterion. The prevalence of inappropriate medications ranged widely from 11 to 92%. Only a few studies reported the relationship between potentially inappropriate medication use and surrogate measures of frailty. These diverse findings indicate the need for a standardized measure for assessing appropriateness of medication in frail older individuals. Prescribing tools should address both medication and patient-related factors such as life expectancy and functional status to minimize inappropriate prescribing in frail individuals.

Key words: frailty, inappropriate prescribing, older people, prescribing criteria, prevalence

Introduction

The number of drug prescriptions for older people has risen progressively and has drawn increasing attention worldwide.[1] While older people are the principal drug consumers, benefits from drug therapy can only be achieved if prescribing is appropriate.[2] Inappropriate prescribing (IP), defined as a situation where pharmacotherapy does not meet the established medical standards, is associated with negative health outcomes such as adverse drug events, hospitalization, redundant healthcare utilization and untimely death.[3] IP is more likely to have its adverse influence on frail older people who often have multiple co-morbidities with signs of impairment in activities of daily living. In frail individuals, their ability to tolerate medications becomes less due to age-related changes in pharmacokinetics and pharmacodynamics, thereby making prescribing a more difficult task.[4] Furthermore, the increasing prevalence of chronic illness in frail individuals leads to an increase in the number of total prescriptions.

Several criteria have been developed to identify potentially inappropriate medications (PIMs) in older patients, particularly certain aspects of prescribing such as indication, drug–drug interactions, drug–disease interaction, drug duplication and under-prescribing. PIMs can be detected using explicit (criterion-based) or implicit (judgement-based) prescribing criteria.[5] Explicit criteria are derived from expert reports or published reviews. They have high reliability and reproducibility but focus mainly on specific drugs and disease states. In contrast, implicit criteria are person specific and explore patient preferences rather than disease and medications; they rely on evaluator judgement and may have low reliability and low practical utility.[6] Yet these guides and criteria are applicable only to robust, healthy older adults and cannot be generalized to frail patients.[7] Consequently, optimizing prescribing warrants measuring the frailty level of individual patients using clinically validated tools and prescribing criteria that consider a patient's quality of life, functional status, life expectancy and goals of care for optimal choice of drug with the paramount risk–benefit ratio.

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We conducted a systematic review to identify studies that measured the prevalence of potentially inappropriate prescribing in older people assessed as 'frail', based on the presence of deficits defined as symptoms, signs, disabilities and diseases contributing to frailty.

Methods

Types of studies

Original studies measuring inappropriate prescribing using well-validated tools in a population assessed as frail using at least two indices of frailty were included in the review.

Types of participants

Studies involved individuals aged 65 years and older with an indication of frailty or disability. Patients were included in the study if they met two or more of the following criteria of frailty:[8] disability in activities of daily living (ADL) and instrumental activities of daily living (IADL), impairments in general cognition and mobility, history of falls, malnutrition, low level of physical activity, incontinence and depression.

Information sources

The search was conducted using PubMed and EMBASE. Articles published in English between January 1990 and December 2013 were retrieved for analysis.

Search strategies

Keyword searches and MeSH headings were used that included the following terms: frail elderly, inappropriate prescribing, suboptimal prescribing, potentially inappropriate medication, and inappropriate medication. Detailed search strategies are provided in the Appendix.

Study selection

Initial eligibility assessment was performed by a single investigator (A.P.) who reviewed abstracts based on the inclusion criteria and was confirmed by a second reviewer (N.P.). Full articles were reviewed for final inclusion. This systematic review is reported according to the PRISMA guidelines.[9]

Data abstraction and risk of bias assessment

For each paper, data extracted included study design, study setting, sample size, participant age, frailty measures, implicit/explicit criteria used and the prevalence of PIM use. An association between PIM use and patient characteristics was also recorded in a specially designed data abstraction tool.

Results

Study selection

The initial search found 466 citations (Fig. 1). Of these, 135 were excluded because of duplication and 284 were excluded after reviewing the abstracts, as they failed to meet the inclusion criteria. After abstract review, full text was sought for 47 articles, from which 28 articles were excluded that did not meet the following criteria: not an original article ($n = 1$), prescribing criteria not well defined ($n = 1$), age less than 65 years ($n = 1$), frailty measurement not well defined ($n = 9$), studies focusing on particular drug or disease condition ($n = 13$) and studies on the same population ($n = 3$). Finally, 25 studies met the inclusion criteria including six additional studies from manual search in bibliographies.

Study characteristics

Table 1 summarizes detailed description of reviewed studies. The majority of studies were conducted in the in-patient hospital settings ($n = 8$), nursing homes or assisted living settings ($n = 8$) and in community-dwellers ($n = 8$) with one study in home care. The studies were conducted in Europe ($n = 12$), USA ($n = 9$) and Oceania and Asia ($n = 4$).

Synthesis of results

A total of 15 explicit and implicit criteria were used in the 25 studies. Of these, 14 were explicit (Beers, HEDIS, German PRISCUS list, STOPP/START, Rancourt, Laroche,

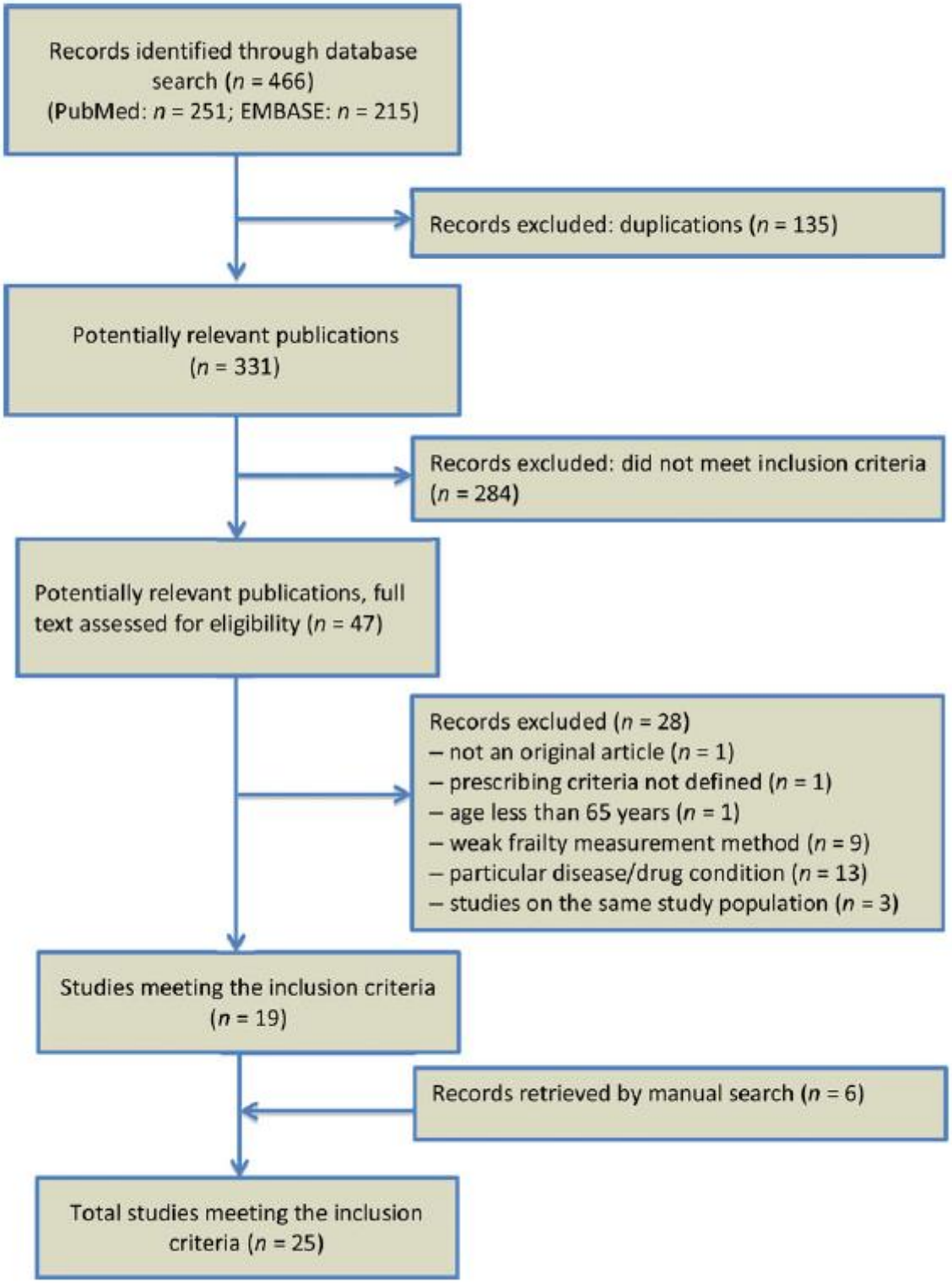

Figure 1. Flowchart of study

Table 1. *Studies evaluating frailty status and describing the criteria for evaluating inappropriate prescribing in frail older individuals*

Reference, year, country	Study design/setting	Population characteristics Sample (*n*); Age (years)	Methods used for frailty assessment	Implicit/explicit criteria used	Results – prevalence of PIMs – population characteristics associated with PIM use
Dosa *et al.*, 2013, USA[10]	Retrospective, cross-sectional study in Veteran Affairs nursing homes	$n = 176{,}168$, age ≥75 years (75%)	Minimum data set (MDS) includes – CPS – ADL	HEDIS potentially inappropriate medications	Between 2004 and 2009, 16.4±9.5% veterans admitted to VA nursing homes received at least one HEDIS-listed high-risk medication, while in the facility the rate decreased from 23.9±10% in 2004 to 10.0±6.6% in 2009. High-risk medication use was associated with being female, age 75 and older and better cognitive and ADL functional status
Fromm *et al.*, 2013, Germany[11]	Retrospective cohort study at discharge from 44 geriatric units	$n = 45{,}809$, median age 82 years (IQR 78–86)	Geriatric assessment including: – Barthel score – timed up-and-go (TUG) test – MMSE – GDS	German PRISCUS list	25.9% received at least one PIM. Use of at least one PIM was independently associated with – being female – slightly higher Barthel score – inability to walk independently
Koyama *et al.*, 2013, USA[12]	Longitudinal cohort study in community-dwelling elderly women	$n = 1484$, mean age 78 ± 3 years	GDS Goldberg Anxiety Scale MMSE	2003 Beers	At baseline, 24.3% of women were PIM users and 23.9% at 10 years follow-up was associated with: – high GDS – poor sleep quality – lower scores on MMSE – increased anxiety – urinary incontinence Over 10 years PIM use increased in those who later developed dementia

Table 1. *Continued*

Reference, year, country	Study design/setting	Population characteristics Sample (*n*); Age (years)	Methods used for frailty assessment	Implicit/explicit criteria used	Results – prevalence of PIMs – population characteristics associated with PIM use
Dalleur *et al.*, 2012, Belgium[13]	Cross-sectional study in teaching hospital	$n = 302$, median age 84 years (IQR 81–88)	A positive frailty profile was defined as having two or more of the six identification of seniors at risk (ISAR) items including: – need for help in activities of daily living – increase in need related to the current illness – nemory problems – altered vision – hospitalization in last 6 months. – daily use of ≥3 medications at home – history of recent multiple falls	STOPP and START	Prevalence of PIMs and PPOs was 48 and 63%, respectively Overall inappropriate prescribing contributed to hospital admission and a history of previous falls
Ubeda *et al.*, 2012, Spain[14]	Descriptive study in a nursing home	$n = 81$, mean age 84 ± 8 years	Barthel index MMSE	2003 Beers STOPP/START	The prevalence of PIMs was 25% according to Beers criteria while STOPP identified 48% of patients using at least one inappropriate medication. START detected 58 potential prescribing omissions in 44% of patients Negative correlation between number of PIMs (STOPP criteria) with Barthel index and MMSE scores was noted

Table 1. *Continued*

Reference, year, country	Study design/setting	Population characteristics Sample (*n*); Age (years)	Methods used for frailty assessment	Implicit/explicit criteria used	Results – prevalence of PIMs – population characteristics associated with PIM use
Chang *et al.*, 2011, Taiwan[15]	Comparative study in teaching hospital	$n = 193$, mean age 76 ± 6 years	Nagi Index IADLs MMSE GDS-15 items Falls Co-morbidities (including urinary incontinence)	2003 Beers Rancourt Laroche STOPP Winit-Watjana NORGEP	The prevalence of PIMs varied from 24% (the NORGEP criteria) to 73% (the Winit-Watjana criteria) Depending on criteria prevalence of PIMs are associated with – higher number of chronic conditions – higher number of chronic medications – history of falls – higher IADL score – higher physical performance – higher GDS score
Pozzi *et al.*, 2010, Italy[16]	Longitudinal study in community dwellers	$n = 1022$, mean age 73 ±7 years	BADL IADL	1991 Beers	Of the 776 participants receiving at least one medication at baseline, prevalence of at least one PIM was 9%
Berdot *et al.*, 2009, France[17]	Multicentre prospective cohort study in community dwellers	$n = 6343$, age <75 years (64%)	CES-D scale MMSE Impaired mobility was assessed by three items of the Rosow and Breslau scale: – doing heavy housework, walking half a mile and – going up and down to the second floor	1997 Beers Fick Laroche	31.6% of subjects reported inappropriate medication use at baseline Use of PIMs is associated with increased risk of falling mainly due to long-acting benzodiazepines and other inappropriate psychotropics

Table 1. *Continued*

Reference, year, country	Study design/setting	Population characteristics Sample (*n*); Age (years)	Methods used for frailty assessment	Implicit/explicit criteria used	Results – prevalence of PIMs – population characteristics associated with PIM use
Gnjidic *et al.*, 2009, Australia[18]	A cross-sectional survey on community-dwelling older men	$n = 1705$, mean age 77 ± 6 years	MMSE (score ≤ 26) GDS (score ≥ 5) IADL 6 m walking speed 20 cm narrow 6 m walking speed Chair stand Balance score Grip strength History of falls	DBI	Of 1527 medications 21% were exposed to anticholinergic and 13% to sedative drugs Higher DBI was associated with poorer physical performance and functional status
Hosia-Randell *et al.*, 2008, Finland[19]	Cross-sectional assessment of nursing home residents	$n = 1987$, mean age 84 ± 8 years	RAI depression score Mini Nutritional Assessment score Dementia Ability to move independently	2003 Beers	34.9% regularly used at least one PIM Residents taking PIMs were less likely to have a diagnosis of dementia
Landi *et al.*, 2007, Italy[20]	Prospective cohort study in community	$n = 364$, mean age 86 ± 5 years	Physical performance was assessed by the 4 m walking speed and the S SPPB score Muscle strength was assessed by hand grip strength measured by a dynamometer BADL IADL CPS Physical activity level Fall history	2003 Beers	At baseline prevalence of inappropriate drug use was 26% Prevalence was associated with – cognitive impairment (higher CPS) – lower level of physical activity – higher number of medicines – lower score on SPPB Two or more PIMs was associated with – slower gait speed – lower ADL score

Table 1. *Continued*

Reference, year, country	Study design/setting	Population characteristics Sample (*n*); Age (years)	Methods used for frailty assessment	Implicit/explicit criteria used	Results – prevalence of PIMs – population characteristics associated with PIM use
Spinewine *et al.*, 2007, Belgium[21]	Randomized, controlled trial in GEM unit	$n = 203$, mean age 82 ± 6 years	Cognitive impairment Falls ADL Self-rated health	2003 Beers MAI ACOVE	Almost 60% of prescriptions for all patients included in the study had at least one inappropriate rating at baseline (MAI). Approximately 30% of all patients included in the study were taking at least one drug to avoid at admission (drugs to avoid in older people) Seventy-eight per cent of patients were eligible for at least one indicator (ACOVE criteria of underuse)
Niwata *et al.*, 2006, Japan[22]	Cross-sectional study in long-term care facilities	$n = 1669$, mean age 84.5 years	MDS assessment – ADL – CPS – depression rating scale	2003 Beers	A total of 21.1% of the patients were treated with PIMs Increase in number of medications and older age increased risk of PIMs
Fialova *et al.*, 2005, Europe[23]	Retrospective cross-sectional study of elderly patients receiving home care	$n = 2707$, mean age 82 ± 7 years	The inter-RAI MDS-HC instrument – IADL – ADL – cognition – depression	2003 Beers McLeod	19.8% of patients in the total sample used at least one inappropriate medication combining all 3 sets of criteria. Substantial differences across Europe (5.8% in Denmark to 41.1% in Czech Republic). PIM use is associated with polypharmacy, depression and younger age (< 85 years)

Table 1. *Continued*

Reference, year, country	Study design/setting	Population characteristics Sample (*n*); Age (years)	Methods used for frailty assessment	Implicit/explicit criteria used	Results – prevalence of PIMs – population characteristics associated with PIM use
Hajjar *et al.*, 2005, USA[24]	Cross-sectional study in VA Medical Centres	$n = 384$, age ≥75 years (46%)	Patients were defined as frail if they meet at least two of the following 10 criteria: – limitations in at least one activity of daily living (ADL) – cerebrovascular accident within previous 30 days – history of falls, – documented difficulty in ambulating – malnutrition – dementia – depression	MAI	44% of patients had at least one unnecessary drug, with the most common reason being lack of indication. PIM use is associated with polypharmacy
Lau *et al.*, 2005, USA[25]	Longitudinal study in nursing home	$n = 3372$, age ≥85 years (50%)	MDS assessment – ADL – mental status	1997 Beers 2003 Beers	50% of all residents with an Nursing home stay of 3 months or longer received at least one PIMs A non-dementia mental disorder was associated with greater odds of PIMs as was having communication problems and less impairment in ADL. Having dementia was associated with less likelihood of PIM use
Lechevallier-Michel *et al.*, 2005, France[26]	Retrospective, cross-sectional study in community-dwelling elderly	$n = 9,294$, mean age 74 ± 6 years	Lawton's IADL MMSE CES-D	French criteria adapted from 2003 Beers	Nearly 40% of the participants used at least one PIM This use was significantly more frequent among women, older subjects and poorly educated subjects
Onder *et al.*, 2005, Italy[27]	Retrospective cohort study in 81 hospitals	$n = 5152$, mean age 79 ± 9 years	ADL Hodkinson Abbreviated Mental Test	2003 Beers	During hospital stay, 28.6% patients received one or more inappropriate drugs Lower prevalence of PIMs was observed in those more impaired in ADL and cognition. Higher PIM use was associated with polypharmacy

Table 1. *Continued*

Reference, year, country	Study design/setting	Population characteristics Sample (*n*); Age (years)	Methods used for frailty assessment	Implicit/explicit criteria used	Results – prevalence of PIMs – population characteristics associated with PIM use
Saltvedt *et al.*, 2005, Norway[28]	Randomized study in geriatric unit	$n = 127$ in each unit (GEM and MW), age 82 ± 5 years	Winograd targeting criteria: – acute impairment of a single ADL – impaired mobility – falls – confusion – depression – dementia – malnutrition – vision or hearing impairment – urinary incontinence – polypharmacy	1997 Beers	10% of patients in geriatric evaluation and management unit (GEMU) had at least one PIMs and 9% of patients in general medical wards (MW) had at least one PIM
Mamun *et al.*, 2004, Singapore[29]	Cross-sectional study in 3 randomly selected nursing homes	$n = 454$, mean age 80 years	Resident assessment form that measures functional category as I– IV	1997 Beers	Inappropriate medication use was seen in 70% of residents with a significant association between polypharmacy and inappropriate medication use
Gray *et al.*, 2003, USA[30]	A cohort study in community residential care facilities	$n = 282$, mean age 83 ± 8 years	ADL Global Health Status Cognitive Status	1997 Beers	22% of residents took potentially inappropriate medications Potentially inappropriate use was related to self-reported fair or poor health and number of prescription drugs
Raji *et al.*, 2003, USA[31]	Cross-sectional study of community-dwelling elderly	$n = 3050$, age <75 years (65%)	MMSE CES-D	1997 Beers Zhan	Approximately 12% of the patients had at least one PIMs Those with ≥1 chronic diseases and with high depressive symptoms were more likely to have used at least one PIM

Table 1. *Continued*

Reference, year, country	Study design/setting	Population characteristics Sample (*n*); Age (years)	Methods used for frailty assessment	Implicit/explicit criteria used	Results – prevalence of PIMs – population characteristics associated with PIM use
Hanlon *et al.*, 2002, USA[32]	Cohort study in community-dwelling elderly	$n = 3234$, age <75 years (49%)	SPMSQ ADL	1997 Beers	At baseline 21.0% of the population were using one or more inappropriate medications according to the Drug Utilization Review (DUR) criteria The drugs-to-avoid criteria identified no significant associations between use of these drugs and decline in functional status. With DUR criteria, however, the association was observed between use of inappropriate drugs and basic self-care
Sloane *et al.*, 2002, USA[33]	Cross-sectional study in long term care facilities	$n = 2078$, age ≥85 years (52%)	ADL MMSE	1997 Beers	About 16.0% of these patients were receiving PIMs PIM use is associated with absence of dementia
Chin *et al.*, 1999, USA[34]	Prospective cohort study in an emergency department (ED)	$n = 898$, mean age 76 ± 8 years	ADL MMSE	1997 Beers	A total of 10.6% of the patients were taking a PIM PIMS and adverse drug–disease interactions in the ED were correlated with worse physical function and pain

ACOVE: assessing care of vulnerable elders; ADL: activity of daily living; ADR: adverse drug reactions; BADL: basic activities of daily living; CES-D: Centre for Epidemiologic Studies Depression; CPS: cognitive performance scale; DBI: drug burden index; GDS: geriatric depression scale; GEM: geriatric evaluation and management; HEDIS: healthcare effectiveness data and information set; IADL: instrumental activities of daily living; ISAR: identification of seniors at risk; MAI: medication appropriateness index; MDS-HC: minimum data set for home care; MMSE: mini-mental state examination; MW: medical ward; NORGEP: Norwegian General Practice; SPMSQ: short portable mental status questionnaire; SPPB: short physical performance battery; STOPP: screening tool of older person's prescription; START: screening tool to alert doctors to right treatment; VA: veterans affairs.

Winit-Watjana, NORGEP, Fick, DBI, ACOVE, McLeod, French criteria adapted from 2003 Beers, Zhan) and only one was implicit (Medication Appropriate Index). The most commonly used criteria were one of the three versions of Beers criteria (1991, 1997 and 2003), which were used in 20 studies (74%). Beers criteria are one of the best known and widely used explicit list of medications for evaluating inappropriate medication use.[35] Three studies used Screening Tool of Older Person's Prescriptions (STOPP)/Screening Tool to Alert doctors to Right Treatment (START) criteria to identify inappropriate medications. These latter tools identify, respectively, overuse of inappropriate medications and underuse of potentially appropriate medications. This differentiates them from Beers criteria.[36] Two studies used the Laroche approach developed by a French consensus panel that proposed 36 criteria applicable to older people to assess inappropriate medications.[37] More than one criteria was used in 34% (9/27) of the studies to evaluate combined inappropriate medication use. Clear variation among the prevalence of inappropriate medications use was observed that ranged from 10.6% up to almost 92%.

Frailty in patients was measured using different scales. ADLs were assessed in 15 studies, mental status in 14, depression and cognitive status each in 10 studies, falls in eight studies, and IADL and physical performance in six studies. Less frequently, malnutrition was reported in three studies, walking speed in three studies, and incontinence and grip strength in two studies. None of these studies used established frailty measures.

Discussion

In this overview, we compiled studies that measured the prevalence of inappropriate prescribing in older people assessed as frail based on presence of geriatric syndromes. Large variation was observed in the prevalence of inappropriate medications. The study settings, population characteristics and the inter-country differences on availability of some of the listed drugs[22] might account for this variation. The study setting does not fully explain the differences in the prevalence of PIMs. In NH/institutionalized settings where the population would be expected to be frail, the prevalence ranged from 9.5 to 70%. While the maximum prevalence was lower in community settings where the participants would be expected to be less frail, the prevalence still ranged from 9 to 40%. The age of the population under study might have been a factor in determining prevalence of PIMs. Since polypharmacy increases with frailty and frailty increases with age,[38] it might be expected that the younger population has a lower prevalence of PIMs. For example, the prevalence of PIMs was 9% in the community-based study of Pozzi *et al.*[16] with the mean age of 73 years, while in the study of Landi *et al.*[20] where the mean age was 86, the prevalence of PIMs was 26%.

The criteria used for assessing PIMs might also have a significant role in this variation as some of the studies compared different criteria for prevalence of PIMs in the one population. For example, a study in geriatric out-patients using six sets of published explicit criteria reported the variation of PIMs from 24% (the NORGEP criteria) to 73% (the Winit-Watjana criteria).[15] The majority of criteria used for identifying inappropriate medications specifically focus on the clinical appropriateness of prescribed drugs. The MAI is the only criterion that goes beyond the pharmacological appropriateness of a drug and explores other aspects of the medication management process.[39] The MAI questions whether the dose is correct. The MAI is also the only criterion that includes drug costs.[39] Most of these criteria are aimed at a healthy or robust population aged 65 years and older and are probably not appropriate in the frail older population.

Objective measures of physical, cognitive and mental functioning are significant for older people as they predict subsequent adverse health outcomes such as disability, hospitalization, nursing home admission and death.[18] Here, frailty in older individuals was measured using different clinical features that included functional status, physical performance, mental status and vulnerability or a combination of these. Generating a composite measure that would meet all the criteria is difficult. Although few studies reported the association between PIMs with the surrogate measures of frailty or the geriatric syndromes, they had diverse findings. Dosa *et al.*[10] reported that the prevalence of PIM was associated with better cognitive and ADL functional status; however, Landi *et al.*[20] reported lower levels of physical activities and

worsening results on ADL score associated with the prevalence of PIMs. Similarly, a study by Fialova *et al.*[23] suggested that PIM use was associated with younger age (<85 years) while a study by Niwata *et al.*[22] found that older age was associated with increased risk of PIMs. Hence the measures of frailty used in these studies cannot be considered as a gold standard.

Frailty can now be measured objectively, rather than by using surrogate markers. While several different measures have been validated,[40] the frailty index derived from Comprehensive Geriatric Assessment has high potential utility for older in-patients since it does not rely on performance-based tests and, as a continuous variable, has greater granularity for those at the 'frail' end of the health spectrum.[41] Assessment of frailty may inform decision making on medication, based on the health status and risk profile of an individual patient.[4] Utilization of a clinically validated tool is of utmost importance in identifying frail patients in clinical practice so that their management can be more appropriately determined. Ultimately, such a tool combined with the optimal choice of drug and patients' preferences should result in better and more cost-effective care.

There were limitations to our study. The literature search was limited to articles published in English, so criteria published in other languages might have been missed. We acknowledge that the search term may not be sufficient, although the most relevant criteria are likely to be included. Although we had a broad definition of frailty we might have missed other criteria of assessing frailty in some studies.

Conclusion

Most of the criteria used for assessing inappropriate medications are explicit, which are applicable only to the robust older population. While surrogate measures of frailty were included in the studies, frailty was poorly defined. Populations were considered frail based on age (such as >75 years) or setting (such as nursing homes). For appropriate prescribing in frail populations, implementing a clinically validated tool (such as frailty index) for assessing frailty as well as a specific tool to assess the appropriateness of therapy that considers patient factors such as quality of life, functional status, goal of care, and remaining life expectancy is warranted.

Conflicts of interest

None

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Appendix: search strategy

Database: Medline: 251 articles retrieved

Search ((((frail elderly [MeSH Terms])
AND 'inappropriate prescribing')
OR 'suboptimal prescribing')
OR 'inappropriate medication')
OR 'potentially inappropriate medication'
Filters: Publication date from 1990/01/01 to 2013/12/31;
Humans;
English;
Aged: 65+ years

Database: Embase: 215 articles retrieved

'frail elderly'/exp
AND 'inappropriate prescribing'/exp
OR 'suboptimal prescribing'
OR 'inappropriate medication'
OR 'potentially inappropriate medication'
AND [humans]/lim
AND [embase]/lim
AND [article]/lim
AND [aged]/lim
AND [english]/lim
AND [1990–2013]/py

Appendix B: Published Paper: Potentially Inappropriate Prescribing in Older Patients Discharged from Acute Care Hospitals to Residential Aged Care Facilities

Research Report

Annals of Pharmacotherapy
2014, Vol. 48(11) 1425–1433

DOI: 10.1177/1060028014548568
aop.sagepub.com
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Potentially Inappropriate Prescribing in Older Patients Discharged From Acute Care Hospitals to Residential Aged Care Facilities

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Abstract

Background: The frequency of prescribing potentially inappropriate medications (PIMs) in older patients remains high despite evidence of adverse outcomes from their use. Little is known about whether admission to hospital has any effect on appropriateness of prescribing. **Objectives:** This study aimed to identify the prevalence and nature of PIMs and explore the association of risk factors for receiving a PIM. **Methods:** This was a prospective study of 206 patients discharged to residential aged care facilities from acute care. All patients were at least 70 years old and were admitted between July 2005 and May 2010; their admission and discharge medications were evaluated. **Results:** Mean patient age was 84.8 ± 6.7 years; the majority (57%) were older than 85 years, and mean (SD) Frailty Index was 0.42 (0.15). At least 1 PIM was identified in 112 (54.4%) patients on admission and 102 (49.5%) patients on discharge. Of all medications prescribed at admission (1728), 10.8% were PIMs, and at discharge, of 1759 medications, 9.6% were PIMs. Of the total 187 PIMs on admission, 56 (30%) were stopped and 131 were continued; 32 new PIMs were introduced. Of the potential risk factors considered, in-hospital cognitive decline and frailty status were the only significant predictors of PIMs. **Conclusions:** Although admission to hospital is an opportunity to review the indications for specific medications, a high prevalence of inappropriate drug use was observed. The only associations with PIM use were the frailty status and in-hospital cognitive decline. Additional studies are needed to further evaluate this association.

Keywords

Beers criteria, frailty, inappropriate prescribing, older patients, residential aged care facilities

Introduction

Our aging population, while a consequence of societal success, does present a challenge to the health care system. Older people are prescribed multiple medications and are more prone to adverse drug events (ADEs) that lead to increased mortality and morbidity and higher health care cost.[1-3] Advancing age is associated with substantial pharmacokinetic and pharmacodynamic changes, impaired homeostasis, and increased risk of ADEs because the physiological changes that occur with aging make the body more sensitive to the effects of medications.[4] Renal function declines in older age, and body composition changes with advancing age (relative lipid content increases; total body water and lean body mass decrease), which can affect drug distribution and often will result in drug retention and a prolonged half-life.[5] Age-related changes in pharmacokinetics and pharmacodynamics will occur with several drugs, and the action of drugs can be altered as a result of age-related up and down regulation of target receptors, transmitters, and signaling pathways. Hence, the appropriate use of available pharmacotherapy requires consideration of both the benefits and risks of the medications. Drugs are classified as potentially inappropriate when the risks of treatment outweigh the benefits,[6] they are prescribed for longer periods than clinically indicated or without any clear indication, they are not prescribed when indicated,[7] and they are likely to interact with other drugs and diseases.[8]

Inappropriate prescribing in older patients can be detected using either explicit (criterion based) or implicit (judgment-based) screening tools.[9-11] Explicit criteria are derived from expert reports or published reviews. They have high reliability and reproducibility but focus mainly

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on specific drugs and disease states. In contrast, implicit criteria are person specific and explore patient preferences, rather than the disease and medications; they rely on evaluator judgment and tend to have low reliability and poor clinical utility.[12] Although these criteria address some aspects of prescribing in older patients, they seldom consider the frailty of such patients. The omission of health status from established prescribing tools may help explain the lack of clinical benefit from algorithm-based medication reviews.[2] The Beers criteria are commonly used, and they do measure some surrogates of frailty. They were originally developed in 1991[13] for use in the older nursing home population and have been subsequently updated in 1997, 2002, and 2012, so as to be applicable to all persons older than 65 years, regardless of their place of residence.[14] The recently updated Beers criteria divide medications into 3 main categories according to major therapeutic classes and organ systems: 34 medications are considered potentially inappropriate, independent of diagnosis; 14 are to be avoided in older adults with certain diseases and syndromes that can be exacerbated by the listed drug; and 14 others are to be used with caution in older adults.[14] Although many medications on the Beers list are not available in Australia, use of these criteria for evaluation of prescribing has the advantage of enabling international comparison.

Admission to hospital is an opportune time to review and rationalize prescribing, weighing up the benefits of pharmacotherapy against significant risks of polypharmacy and inappropriate prescribing in older adults, particularly those who are frail. Pharmacists in hospitals can play a significant role in the initiation of changes to patient's therapy and management. In Australia, all major government-funded hospitals provide inpatient clinical pharmacy services.[15] These services encompass medication management reviews during inpatient episodes, clinical reviews, medication reconciliation, ADE monitoring, patient medication counseling, and provision of drug information.[16] However, little is known about whether admission to hospital has any effect on appropriateness of prescribing. Potentially inappropriate prescribing (PIP) is particularly common in long-term residents of aged care facilities; indeed, institutionalization itself is an established independent risk factor for PIP.[17] Studies that have compared prevalence of potentially inappropriate medications (PIMs) at admission to hospital and discharge have reported inconsistent results. A prospective drug surveillance in an acute medical geriatric unit in France reported a decreased prevalence of PIMs, from 66% at admission to 43.6% at discharge.[18] A retrospective, nonrandomized study in the Specialist Health and Ageing Unit in England, UK, found a decreased prevalence, from 26.7% at admission to 22.6% at discharge.[19] In contrast, a similar study in Norway showed increased prevalence of PIMs, from 24% at admission to 35% at discharge.[20]

Similar reports from Australian health care settings are limited, and we cannot assume identical prevalence rates and PIM types in Australia because of the variations in health care systems and prescribing practices across countries. Therefore, the main objective of this study was to determine the prevalence of PIP using the 2012 version of the American Geriatrics Society Beers Criteria in patients discharged from acute care to residential aged care facilities (RACFs). We also aimed to identify whether polypharmacy, age, gender, in-hospital falls, delirium, functional and cognitive decline, and the frailty status of patients were independent risk factors for receiving an inappropriate medication.

Methods

Study Population

In this study, we undertook secondary data analyses of patients recruited as 3 separate prospective cohorts in studies originally designed to investigate the prevalence of geriatric syndromes and quality of care in acute care settings.[21-23] This is a prospective study of patients, aged 70 years and older, who were discharged to RACFs (206 out of total 1418 patients) following admission to 11 acute care hospitals in Queensland and Victoria, Australia. The sites ranged from small secondary care centers (with 120-160 beds, n = 2), through rural hospitals (250-280 beds, n = 2) to metropolitan teaching facilities (300-450 beds, n = 4) and major tertiary referral centers (>650 beds; n = 3). All patients were admitted to the acute care hospitals between July 2005 and May 2010. Patient recruitment has been described in detail elsewhere.[21,22] Patients were excluded if they were admitted to coronary or intensive care units, for terminal care only, or were discharged from hospital within 24 hours. Only those patients entering RACFs at discharge were included in the study.

Data Collection and Measurement Tools

The interRAI Acute Care assessment tool was used for data collection.[24] interRAI is a not-for-profit research consortium with international collaboration from more than 30 countries. It aims to improve the quality of life of vulnerable persons through a unified comprehensive assessment system. The interRAI suite consists of tools to support assessment and care planning of persons with chronic illness, frailty, disability, or mental health problems across care settings.[25] One of these tools is the interRAI Acute Care (interRAI AC) instrument that has been specifically developed for use in the acute setting to support Comprehensive Geriatric Assessment (CGA) for older inpatients.[26] This instrument screens a large number of domains around sociodemographic information; physical,

cognitive, and psychosocial functioning; medications; medical diagnoses; advance directives; and discharge destination.[26] A number of scales embedded within the interRAI instruments combine single items belonging to domains such as activities of daily living (ADL), instrumental ADL, and cognition, which are used to describe the presence and extent of deficits in these domains.[25] Trained nurse assessors gathered data at admission (within 24 hours in the ward) and at discharge. In completing the interRAI assessment, all available sources of information, including the patient, carers, and medical/nursing/allied health staff were utilized, either directly as verbal reports or from written entries in hospital records. For each patient, all prescribed medication, including Anatomical Therapeutic Classification (ATC) codes, was recorded on admission and at discharge. Data were entered by pharmacists or pharmacy students and verified by a second pharmacist or geriatrician.

Deriving a Frailty Index

A Frailty Index (FI), an index of accumulated deficits, was calculated for each individual at admission using a well-defined methodology.[27] Data collected using the interRAI assessment tool was coded as deficits. For example, in the domain of cognition, an acute change in mental status is recorded as a dichotomous, yes/no response, and this was coded as deficit present (1 point) or absent (0 points). Other data were recorded on an ordinal scale with cutoffs for 0/0.5/1 deficit coded according to the distribution of the data. For example, the domain of vision classified into 5 categories (0, adequate; 1, minimal difficulty; 2, moderate difficulty; 3, severe difficulty; 4, no vision) is coded with cutoffs of 0/0.5/1 (ie, 0 − 0; 1 − 0.5; 2-4 − 1). Deficits crossed the domains of function, cognition, mood and behavior, disease diagnoses, and sensory impairments. Medication use was excluded from the FI. Each individual's deficit points were then summed and divided by the total number of deficits considered (here, 52). For example, someone with 6 deficits out of 40 counted has a FI of 0.15. The FI has a potential score of 0 to 1, where 0 − absence of all deficits and 1 − all deficits present.[28] Although the FI can be considered as a continuous variable with higher values representing greater frailty, 0.25 has been proposed as the cutoff between fit and frail individuals.[29]

Polypharmacy

Polypharmacy was categorized into 3 groups based on the number of drugs documented by the interRAI assessors who transcribed the patients' drug charts. All prescribed medications were recorded approximately 24 hours after admission to hospital and again at discharge from hospital. These lists may have included medications used for a finite period in hospital to manage the patients' acute medical conditions. Hyperpolypharmacy was defined as concurrent use of 10 or more drugs; polypharmacy was defined as use of 5 to 9 drugs; and nonpolypharmacy represented patients using 4 or fewer drugs concomitantly. These cutoff points have been selected based on previous studies relating the risk of adverse outcomes in older people to number of prescribed medications.[30,31]

Covariates

Fall in Hospital. In-hospital fall was defined as having at least 1 fall during the period of hospitalization. These data were collected prospectively by daily chart reviews and ward visits by the research nurses using all available sources of information (interviewing the patient and medical staff, reviewing the medical records, and checking the forms or systems for recording adverse events).[32] The process of data collection was based on the detailed instructions provided in the tool manual.[24]

Delirium in Hospital. As part of the interRAI AC, varying mental function and acute changes in mental status from baseline were assessed by a nurse assessor at admission and discharge. The 2 items were combined to screen for delirium.[33] Delirium in hospital was recorded if delirium screened positive at the admission or discharge assessments or if noted in the hospital records on daily ward visits by the nurse assessor.

Failure to Improve in ADL. Failure in improvement of ADL was recorded as a change in the ADL Short Form Scale that consists of 4 items (personal hygiene, walking, toilet use, and eating). Scores on the ADL scale range from 0 to 16, with higher scores indicating greater impairment.[22] Failure to improve in ADL was defined as follows: those with some ADL impairment on admission who had the same or worse (higher) ADL score on discharge compared with admission or who developed a new ADL impairment in hospital.

In-Hospital Cognitive Function Decline. The Cognitive Performance Scale was used to measure cognitive impairment.[22] The score ranges from 0 to 6, with higher scores indicating greater impairment. In-hospital cognitive decline was defined as having a worse Cognitive Performance Scale score on discharge compared with admission.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences 21.0 (IBM SPSS Statistics 21.Ink). STATA, version 12, was used for all regression analysis. A paired sample *t* test was used to observe the relationship between admission and discharge medications. Standard multiple

Table 1. Characteristics of the Study Population.

Characteristics	Number of Patients (%), n = 206		
	Value	At Least 1 PIM at Admission	No PIM at Admission
Age distribution			
Mean age (SD)		84.8 (6.8)	
65-74 years	20 (10)	13 (11.6)	7 (7.5)
75-84 years	69 (33)	41 (36.6)	28 (29.8)
>85 years	117 (57)	58 (51.8)	59 (62.7)
Sex, n (%)			
Female	142 (69)	78 (55)	64 (45)
Male	64 (31)	34 (53.2)	30 (46.8)
Admitted from, n (%)			
Community	73 (35.4)	35 (48)	38 (52)
RACF low care	64 (31.1)	37 (57.8)	27 (42.2)
RACF high care	69 (33.5)	40 (58)	29 (42)
Discharged to, n (%)			
RACF low care	81 (39.3)	48 (59.2)	33 (40.8)
RACF high care	125 (60.7)	64 (51.2)	61 (48.8)
Length of stay: median length of stay, days [IQR]		8 [4-16]	
Frailty Index: mean (SD)		0.42 (0.15)	

Abbreviations: IQR, interquartile range; PIM, potentially inappropriate medication; RACF, residential aged care facility.

regression was used to detect risk factors for PIMs at both admission and discharge. Age, gender, number of admission and discharge medications, in-hospital falls, delirium, functional and cognitive decline, and FI of patients were used as predictive variables for PIMs. A P value of 0.05 was considered statistically significant.

Ethics

Ethics approval was obtained from the human research and ethics committee of each participating hospital and The University of Queensland Medical Research Ethics Committee. All patients or their substitute decision maker gave informed consent for participation.

Results

Patient Characteristics

Of the 206 patients discharged to RACFs, 142 (69%) were female. The principal characteristics of the study population are described in Table 1. They had a mean (SD) age of 84.8 (6.8) years; the majority (57%) were older than 85 years, and the mean (SD) FI was 0.42 (0.15). A total of 35%were admitted from the community and 65% from RACFs. The median length of stay in hospital was 8 days. Of those discharged to RACFs, approximately 60% were discharged to high care (a high-level care setting for older people with 24-hour nursing care), and the remaining 40% were discharged to low care (residents require accommodation and personal care type services but not 24-hour nursing care).

Table 2. Polypharmacy Categories and Potentially Inappropriate Medication (PIM) Distribution at Admission and Discharge.

Variables	Number of patients (%), n = 206	
	Admission	Discharge
Medication category		
0-4 Medications (nonpolypharmacy)	47 (22.8)	35 (17.0)
5-9 Medications (polypharmacy)	106 (51.5)	102 (49.5)
≥10 Medications (excessive polypharmacy)	50 (24.3)	67 (32.5)
Missing	3 (1.5)	2 (1.0)
Total number of medications	1460	1652
Number of PIMs		
No PIMs	94 (45.6)	104 (50.5)
1 PIM	60 (29.1)	59 (28.6)
2 PIMs	34 (16.5)	29 (14.1)
3 PIMs	13 (6.3)	8 (3.9)
4 or More PIMs	5 (2.4)	6 (2.9)
Total number of patients with at least 1 PIM	112 (54.4)	102 (49.5)

General Prescribing Pattern

The number of medications prescribed on admission and discharge is shown in Table 2. Patients were prescribed a mean of 7.2 (±3.81) regular medications at admission and 8.1 (±3.95) on discharge to RACF. Comparing medication regimen at admission and discharge, the prevalence of polypharmacy was stable (106 [51.5%] vs 102 [49.5%], respectively) but with an increase in hyperpolypharmacy (from 50 patients [24.3%] to 67 [32.5%]).

At admission, 2 patients were prescribed 23 medications, with 10 patients receiving at least 20 medications. On discharge, 1 (different from the admission patients) patient was prescribed 23 medications, and 4 patients had at least 20 medications. At discharge, aspirin and antiplatelet agents were the most frequently prescribed medications (109, 54%), followed by antiulcer drugs in 105 (52%) patients. Other prevalent medication included antidepressants (28.2%), benzodiazepines (19.3%), antipsychotics (16.3%), and opioids (16.3%). Of the potential risk factors, frailty status and in-hospital cognitive decline were the only significant predictors of PIMs at both admission ($P = 0.047$) and discharge ($P = 0.032$). However, no association was observed between PIM use, polypharmacy categories, age, gender, in-hospital falls, delirium, and functional decline.

PIMs at Admission

On admission, 112 (54.4%) patients were on at least 1 PIM; 5 patients were on 4 PIMs. Of the 1460 regular medications

prescribed at admission, 187 (12.8%) were PIMs. Of these, 149 (80%) were classified as PIMs for older people independent of diagnosis, and 38 (20%) PIMs were contraindicated in older people with certain diseases or syndromes (Table 3). PIMs to be used with caution accounted for 3.8% of total medications prescribed. Commonly prescribed PIM categories were central nervous, cardiovascular, and gastrointestinal system drugs and analgesics. Multiple logistic regression analysis revealed that frailty status was significantly associated with increased risk of PIMs at admission: $P < 0.05$; odds ratio (OR) − 1.06 (1.01, 2.37). Age (P − 0.125), gender (P − 0.596), and number of admission medications (P − 0.947) were not significantly associated with being prescribed PIMs.

PIMs at Discharge

At discharge, 102 (49.5%) patients were on at least 1 PIM; 1 patient was discharged on 7 PIMs, 5 patients on 4 PIMs, and 8 patients on 3. Of all the 1652 regular medications prescribed at discharge, 168 (10.1%) were PIMs. Of these 168, 129 (77%) were classified as PIMs for older people independent of diagnosis, and 39 (23%) PIMs were contraindicated in older people with certain diseases or syndromes (Table 3). PIMs to be used with caution accounted for 3.7% of total medications prescribed. Commonly prescribed PIM categories were central nervous system (CNS) drugs' cardiovascular, gastrointestinal, and respiratory medications; analgesics; and antimuscarinics. Multiple regression analysis showed that only frailty status was significantly associated with increased risk of PIMs at discharge: $P < 0.05$; OR − 1.08 (1.06, 2.36).

Changes in PIM Between Admission and Discharge

Table 2 shows the number of patients with total PIMs at admission and discharge. Of the 187 PIMs prescribed at admission, 56 (30%) were stopped and 131 (70%) were continued, whereas 32 new PIMs were started. PIMs introduced included CNS drugs—benzodiazepines (14/32), antipsychotics (8/32), and antidepressants (1/32)—respiratory medications (3/32), antiarrhythmics (2/32), gastrointestinal (2/32), and analgesics (2/32).

Discussion

The present study demonstrated frequent use of inappropriate medications in older people discharged from acute care hospitals to RACFs. It was found that 54.4% of patients were on at least 1 PIM at admission to hospital, with a nonsignificant trend to fewer PIMs on discharge (49.5%). The frailty status of patients and in-hospital cognitive decline were the only significant predictors for receiving PIMs at both admission and discharge. To our knowledge, this is the first study to identify this association.

The prevalence of PIMs observed in this study population differ from those of previous studies using the recent updated 2012 Beers criteria. A higher prevalence (82.6%) was observed in a Brazilian long-term care home study,[34] and around 66% was observed in an Argentinian geriatric hospital.[35] Yet a very low prevalence (16% and 25.5%) was noticed in tertiary health care settings in India and Nigeria, respectively.[36,37] Commonly prescribed PIM categories at both admission and discharge were CNS, cardiovascular, gastrointestinal, and respiratory drugs and analgesics, which are similar to those reported in other studies.[38-41] Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and anticholinergics are routinely prescribed to treat many common conditions in older people. Although the efficacy of NSAIDs for the treatment of inflammation and pain of various origins is well established, prescribing these drugs in older patients is a challenge because of a great variety of gastrointestinal and cardiovascular safety issues that need to be considered.[42] Medications with anticholinergic effects are associated with several adverse effects, such as sedation, cognitive decline, delirium, and falls.[20]

Of note, 30% of PIMs were stopped, and other new PIMs were introduced at discharge. Although our study shows that the number of PIMs at discharge was lower than on admission, the reduction was not significant. The proportion of those on PIMs at discharge remained high (49.5%). Australian studies have reported that an average of 5 to 7 changes are made during hospitalization, with cessation of 2 to 3 drugs and initiation of 3 to 4.[43] Overprescribing (benzodiazepines, antipsychotics, and acid suppressants) and inappropriate drug selection (metformin in renal impairment, long-acting oral hypoglycemic) are common in Australian hospitals.[43] This contributes to increased risk of drug-related problems and higher incidence of PIMs during and immediately following hospitalization. Although pharmacists play an important role in medication reconciliation review, it was outside the scope of this study to investigate the appropriateness of medication prescribed. The role of the pharmacist in optimizing medications in older hospitalized patients has been established in several studies.[44,45] Studies suggest that strategies to revaluate drug treatment and reduce PIM use during hospitalization of patients should be undertaken by physicians and pharmacists in a collaborative manner.[46,47]

We found a clear association between the use of PIMs, frailty status, and cognitive decline of patients at admission and discharge. However, no association was observed between PIM use, age, and gender, which is consistent with previous reports.[48,49] Also, no association of PIM use with in-hospital falls, delirium, and functional decline was observed. Furthermore, in contrast to other studies,[50-52] we

Table 3. Potentially Inappropriate Medications on Admission and Discharge as Determined by 2012 Beers Criteria (n = 206).

PIMs Independent of Medical Condition					PIMs in the Presence of Certain Pathologies					PIMs to Be Used With Caution				
	Admission		Discharge			Admission		Discharge			Admission		Discharge	
System/Therapeutic category/Drugs	n	Percentage	n	Percentage	System/Therapeutic category/Drugs	n	Percentage	n	Percentage	System/Therapeutic category/Drugs	n	Percentage	n	Percentage
Central nervous system	106	71.1	102	79	Central nervous system	11	29.9	10	25.6	Antipsychotics	14	25.5	15	24.6
Antidepressants	9	6	8	6.2	Antidepressants	2	5.3	2	5.1	SNRIs	3	5.5	4	6.5
Antipsychotics	50	33.6	40	31	Antipsychotics	9	23.7	8	20.5	SSRIs	31	56.3	35	57.4
Cardiovascular	47	31.5	54	41.8	Cardiovascular	12	31.5	9	23	TCAs	7	12.7	7	11.5
α-Blockers	4	2.7	4	3.1	Gastrointestinal	8	21	10	25.6					
Antiarrhythmic	14	9.4	7	5.4	Respiratory	5	13.1	8	20.5					
Gastrointestinal	23	15.5	12	9.3	Antimuscarinics	2	5.2	2	5.1					
Analgesics	2	1.4	4	3.1										
Total	149	100	129	100		38	100	39	100		55	100	61	100

Abbreviations: PIMs, potentially inappropriate medications; TCAs, tricyclic antidepressants; SNRIs, selective norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

found no association between polypharmacy and PIM use. There might be several reasons behind this, which need to be explored further. The goals of care in this vulnerable group are likely to be an improvement in quality of life rather than focusing on survival.[53] This could result in a higher prevalence of drugs for the prevention of symptoms such as analgesics for pain and laxatives or antiulcer drugs for gastrointestinal symptoms. Consequently, although multiple drugs are used, the probability of having a PIM might be lower. Prolonged length of hospital stay (≥10 days) has been shown to have a significant association with polypharmacy and incidence of PIM use.[54] The median length of hospital stay in this study was only 8 days, which may have minimized the risk of a PIM being prescribed.

There are a number of limitations to this study. The appropriateness of prescribing at the level of individual patients based on clinical indications and contraindications were outside the scope of this study. Although patients were recruited from multiple hospital sites, the sample size is relatively small. The recently updated Beers criteria contain medications that are either not available in Australia (eg, carisoprodol and trimethobenzamide) or that have been withdrawn from use here (chlorpropamide, reserpine, and phenylbutazone). Thus, the relevance of the tool within Australia could be questioned.[7] Moreover, these criteria also fail to address other issues such as drug duplication, underprescribing, and drug-drug interaction.[14,55,56] Hence, the prevalence of PIMs may be higher than those reported in this study. However, this study demonstrated the prevalence of PIMs in frail older patients on admission and discharge and adds to existing research by identifying the patient's frailty status as a unique risk factor associated with the use of PIMs.

These discrepancies in Beers and other established criteria should be addressed either by developing new criteria or by refining the existing tools to make them more applicable to frail older people. The first and foremost step is to identify the frail patient in clinical practice by applying clinically validated tools (eg, FI). Once the frail patient has been identified, there is a need for specific measures or criteria to assess appropriateness of therapy that consider factors such as quality of life, functional status, and remaining life expectancy and thus modified goals of care.[57]

Conclusion

A high prevalence of potentially inappropriate drug prescribing was observed in older patients on admission to acute care hospitals and on discharge to RACFs. Frailty status and in-hospital cognitive decline of patients were risk factors for the use of PIMs. The findings of this study provide a basis for designing interventions to rationalize prescribing in older patients. Further studies in different settings, with a larger population are warranted to evaluate the prevalence of PIMs and deviations in prescribing practices.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Authors' Note

The abstract was presented as a poster in Annual Scientific Meeting of the American Geriatrics Society; May 15-17, 2014; Orlando, FL.

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Appendix C: Published paper: Geriatrician interventions on medication prescribing for frail older people in residential aged care facilities

Clinical Interventions in Aging

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ORIGINAL RESEARCH

Geriatrician interventions on medication prescribing for frail older people in residential aged care facilities

This article was published in the following Dove Press journal:
Clinical Interventions in Aging
18 June 2015
Number of times this article has been viewed

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Objective: In Australian residential aged care facilities (RACFs), the use of certain classes of high-risk medication such as antipsychotics, potent analgesics, and sedatives is high. Here, we examined the prescribed medications and subsequent changes recommended by geriatricians during comprehensive geriatric consultations provided to residents of RACFs via videoconference.

Design: This is a prospective observational study.

Setting: Four RACFs in Queensland, Australia, are included.

Participants: A total of 153 residents referred by general practitioners for comprehensive assessment by geriatricians delivered by video-consultation.

Results: Residents' mean (standard deviation, SD) age was 83.0 (8.1) years and 64.1% were female. They had multiple comorbidities (mean 6), high levels of dependency, and were prescribed a mean (SD) of 9.6 (4.2) regular medications. Ninety-one percent of patients were taking five or more medications daily. Of total medications prescribed (n=1,469), geriatricians recommended withdrawal of 9.8% (n=145) and dose alteration of 3.5% (n=51). New medications were initiated in 47.7% (n=73) patients. Of the 10.3% (n=151) medications considered as high risk, 17.2% were stopped and dose altered in 2.6%.

Conclusion: There was a moderate prevalence of potentially inappropriate high-risk medications. However, geriatricians made relatively few changes, suggesting either that, on balance, prescription of these medications was appropriate or, because of other factors, there was a reluctance to adjust medications. A structured medication review using an algorithm for withdrawing medications of high disutility might help optimize medications in frail patients. Further research, including a broader survey, is required to understand these dynamics.

Keywords: frail older, geriatrician intervention, high-risk medications, residential aged care facilities

Introduction

Many frail older people spend their final years of life in aged care facilities. In Australia, the proportion of older people living in care accommodation increases with age from 2% of people aged 65–74 years to 6% of people aged 75–84 years and 26% of people aged 85 years and over.[1] Those living in care homes often take more medications than noninstitutionalized elderly, and the risk of morbidity as a result of medication is high.[2] Also, the incidence of adverse drug events increases with the number of medications prescribed.[3] Residential aged care facilities (RACFs) in Australia are institutions in which prescribing of high-risk medication such as antipsychotics, potent analgesics, and sedatives is high, with between 25% and 30% of patients receiving such medication.[4–6] Ensuring high-quality care and appropriate medication use for

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these residents is challenging given their frailty, complex disabilities, and multiple chronic conditions.[7]

Despite the growing body of literature indicating that medication errors and potentially inappropriate medications are important causes of morbidity and mortality, evidence for effective interventions and strategies to improve the pharmacological management of patients is still limited.[8] Well-organized approaches are needed to provide specialist advice in nursing homes to ensure quality medical care. Practice models that include a pharmacist as part of the multidisciplinary team represent best practice in inpatient, ambulatory, and community settings, and in care transitions between settings.[9] Geriatrician-led case conference reviews and comprehensive geriatric assessments (CGAs) have been shown to be effective in reducing potentially inappropriate medications use and improved suboptimal prescribing.[7,10] Although access to geriatric services in Australian RACFs is limited, expert advice is increasingly provided by videoconferencing (VC).

In the model offered in relation to this study, a specialist geriatrician provides a comprehensive assessment of the patient and input into care plans via VC. Geriatricians make recommendation about patients' medications, perhaps advising that some medications are stopped or others commenced. We designed this study to examine whether VC-mediated geriatric assessment resulted in changes to medications prescribed, and reduced the prevalence of potentially inappropriate medication use.

Methods

Study population and setting

We conducted a prospective observational cohort study of four RACFs in Queensland, Australia, that currently have regular access to geriatric consultations via VC. The participating facilities were the first four to be supported by the geriatrician service operating out of the Centre for Research in Geriatric Medicine. We were able to record the information for 153 patients assessed by four geriatricians over the research timeframe.

Data collection

At participating facilities, geriatrician-supported CGA is encouraged within 4–12 weeks of admission. All residents are offered CGA at entry into the participating RACF. However, uptake is determined by referral from the treating general practitioners. The CGA is conducted using a structured protocol based on the interRAI (Resident Assessment Instrument) Long-Term Facility assessment system, administered by a senior registered nurse. The assessment includes a comprehensive diagnosis list, justification of all medications documented, functional profile, cognitive assessment confirming the presence or absence of cognitive and mood disorders, recommendations for prevention and management, and advanced care planning. Observations made by the nurse are entered into a clinical decision support system, which generates a draft resident health care profile and care plan. The clinical decision support system is mounted on a web-based platform to permit review and comment by a specialist geriatrician. interRAI is a not-for-profit research consortium with international collaboration from more than 30 countries that aims to improve the quality of life of vulnerable persons through a unified comprehensive assessment system.

Ideally, 1–4 weeks following admission to the facility, residents who have been referred to a geriatrician by the GP are assessed via video-consultation by the specialist. The geriatrician is able to speak with the resident as well as attending RACF staff and resident's family members if present. Recommendations to the GP and RACF are made, as necessary, regarding the resident's care plan following the consultation. CGA is also offered to existing residents on an "as needs" basis. A formal functional profile is prepared, and a report is generated recording the recommendations made by the geriatrician. Data for this study were retrieved from these sources over an 18-month period from January 2013 to August 2014. Ethics approval was obtained from the University of Queensland Medical Research Ethics Committee. All patients or their substitute decision-maker gave informed consent for participation.

Key measures

The primary outcome measure was the appropriateness of prescribing. A high-risk medications list was created based on those recognized by the American Geriatric Society 2012 Beers Criteria,[11] the McLeod criteria,[12] the Laroche criteria,[13] the PRISCUS criteria,[14] and the Norwegian General Practice criteria[15] (Table 1). These criteria consider a medication as high risk when it has a tendency to cause adverse drug events and drug toxicity in older adults due to its pharmacological properties and the physiologic changes of aging. For our study, we defined high-risk medications as those that are listed on any one of these criteria. We excluded medications not available in Australia. Polypharmacy status was categorized into three groups based on the number of medications prescribed: non-polypharmacy (0–4 medications), polypharmacy (5–9 medications), and hyper-polypharmacy (≥10 medications).[16] Complementary and as-required medications were excluded. Three levels of change on current

Table 1 High-risk medications list

Medication	ATC codes	Main concerns	References
Analgesics, anti-inflammatory			
NSAID			
Aspirin >325 mg/day	N02BA01	– Very high risk of gastrointestinal hemorrhage, ulceration, or perforation, which may be fatal	11
Diclofenac	M01AB05	– Risk of renal toxicity especially in patients with preexisting chronic kidney disease	11
Ketoprofen	M01AE03		11,14
Ketorolac	M01AB15		11,12
Mefenamic acid	M01AG01	– Risk of fluid retention and fluid overload leading to decompensated heart failure in patients with underlying cardiac dysfunction	11,12
Meloxicam	M01AC06		11,14
Naproxen	M01AE02		11
Piroxicam	M01AC01	– Indomethacin may also have CNS side effects	11,12,14
Indomethacin	M01AB01		11–14
Etoricoxib	M01AH05		14
Ibuprofen	M01AE01		11
Opioid analgesics			
Pethidine	N02AB02	– Elevated risk of delirium and falls – Risk of neurotoxicity	11,12,14
Antiarrhythmic			
Amiodarone	C01BD01	– Predisposition to bradycardia and heart block	11
Flecainide	C01BC04	– Pro-arrhythmic effects	11,14
Sotalol	C07AA07	– Pro-arrhythmic effects	11,14,15
Disopyramide	C01BA03	– Potent negative inotropic effects predisposing to heart failure – Anticholinergic activity	11–13
Digoxin >0.125 mg/day	C01AA05	– Risk of toxicity especially in presence of renal insufficiency	11,13,14
Nifedipine	C08CA05	– Potential for postural hypotension – Short-acting formulations associated with increased mortality in elderly patients	11,13,14
Spironolactone >25 mg/day	C03DA01	– Risk of hyperkalemia	11
Diltiazem	C08DB01	– Potential to promote fluid retention and exacerbate heart failure	11
Verapamil	C08DA01		11
Antibiotics			
Nitrofurantoin	J01XE01	– Long-term use associated with pulmonary side effects, renal impairment, liver damage	11,13,14
Anticholinergics			
Antihistamines			
Chlorpheniramine	R06AB02	– Risk of anticholinergic effect: constipation, dry mouth, visual disturbance, bladder dysfunction – Clearance reduced with advanced age	11,14
Cyproheptadine	R06AX02		11,13
Dexchlorpheniramine	R06AB02		11,13,15
Diphenhydramine	R06AA02	– Increased risk of confusion and sedation, impaired cognitive performance	11,13,14
Doxylamine	R06AA09		11,13,14
Promethazine	R06AD02		11,13,15
Antiparkinson agents			
Benztropine	N04AC01	– Risk of anticholinergic side effects – Not recommended for prevention of extrapyramidal symptoms due to antipsychotics	11
Antispasmodics			
Propantheline	A03AB05	– Highly anticholinergic, uncertain effectiveness	11
Oxybutynin	G04BD04	– Anticholinergic side effects	11,13,14
Solifenacin	G04BD08	– ECG changes (prolonged QT)	11,13,14
Tolterodine (non-sustained release)	G04BD07		11,13,14
Antithrombotics			
Dipyridamole (short-acting)	B01AC07	– Risk of orthostatic hypotension	11–13
Warfarin	B01AA03	– Increased risk of bleeding	11,14
Prasugrel	B01AC22		11,14
Ticlopidine	B01AC05		11,14

(Continued)

Table 1 (*Continued*)

Medication	ATC codes	Main concerns	References
Antidepressants			
TCA			
Amitriptyline	N06AA09	– Peripheral anticholinergic side effects (eg, constipation, dry mouth, orthostatic hypotension, and cardiac arrhythmia)	11–15
Clomipramine	N06AA04		11,13–15
Doxepin (>6 mg)	N06AA12	– Central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium)	11,13–15
Imipramine	N06AA02	– Cognitive impairment	11–14
Nortriptyline	N06AA10	– Increased risk of falls	11
SSRI			
Fluoxetine (daily use)	N06AB03	– CNS side effects (nausea, insomnia, dizziness, confusion) – Hyponatremia	11,14,15
Paroxetine	N06AB05	– Confusion and other types of delirium – Cognitive impairment	11
MAO inhibitors			
Tranylcypromine	N06AF04	– Hypertensive crises – Cerebral hemorrhage – Malignant hyperthermia	11,14
Antiemetic drugs			
Trimethobenzamide	NA	– Can cause extrapyramidal adverse effects	11
Antiepileptic drugs (AEDs)			
Phenobarbitone	N03AA02	– Sedation – Paradoxical excitation – Highly addictive	11,14
Antihypertensive agents			
Clonidine	C02AC01	– Hypotension (orthostatic), bradycardia, syncope	11,13,14
Methyldopa	C01AB01	– CNS side effects: sedation, cognitive impairment	11,13,14
Moxonidine	C02AC05	– Hypotension (orthostatic) – Bradycardia – Sedation	13
Nifedipine	C08CA05	– Short-acting nifedipine associated with increased risk of myocardial infarction, increased mortality in elderly patients	11,13
Prazosin	C02CA01	– Hypotension	11,13,14
Terazosin	G04CA03	– Dry mouth – Urinary incontinence/impaired micturition – Increased risk of cerebrovascular and cardiovascular disease	11,14
Antipsychotics (neuroleptic drugs)			
First-generation (conventional) agents			
Chlorpromazine	N05AA01	– Anticholinergic and extrapyramidal side effects	11–13,15
Fluphenazine	N05AB02	– Parkinsonism	11,13,14
Haloperidol (>2 mg)	N05AD01	– Hypotonia	11,14
Promazine	N05AA03	– Sedation and risk of falls	11,13
Trifluoperazine	N05AB06	– Increased mortality in patients with dementia	11
Prochlorperazine	N05AB04		11,13–15
Second-generation (atypical) agents			
Aripiprazole	N05AX12	– Fewer extrapyramidal side effects	11
Asenapine	N05AH05	– Clozapine: increased risk of agranulocytosis and myocarditis	11
Clozapine	N05AH02		11,13,14
Olanzapine (>10 mg)	N05AH03		11,13–15
Muscle relaxants			
Baclofen	M03BX01	– CNS side effects: amnesia, confusion, falls	13,14
Solifenacin	G04BD08	– Anticholinergic side effects: constipation, dry mouth, CNS side effects	11,13,14
Orphenadrine	N04AB02	– More sedation and anticholinergic side effects than safer alternatives	11

(*Continued*)

Table 1 (*Continued*)

Medication	ATC codes	Main concerns	References
Sedative and hypnotics			
Long-acting benzodiazepines			
Clonazepam	N03AE01	In general, all benzodiazepines increase the risk of cognitive impairment, delirium, falls (muscle-relaxing effect, prolonged sedation) with risk of hip fracture, depression, psychiatric reactions (can cause paradoxical reactions, eg, agitation, irritability, hallucinations, and psychosis) and motor vehicle accidents in older adults	11
Diazepam	N05BA01		11–15
Bromazepam	N05BA08		13,14
Clobazam	N05BA09		13
Nitrazepam	N05CD02		13–15
Flunitrazepam	N05CD03		13–15
Short- and intermediate-acting benzodiazepines			
Alprazolam	N05BA12		11,13,14
Lorazepam	N05BA06		11,13,14
Oxazepam	N05BA04		11,13–15
Temazepam	N05CD07		11,13,14
Triazolam	N05CD05		11–14
Non-benzodiazepine hypnotics			11–14
Zolpidem	N05CF02		11,13,14
Zopiclone	N05CF01		13–15
Chloral hydrate	N05CC01		11,14
Others			
Theophylline	R03DA02	– Risk of arrhythmias – No proof of efficacy in COPD	11,15
Glipizide	A10BB07	– Long half-life leading to possible prolonged hypoglycemia	13
Cimetidine	A02BA01	– Confusion – More interactions than other H2 antagonists	11–13
Diphenoxylate	A07DA01	– No proof of efficacy – Blocks the muscarinic receptors	12,13

Abbreviations: ATC, anatomical therapeutic chemical; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; ECG, electrocardiogram; MAO, monoamine oxidase; NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

prescription were defined as drug stopped, dose altered, and new drug started.

Statistical analysis

The Statistical Package for Social Science 21.0 (IBM SPSS Statistics 21. Ink) was used for statistical analysis. Categorical variables were summarized using proportions and continuous variables using mean, standard deviation (SD), and range. In univariate analysis, the differences in the distribution of variables between patients with or without high-risk medications were compared using the chi-squared test for categorical variables, and nonparametric or parametric comparison of means for continuous variables, depending on the distribution of the data. Tests of significance were two-tailed, using a significance level of $P \leq 0.05$.

Results

Over the course of the study, 153 patients were assessed by the four participating geriatricians across four facilities. Demographics and clinical characteristics of the study population are presented in Table 2. The mean (± SD) patient age was 83.0 (±8.1) years and 64.1% were female. The median length of stay in the facility at the time of assessment was 488 days (range 6–3,213 days). Twenty-four percent of patients were assessed within 12 weeks of admission to the facility. Patients had multiple comorbidities (mean 6), including dementia diagnosed in 67.3%, depression in 46.4%, and delirium in 11.7%. Other prevalent comorbidities were hypertension (35.9%), diabetes (20.9%), heart diseases (13.7%), and respiratory diseases (11.1%). Patients were prescribed a mean (± SD) of 9.6 (±4.2) regular medications. Polypharmacy (≥5 medications) was seen in 91% (n=139) residents, half of whom (n=69) were exposed to hyper-polypharmacy (≥10 medications).

Of all medications prescribed (n=1,469), the geriatrician recommended withdrawal of 9.8% (n=145) and dose alteration for 3.5% (n=51) medications. Medications were stopped because of adverse effects (n=66), no clear

Table 2 Demographic and clinical characteristics of study population

Characteristics	Total, N=153
Age, years	
Mean ± SD	83.0±8.1
Median	83
Females, n (%)	98 (64.1)
Length of stay at the time of assessment: median length of stay, days (IQR)	488 (6–3,213)
Marital status (%)	
Married	50 (32.6)
Widowed	73 (47.7)
Separated/divorced	19 (12.4)
Never married	11 (7.1)
Comorbidities (%)	
Dementia	103 (67.3)
Delirium	18 (11.7)
Depression	71 (46.4)
Under nutrition	49 (32.0)
COPD/asthma	17 (11.1)
Hypertension	55 (35.9)
Diabetes	32 (20.9)
Ischemic heart disease	21 (13.7)
Prescription medications	
Total number of prescribed medications	1,469
Mean ± SD	9.6±4.2
Polypharmacy categories (%)	
0–4 medications (non-polypharmacy)	14 (9.2)
5–9 medications (polypharmacy)	70 (45.8)
≥10 medications (hyper-polypharmacy)	69 (45.1)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation.

indication/medication burden (n=63), and disease cured (n=16). Similarly, the medication dose was altered because of adverse effects and other factors (n=36), changed to "as required" (n=5), and ineffective dose (n=10). New medications were initiated in 47.7% (n=73) patients (Table 3). High-risk medications prescribed (10.3%; n=151) and intervention by geriatricians are listed by drug classes in Table 4. At least one high-risk medication was prescribed to 58.2% (n=89) patients. The univariate analysis showed that the length of stay was the only variable significantly associated with patients having at least one high-risk medication (Table 5). Of the high-risk medications, the geriatrician ceased 17.2% (n=26) medications and altered the dose in 2.6% (n=4). High-risk medications stopped were analgesics (n=6), antispasmodics (n=5), sedative and hypnotics (n=5), antipsychotics (n=3), antiarrhythmic (n=3), antihypertensive (n=2), gastrointestinal medications (n=1), and antibiotics (n=1). The dose was altered for antiarrhythmic (n=2), antidepressants (n=1), and sedative and hypnotics (n=1).

Discussion

To our knowledge, this is the first study of a geriatrician intervention where the medication advice for residents at long-term residential care facilities was specifically assessed via video-consultation. We found moderate levels of high-risk medications prescribed to residents in RACFs. Geriatricians made relatively few changes. This suggests that either the prescription of these medications was appropriate or other factors influenced the decision not to adjust medications.

The aim of defining high-risk medication use is to focus on a group of medications for which there is common consensus about potential inappropriateness. In principle, the high-risk medications prescribed to RACF residents in our study should not have been started or continued except under certain conditions; for example, amiodarone, a high-risk medication used in older people, is a therapy that may be indicated to treat supraventricular arrhythmias effectively in patients with heart failure;[17] and benzodiazepines, that may increase the risk of mental decline, delirium, falls, and fractures in older adults, may be appropriate for treating seizures, certain sleep disorders, and anxiety disorders.[11] The reluctance on the part of the geriatrician in adjusting/stopping many of these high-risk medications might suggest that prescription of some of these medications was appropriate. It is also possible that patients' (or primary care

Table 3 Outcomes of geriatrician intervention

Interventions	No of medications	Reasons
Drug stopped (145 [9.8%])	66	Adverse effects
	63	No clear indication/medication burden
	16	Disease cured or quiescent
Dose altered (51 [3.5%])	36	Dose reduced (because of adverse effects and other factors)
	10	Dose increased (because of ineffective dose)
	5	Changed to "as required"
New drug started (102 [6.9%])	58	Untreated morbidity
	23	Better alternative to present therapy
	21	Symptom relief

Notes: Total medication prescribed: 1,469; total high-risk medications prescribed: 151 (10.3%).

Table 4 High-risk medication prescribed and geriatrician intervention

System/therapeutic category/medications	High-risk medications prescribed, N (%)	Result of geriatrician intervention
Central nervous system medications	80 (52.9)	
Antidepressants	10 (6.6)	DA – 1
Antipsychotics	21 (13.9)	DS – 3 NDS – 1
Sedative and hypnotics	49 (32.4)	DS – 5 DA – 1 NDS – 2
Cardiovascular system medications	21 (13.9)	
Antiarrhythmic	12 (7.9)	DS – 3 DA – 2 NDS – 1
Antihypertensive	9 (5.9)	DS – 2
Gastrointestinal	6 (3.9)	DS – 1
Antihistamines	5 (3.3)	
Antithrombotic	22 (14.5)	
Antiparkinson agents	1 (0.6)	
Antispasmodics	5 (3.3)	DS – 5
Analgesics	9 (5.9)	DS – 6
Antibiotics	2 (1.3)	DS – 1
Total	151 (100)	DA – 4 DS – 26 NDS – 4

Abbreviations: DA, dose altered; DS, drug stopped; NDS, new drug started.

medical practitioners') strong belief in their medications might impact on an otherwise appropriate reduction in the number of medications taken, but this was not specifically explored in our study. In addition to these patient-related factors, there might be some prescriber-related factors that hinder medication adjustment, such as involvement of several prescribers, the use of preventive medication, and evidence-based medicine guidelines that often induce polypharmacy, uncertainties of precipitating disease relapse or drug withdrawal syndromes, and lack of risk/benefit information for the frail older residents.[18]

Interventions for appropriate prescribing in older people such as education, medication reviews, computerized support systems, and interdisciplinary team review have a positive impact on prescribing.[10] Yet, evidence for effective interventions to improve care in residential care settings is limited. A study by Crotty et al suggested that case conferences help an outreach geriatrician team to optimize medication management.[7] They describe the use of multidisciplinary case conference meetings to review medication in RACFs with significant improvement in medication appropriateness in the intervention group. There is conflicting evidence, however, concerning the efficacy of case conference medication reviews. One study using case conferencing to review the prescription and use of medications for community-dwelling older adults was unsuccessful in demonstrating the change in inappropriate use of medications.[19] A similar study in residential care facilities was unsuccessful in establishing changes in the number of medications.[20] Other approaches to optimize prescribing in frail older people might be the integration of a pharmacist in a team to make a collaborative approach on the quality of prescribing. Studies from inpatient settings suggest that the addition of a pharmacist to health care teams could lead to major reductions in morbidity and improved patient outcomes.[21,22] Another study on older patients transferring from hospital to a long-term care facility showed that adding a pharmacist transition coordinator on evidence-based medication management and

Table 5 Univariate analysis of variables influencing the use of high-risk medications

Characteristics	Patients		*P*-value
	Without high-risk medications (n=64)	With at least one high-risk medication (n=89)	
Socio-demographic			
Age	83.55±8.5	82.67±7.8	0.513
Sex (female)	44 (68.8)	54 (60.7)	0.304
Clinical			
Length of stay	303 (70.75–780.50)	630 (100–1,022.50)	0.044
Assessment status (within 12 weeks of admission)	18 (28.1)	19 (21.3)	0.334
Polypharmacy (>4 medications)	57 (89.1)	82 (92.1)	0.516
Comorbid conditions			
Delirium	7 (10.9)	11 (12.4)	0.788
Dementia	44 (68.8)	59 (66.3)	0.749
Depression	27 (42.2)	44 (49.4)	0.375
Under nutrition	24 (37.5)	25 (28.1)	0.218

Note: Values represent frequency (% of n).

health outcomes could improve the aspects of inappropriate use of medications.[23]

Optimizing prescribing requires appropriate ways to taper or withdraw high-risk medications in older adults. Available explicit and implicit criteria for appropriate prescribing encompass medications that have been validated in, and applied to, robust, healthy populations aged 65 and older. Therefore, these approaches may not be applicable to the more frail and multimorbid oldest old who reside in RACFs.[24] Most attention has been paid to the development of guidelines on how to initiate medications, but there are limited studies on the most effective way to cease medications.[25,26] Barriers to cease medications include time constraints on medical practitioners. This had led some to advocate that there should be some systematic approaches to follow in ceasing medications.[27,28] In responding to polypharmacy and minimizing high-risk medications, there appears a need for a practical algorithm that helps clinicians identify and discontinue potentially inappropriate high-risk medications using a systematic approach. This algorithm should signify a range of different clinical scenarios in relation to high-risk medications and offer an evidence-based approach to identify and, if appropriate, discontinue such medications and/or suggesting alternative treatments when required.

Our study has several limitations. Although, combining five different explicit criteria gives us an opportunity to extract a comprehensive list of high-risk medications, this list is not meant to regulate practice in a manner that surpasses the clinical judgment and the assessment of a prescriber. Also, because of our definition of high-risk medications as a list of drugs, the further domains of inappropriate prescribing such as underuse of medications and drug–drug interaction might be missed. Any adverse health events occurring among the residents using high-risk medications were also not investigated in our study. Considering the small sample size of 153 patients, the study results may not be representative of larger sample size in different nursing home settings.

Conclusion

In this study of 153 residents of four RACFs, we found a moderate prevalence of potentially inappropriate high-risk medications. However, geriatricians made relatively few changes, suggesting either that, on balance, prescription of these medications was appropriate or, because of other factors, there was a reluctance to adjust medications. Further research, including a broader survey, is required to understand these dynamics. A structured medication review using an algorithm for withdrawing medications of high disutility might help optimize medication prescribing in frail older people.

Acknowledgments

The authors would like to thank Elena Klestov and Eamonn Eeles, participating geriatricians for their support during the video-consultation; Melinda Martin Khan, research fellow in Centre for Research in Geriatric Medicine, for her help in ethics application; and staffs in Masonic Care Queensland for their assistance in data collection phase of this study. An abstract of preliminary study results on the first 75 patients was accepted as a poster in British Geriatrics Society (BGS) Autumn Meeting 2014, 15–17th October, Brighton, UK.

Disclosure

The authors report no conflicts of interest in this work.

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Appendix D: Published paper: Letter to the editor

The Journal of Frailty & Aging©
Volume 2, Number 4, 2013

LETTER TO THE EDITOR

ARE PRESCRIBING INDICATORS ESSENTIALLY REPRESENTING THE FRAIL OLDER POPULATION?

To the Editor: Older populations have multiple comorbid chronic diseases that require multiple treatments, which make them the larger consumer of medications (1). As a person grows older the ability to tolerate medications become poor due to age-related changes in pharmacokinetics and pharmacodynamics. The number of comorbidities increases with age that leads to the increase in number of medication prescribed which is associated with increased risk of adverse drug events (ADEs), impaired mobility, morbidity, hospitalization and death. However, while one person becomes hale and healthy another, who had seemed just as healthy, starts to weaken and slow down, often heading along a path that ends up in a medical condition known as frailty (2). Frailty in older population is well defined as a reduced ability to withstand illness without loss of function. Frail older persons often have multiple comorbidities with signs of impairment in activities of daily living. Prescribing drugs for these vulnerable populations is complex and potentially unsafe. Factors such as polypharmacy, multiple comorbidities, age-related changes in pharmacokinetics and pharmacodynamics and other functional impairment in frail older people make pharmacotherapy a complex issue. Prescribing physician should realize the fact that complying with the evidence based clinical guidelines is usually acceptable for patients with less comorbidity, but as the patients' clinical and functional states deteriorate leading to the progression towards frailty and disability, the goals of care and treatment targets need to be readjusted (3).

Worldwide, inappropriate prescribing in older population has drawn a significant attention as a major public health concern due to its direct correlation with morbidity, mortality and wastage of health resources. Several criteria have been developed worldwide to identify the instances of inappropriate prescribing in older patients that addresses certain aspects of medication prescribing such as indication, drug-drug interactions, drug-disease interaction, drug duplication, under prescribing. Inappropriate prescribing can be detected using explicit (criterion-based) or implicit (judgment-based) prescribing indicators. Explicit criteria are derived from expert reports or published reviews. They have high reliability and reproducibility but focuses mainly on specific drugs and the disease state. In contrast, implicit criteria are person specific that explores patient preferences, rather than disease and medications they rely on evaluator judgement and may have low reliability and low practical utility (4).

Unfortunately, there appear no specific criteria for assessing appropriateness of therapy in frail older patients. The guides and criteria currently available are applicable to robust, healthy older adults aged 65 and older which can't be generalized in to frail patients (2). In several instances prescribing is better guided by outcomes from randomized controlled trails, which are mainly targeted to robust elder patients while the typical frail older are excluded (1). Only few proportions of randomised, controlled trials and meta-analyses are published about people over 65 years of age because older people are rarely involved into clinical trials. For example, 37% of all patients with acute myocardial infarctions are older than 75 years of age; however this age group only represents 2–9% of clinical trial subjects (5). This discrepancy should be addressed either by developing new criteria or by refining the existing tools to be applicable in frail older people. These tools support the prescribing practices and improve the overall well-being of patients (6). The first and foremost step is to identify the frail patients in clinical practice by developing a clinically validated tool. Once, the frail patients are identified, there is a need of a specific measures or a criteria to assess appropriateness of therapy that considers patients quality of life, functional status, remaining life expectancy and goal of care with optimal choice of drug with the paramount risk-benefit ratio.

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Received April 3, 2013
Accepted for publication April 16, 2013

Appendix E: Published paper: Commentary

Q J Med 2013; **106**:969–975
doi:10.1093/qjmed/hct146 Advance Access Publication 2 July 2013

Commentary

QJM

Frailty: a key indicator to minimize inappropriate medication in older people

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Summary

Older populations are more likely to have multiple co-morbid diseases that require multiple treatments, which make them a large consumer of medications. As a person grows older, their ability to tolerate medications becomes less due to age-related changes in pharmacokinetics and pharmacodynamics often heading along a path that leads to frailty. Frail older persons often have multiple co-morbidities with signs of impairment in activities of daily living. Prescribing drugs for these vulnerable individuals is difficult and is a potentially unsafe activity. Inappropriate prescribing in older population can be detected using explicit (criterion-based) or implicit (judgment-based) criteria. Unfortunately, most current therapeutic guidelines are applicable only to healthy older adults and cannot be generalized to frail patients. These discrepancies should be addressed either by developing new criteria or by refining the existing tools for frail older people. The first and foremost step is to identify the frail patient in clinical practice by applying clinically validated tools. Once the frail patient has been identified, there is a need for specific measures or criteria to assess appropriateness of therapy that consider such factors as quality of life, functional status and remaining life expectancy and thus modified goals of care.

Introduction

The population of older people is growing and is prescribed more medicines.[1] This ageing population presents a challenge to the healthcare system as older people are more prone to chronic diseases and more likely to be prescribed multiple medications.[2] Polypharmacy, defined as taking at least five drugs, results in increased risk for inappropriate drug use and adverse drug reactions, with attendant higher morbidity and hospitalization.[2] It is now a major public health concern worldwide.

The appropriate use of available pharmacotherapy in older people requires a balance between the risks and benefits of medications. Rational prescribing in older people is complex because of the limited evidence on effectiveness of medication in this age group. Factors such as age-related changes in drug pharmacokinetics and pharmacodynamics and the presence of multiple co-morbidities make prescribing a difficult task.[3] Moreover, there is limited evidence for drug efficacy in older people and this group are more susceptible to adverse drug

events (ADEs). Mostly, prescribing is guided by evidence from randomized controlled trials, from which older patients, particularly those who are frail would be excluded.[4] Furthermore, the potential impact of medication in frail older people is usually generalized from non-frail or robust populations.[5] Understanding and incorporating the concept of frailty in older people may be of benefit to minimize inappropriate medication. This study briefly describes the concept of frailty and some of the tools used to measure inappropriate medication use in older people and advocates the incorporation of frailty assessment to optimize prescribing practice.

Frailty: definition and measurement

Although one person remains hale and hearty, another, who until recently seemed to be well, starts to weaken and slow down, sometimes as early as middle age. This is a central issue that is now being systematically addressed as why some age well and others do not, often heading along a path that ends up in a medical condition known as frailty.[5] The term frail is used to identify the vulnerable group of older people at high risk of adverse outcomes, including falls, worsening disability, prolonged hospital stays, institutionalization and death.[6]

Frailty can be measured in many ways but there are three established methods. The first method is a rules-based approach that identifies frailty as a 'clinical syndrome or phenotype' (a set of symptoms and signs that tend to occur together, thus characterizing a specific medical condition). The most well-known and widely used phenotype, developed by Fried *et al.* in 2001[7], identifies frailty on the basis of five criteria: weight loss, exhaustion, weak grip strength, slow walking speed and low physical activity. People having three or more of these deficits are considered to be frail, those with none are considered robust and the term 'pre-frail' is used for those with one or two deficits. This phenotype has been validated as a predictor of adverse outcomes in large epidemiological studies[8] and was used to identify frailty as the most common condition leading to death in community dwelling older people.[9] While this model is clinically coherent and reproducible, the omission of measures of cognition and mood has made it controversial; some argue that frailty consists of more than weakness, slowness and wasting.[10]

The second method is based on clinicians' 'subjective opinion'.[11] Although this has strong face validity, generalizability is limited. The third method conceptualizes frailty as a 'multidimensional risk state' that measures frailty based on the quantity rather than by the nature of health problems.[12] The Frailty Index (FI) counts deficits as an aggregation of measures such as symptoms, signs, diseases and disabilities with the hypothesis that 'the more deficits a person has, the more likely that person is to be frail'.[6] The FI is expressed as a ratio of deficits present to the total number of deficits considered. For example, if a patient has 15 of 40 assessed deficits, the FI of that person would be $15/40 = 0.37$. Several studies have shown consistent results generated by the FI which suggests, the higher the deficit count, the frailer the person is and more vulnerable to adverse outcomes.[13–15]

Frailty assessment as a part of a comprehensive geriatric assessment

Comprehensive geriatric assessment (CGA) is a multidimensional process that has long been recognized as the best approach to the management of the clinical complexity in older populations.[16] A CGA explores clinical, functional, cognitive, nutritional and social parameters, leading to an all inclusive assessment which helps to optimize long-term treatments, resource planning and the use of services.[17] The proven benefit of CGA has been supported by several studies. One study that randomly assigned 63 frail elderly inpatients with a high probability of nursing home placement to an innovative geriatric evaluation unit showed that a multidimensional assessment led to an improvement in functional status, discontinuation in the number of prescribed drugs, lower mortality and less time spent in hospital.[18] Another showed an increased survival in frail older patients with a CGA admitted to a geriatric ward as opposed to a general medical ward.[19] CGA has the potential to optimize drug therapy by the detection of both over- and undertreated disease conditions.[20,21] Importantly, a FI can be derived from the information collected as part of CGA.[22]

These approaches differ not only in their processes for measuring frailty but in their conceptualization of the aetiology and implications of frailty itself. The frailty phenotype views frailty as a clinical syndrome with the core pathophysiological feature of sarcopenia caused mainly by age-related changes in hormones.[23] In this model, co-morbidity is distinct from frailty, though the presence of multiple chronic diseases is recognized, somewhat separately, as necessitating a different approach to prescribing.[24] The FI approach, on the other hand, conceptualizes frailty as a state of increased risk of adverse health outcomes due to a variety of

accumulated health deficits.[25] These deficits may or may not relate to sarcopenia, and are sometimes, but not always, secondary to co-morbid disease.

Prescribing in frail older people should differ from that in non-frail older people. The primary focus in frail patients with life-limiting conditions is to improve quality of life by reducing the severity of symptoms or by controlling a disease in the short term.[26] Many medications that are commonly prescribed in older people such as psychotropic drugs, cardiovascular agents and analgesics are commonly associated with high risk of ADEs.[27] It is essential that frailty status be considered when treatment plans shift away from a curative towards an individualized symptom controlling approach. Understanding frailty could assist the treating hospital medical practitioner to better manage patients who do not fit well into clinical practice guidelines (CPG) and management algorithms.[28]

We propose that potentially vulnerable older patients undergo a frailty assessment as a part of a comprehensive geriatric assessment as shown in Figure 1. In non-frail older patients, the disease-specific evidence-based CPG should be followed. In contrast, frail older people would undergo a multidimensional approach that evaluates the patient's life expectancy and identifies the disease with the highest priority for treatment instead of treating all diseases according to CPGs. A common example in a frail patient with a life expectancy of few months is the use of statins for cardiovascular diseases or antiresorptive therapy for osteoporosis which will have no benefit as the onset of measurable effects will occur too late to be of benefit.[17] If a disease with high priority for treatment is identified, the most appropriate therapy based on the recommendations of the CPGs should be followed, taking into consideration the frailty status of the patient. This involves the use of various tools to optimize appropriate use of medication along with the available Guidance for Prescribing in Frail Adults.[29]

Criteria for assessing quality of medication prescribing

Inappropriate prescribing in older people can be detected using explicit (criterion-based) or implicit (judgment-based) tools. Explicit criteria are derived from expert reports or published reviews. They have high reliability and reproducibility but focus mainly on specific drugs and disease states. In contrast, implicit criteria are person-specific and explore patient preferences, rather than the disease and medications; they rely on evaluator judgment and invariably have low reliability and low practical utility.[5] The factors addressed by the tools and criteria involved in assessing quality of medication prescribing in older people are shown in Table 1. Some criteria assess medications alone, some medication and disease states and others factors related to the individual patient. Some approaches use a combination of all of these but none of them address frailty although some measure the surrogates of frailty.

The omission of frailty status from established prescribing tools may help to explain the lack of clinical benefit secondary to algorithm-based medication reviews. For example, in a randomized controlled trial of 872 community dwellers aged over 80 years, home-based medication review by pharmacists was associated with a significantly higher rate of hospital admissions and did not improve quality of life.[30] Similarly, the PLOYMED randomized controlled trial of pharmacist-led medication review showed no positive impact on clinical outcomes or quality of life.[31] Only a medication review underpinned by careful consideration of the health status of the patient concerned, including estimation of life expectancy and exploration of individual goals of care, is likely to result in clinically meaningful outcomes.

A brief summary of the various approaches follows.

Beers criteria

These criteria present a list of potentially inappropriate medications for older patients, irrespective of burden of disease or patient preferences. The Beers criteria are the most widely used since their initial development in the USA in 1991. They were designed for older nursing home residents and revised in 1997, 2003 and 2012 to enable application in all older patients. They comprise two different lists of medications, one considering diagnosis and the other independent of diagnosis. In addition, they do not address underprescribing, drug duplication and drug–drug interaction.[32]

McLeod criteria

These criteria for identifying inappropriate practice in older patients were developed in 1997 in Canada and list inappropriate prescribing of non-steroidal anti-inflammatory drugs, cardiovascular diseases, psychotropic drugs, analgesics and some miscellaneous drugs. They are based on risk–benefit ratios and allow the assessment of drug–drug and drug–disease interactions.[33] They have been criticized as having limited applicability in geriatric clinical practice.[39]

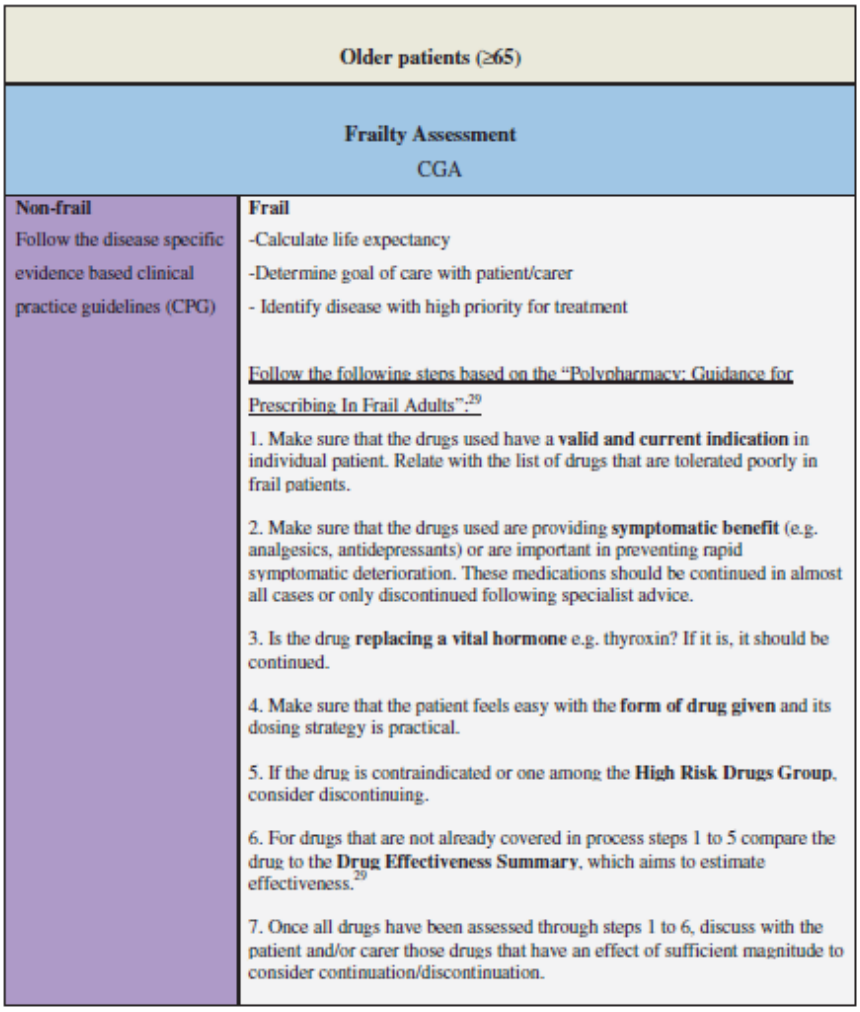

Figure 1. The two different paths for assessing frail versus non-frail older patients to ensure appropriate medical treatment.

Screening Tool of Older Person's Prescriptions and Screening Tool to Alert doctors to Right Treatment

These explicit tools were developed to overcome some of the deficiencies of the Beers criteria. They capture the common and important instances of potentially inappropriate prescribing in older people. The Screening Tool to Alert doctors to Right Treatment (START) criteria report 22 evidence-based prescribing indicators and highlight the potentially serious errors of prescribing omission in older people. The Screening Tool of Older Person's Prescriptions (STOPP) criteria address 65 indicators of inappropriate prescribing with special attention to drugs that adversely affect older patients at risk of falls, drug–drug interaction, drug–disease interaction and drug duplication.[34] However, both STOPP and START criteria are complex, making their application time consuming.

Inappropriate Medication Use and Prescribing Indicators in Elderly Australians

A list of prescribing indicators for older people based on the most common medications prescribed and the most common presenting was developed in Australia. About 48 prescribing indicators were identified and a prescribing indicator tool was developed to address the common problem of adverse medication-related events. In addition to addressing the medication-related indicators, they also address other medication management issues in patients.[35]

Table 1 Prescribing indicators that are addressed by the tools/criteria involved in assessing quality of medication prescribing in older people

Components that measure prescribing appropriateness	Assessment criteria									
	Addressed by Beers criteria[32]				McLeod Criteria[33]	STOPP and START[34]	IMU & PIT[35]	MAI[36]	A 10-step Conceptual Framework[37]	Good Palliative-Geriatric Practice Algorithm[38]
	1991	1997	2003	2012						
	Medication- and disease-related									
Drugs	✓	✓	✓	✓					✓	✓
Dose	✓	✓	✓	✓		✓	✓	✓	✓	✓
Duration	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Under prescribing						✓	✓			
Drug–drug interactions					✓	✓	✓	✓		✓
Drug–disease interactions		✓	✓	✓	✓	✓	✓	✓	✓	✓
Effectiveness				✓			✓	✓	✓	
Drug indication						✓	✓		✓	✓
Drug duplication						✓	✓	✓	✓	
Medication cost								✓		
	Patient-related									
Frailty [Cognition, mood and behaviour, functional status (ADL), continence, etc.]							✓[a]		✓[a]	✓[a]
Falls, fatigue						✓	✓			
Life expectancy									✓	

[a]No studies measured the frailty but some measure the surrogates of frailty. ADL, Activities of Daily Living.

Medication Appropriateness Index

The Medication Appropriateness Index (MAI) is a refined implicit method, developed in USA that rates 10 elements of prescribing: indication, effectiveness, dose, correct directions, practical directions, drug–drug and drug–disease interactions, duplication, duration and cost.[40] Medications are rated as appropriate, marginally appropriate, or inappropriate for each criterion. Although the MAI has a good reliability in ambulatory settings, there is no clear evidence that it would be effective in community settings and the generalizability of the instrument as used by other investigators is unknown.[36] Furthermore, it does not address the indication of drug.

A 10-step conceptual framework

To minimize inappropriate medications in older population, a quality use of medicine framework was developed in Australia. This framework comprises 10 steps that aim to decrease the number of medications in older patients to the minimum number of essential drugs. The systematic and individualized approach of this framework identifies the medications that are of little or no benefit in older patients and ultimately aids in discontinuing them. Unlike most of the alternative methods, it focuses on both medication-related and medication management-related aspects of appropriate prescribing, which ultimately addresses the gap observed in other tools. However, further studies are needed to validate its effectiveness in older patients in various settings.[37]

The Good Palliative-Geriatric Practice algorithm

This palliative approach was introduced to combat the problem of polypharmacy and improve the quality of care in older people in the nursing home setting. The theory behind this algorithm was that many drugs can be discontinued in the frailest older people without significant negative consequences on mortality, morbidity and the quality of life, with limited financial costs and referrals to acute care facilities. Application of this methodology also showed feasibility in decreasing medication burden in community-dwelling older patients and in larger randomized controlled trials in different clinical settings.[38]

These criteria are generalized to the older population where the combination of both explicit and implicit indicators is suggested as more useful than either one alone.[41] However, there are no specific criteria to guide prescribing for frail older people or patients with reduced life expectancy.[42]

Conclusion

Prescribers should be mindful that the criteria used in identifying potentially inappropriate prescribing are appropriate for many older people but are not applicable to critically ill or frail patients. Improving the existing tools to be more user-friendly or establishing a new specific tool to minimize inappropriate prescribing in frail older people is required. The issues can be addressed to some extent by incorporating frailty status in the patient assessment and evaluating medications based on the guidelines for prescribing in frail adults. By assessing frailty, we are making a more informed decision about the physical function and capabilities of a patient and making judgments about medication more appropriate to the individual patient.

Conflict of interest: None declared.

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Appendix F: Logistic regression analysis for relationship between polypharmacy and frailty on having at least one adverse outcome

Variables	**OR (95% CI)**	**p-value**
Low FI, 0-4 meds	2.03 (1.01 – 4.08)	0.045
Low FI, 5-9 meds	1.89 (1.03 – 3.47)	0.038
Intermediate FI, 0-4 meds	11.72 (5.72 – 24.01)	0.000
Intermediate FI, 5-9 meds	6.01 (3.36 – 10.76)	0.000
Intermediate FI, ≥ 10 meds	4.28 (2.37 – 7.74)	0.000
High FI, 0-4 meds	28.51 (12.52 – 64.87)	0.000
High FI, 5-9 meds	21.07 (11.37 – 39.05)	0.000
High FI, ≥ 10 meds	15.72 (8.34 – 29.61)	0.000

Outcome variable: Composite Adverse Outcome, FI: Frailty Index
Reference group: Low FI, 10+ meds

Appendix G: Logistic regression for risk factors of receiving potentially inappropriate medications

PIMS at admission								
Variables							**95% confidence interval for Exp (B)**	
	B	**Std. Error**	**Wald**	**df**	**Sig**	**Exp (B)**	**Lower Bound**	**Upper Bound**
Age (yrs)								
65-74[a]	-	-	-	-	-	1.00	-	-
75-84	.168	.218	.594	1	.471	.912	.742	1.124
≥ 85	.188	.221	.721	1	.877	.981	.767	1.227
Sex								
Female	.028	.253	.012	1	.643	1.031	.814	1.325
Fall in hospital	.475	.286	.382	1	.293	1.231	.836	1.854
Delirium in hospital	.158	.708	.501	1	.906	.945	.326	2.152
Failure to improve in ADL	.024	.021	1.262	1	.267	.965	.913	1.026
In-hospital cognitive function decline	.816	.395	4.362	1	**.032**	.821	.625	.991
Frailty Index	.041	.020	4.671	1	**.037**	.923	.764	1.124

PIM: Potentially Inappropriate Medication; a: Reference category; Cox & Snell R Square: 0.382

Appendix G (continued)

PIMS at discharge								
Variables							**95% confidence interval for Exp (B)**	
	B	**Std. Error**	**Wald**	**df**	**Sig**	**Exp (B)**	**Lower Bound**	**Upper Bound**
Age (yrs)								
65-74[a]	-	-	-	-	-	1.00	-	-
75-84	.168	.218	.594	1	.462	.912	.742	1.124
≥ 85	.187	.215	.624	1	.881	.914	.767	1.127
Sex								
Female	.028	.253	.012	1	.643	1.031	.814	1.325
Fall in hospital	.351	.218	.318	1	.561	1.121	.794	1.144
Delirium in hospital	.213	.762	1.201	1	.291	1.214	.823	1.815
Failure to improve in ADL	.026	.023	1.261	1	.266	.975	.862	1.032
In-hospital cognitive function decline	.831	.326	4.272	1	**.021**	.853	.652	.962
Frailty Index	.044	.031	4.622	1	**.031**	.932	.771	1.134

PIM: Potentially Inappropriate Medication; a: Reference category; Cox & Snell R Square: 0.335

Appendix H: Ethical approval (A)

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	An Outcomes Oriented Study Identifying Contributions Of Geriatric Consultation Via Video Conferencing
Chief Investigator:	Prof Len Gray
Supervisor:	None
Co-Investigator(s):	Dr Melinda Martin-Khan, Janice Lee, Arjun Poudel
School(s):	School of Medicine
Approval Number:	2013000009
Granting Agency/Degree:	UQ SOM
Duration:	31st December 2013

Comments:

Participant Information Sheets – 2nd sentence – "*The purpose of this project is to survey geriatricians…*" Please add GPs and RACF staff.

Note: if this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Signature _____ Date 4 JUN 2013

Appendix I: Ethical approval (B)

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	A Prospective Review Of Residential Aged Care Facility Patient Medication Charts To Assess The Impact Of Medication Changes Recommended By Consultant Geriatricians
Chief Investigator:	Mr Arjun Poudel
Supervisor:	A/Prof Charles Mitchell, Prof Lisa Nissen
Co-Investigator(s):	Dr Ruth E. Hubbard, Prof Len Gray
School(s):	Pharmacy; Pharmacy Australia Centre of Excellence (PACE); School of Medicine, Centre for Research in Geriatrics Medicine
Approval Number:	2013001071
Granting Agency/Degree:	PhD
Duration:	28th February 2014

Comments:

Expedited Review - low risk.

Note: If this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Behavioural & Social Sciences Ethical Review Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Associate Professor John McLean
Chairperson
Behavioural & Social Sciences Ethical Review Committee

Signature _____ Date 20/8/2013