Multimorbidity: A Key Influencer of Complexity and Care Integration within Primary Care

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A thesis submitted in partial fulfilment of the
requirements of Edinburgh Napier University,
for the award of Doctor of Philosophy by Published Works

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Declaration

I hereby declare that the body of work presented in this thesis has not been submitted for any other degree or professional qualification, and that it is the result of my own independent work. With regards to the six papers which for the basis of this PhD by Published Works, the contribution of the candidate and the other authors to this work has been explicitly indicated below. This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement. The candidate has obtained permission for full-text articles to be included in this PhD by Published Works.

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[redacted]

Date: 18st March 2024

Abstract

This paper represents a connective narrative towards the award of a PhD by Published Works by Edinburgh Napier University. The papers represent a body of literature that investigate responses to demands on primary care in Scotland in the context of an increasing prevalence of multimorbidity. This is a key area for health policy given population trends. Multimorbidity is challenging given the attendant complexity resulting from interactions between conditions as well as treatments. Papers have thus investigated implications for prescribing, clinical guidelines and hospital readmission. These are issues for which policy urgently needs evidence if it is to provide health and social care provision that is sustainable for the future.

The narrative provides an overview of the six papers that form the body of literature and how they relate to the three requirements of a PhD by publication specifically, independence, originality, and significance. It then considers them within the framework of the Ariadne Principles highlighting the importance of evidence in enabling informed decision making by patients supported by their general practitioners. This demonstrates how clinicians can involve patients in care decisions that addresses their primary concerns, such as issues to prioritise symptom control, whilst still being realistic and involving judicious prescribing.

It then moves on to consider the future of the field arguing that there needs to be nuance and pragmatism within a strong primary care system. Wider changes will be needed to address the challenges of increasing prevalence of people who have multimorbidity, but change is also required at the consultation level.

Understanding of multimorbidity is constantly evolving. However, the issues of appropriate prescribing, guidelines that go beyond simplistic single condition advice, and avoidance of unnecessary hospitalisations will continue to be fundamental issues for which ongoing research will be crucial to health and social care sustainability.

Publications associated with this PhD by Published Works

Paper 1: Hughes LD. Utilizing Clinical Practice Guidelines in Multimorbid Older Patients – A Challenging Clinical Dilemma. *Journal American Academy of Geriatrics.* **2012**. 60:2180-1.

Paper 2: Hughes LD, McMurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to older people with multiple co-morbidities*. Age Ageing* **2013**; 42:62-69

Paper 3: Hughes LD, Hanslip J & Witham MD. Centrally Active Prescribing for Nursing Home Residents-how are we doing? *European Geriatric Medicine.* **2012.** 3(5):304–307

Paper 4: Hughes LD, Raitt N, Riaz MA, Baldwin SJ, Erskine K, Graham G. Primary Care Hypnotic and Anxiolytic Prescription - Reviewing Prescribing Practice Over Eight Years. *Journal of Family Medicine and Primary Care*. **2016** 5(3):652-657

Paper 5: Hughes LD, Cochrane L, McMurdo MET & Guthrie B. Psychoactive Prescribing for Older People – What difference does 15 years make? *International Journal of Geriatric Psychiatry*. **2016**;31(1):49-57

Paper 6: Hughes LD & Witham MD. Causes and correlates of 30 day and 180-day readmission following discharge from a Medicine for the Elderly Rehabilitation unit. *BMC Geriatrics.* **2018**. 18:197

Full papers are included in appendix A. Copyright permission agreement information for four papers (Paper 1, 2, 3, and 5) are included appendix B.

Paper 4 and Paper 6 have both been published as open access articles distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Acknowledgements

Dr Iain Atherton, Professor Nadine Dougall and Dr Helen Frost for their exceptional expertise, guidance and professionalism during the course of this PhD by Published Works process.

Professor Bruce Guthrie, Professor Marion McMurdo and Professor Miles Witham for inspiring my interest in clinical research and showing me how clinical research can be used as a driver for clinical change.

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My co-researchers, co-authors and funders (including National Education Scotland, University of Dundee, Carnegie Trust & Muir Russell Trust) involved in all six papers.

My lovely family and friends, in particular my wife Rachel, daughter Elyn and son George. I could not have completed this PhD without their unwavering support.

Table of contents

List of figures

List of tables

List of abbreviations

CGA: Comprehensive Geriatric Assessment

CKD: Chronic Kidney Disease

ERC: Ethics Review Committee

GP: General Practitioner

HIC: Health Informatics Centre

IPD: Individual Level Participant data

Medical Research Council: MRC

NICE: National Institute of Health and Care Excellence

NIHR: The National Institute for Health and Care Research

NHS: National Health Service

P4P: Pay-for-Performance

PCC: Patient-Centred Care

PPIE: Patient and Public Involvement and Engagement

QOF: Quality and Outcomes Framework

RCT: Randomised Controlled Trial

UK: United Kingdom

Chapter 1

Introduction to PhD by Published Works

1. Introduction to PhD by Published Works

1.1. Introduction

The narrative that follows has been written to support a submission to Edinburgh Napier University toward a doctorate by published works. It is based on six studies which are reported in papers that have been published since 2012 on which I have been the lead author. This work was the product of my passion and commitment to patients to whom I provide care and whose lives are lived in the context of wider circumstances that raise major challenges for general practice.

All 32 Scottish council areas have seen an increase in their population aged 65 and over in the last decade, with a 33% increase in the number of people over 65 when compared to 2000 [1]. The ageing of the Scottish population presents the health, long-term care, and welfare systems with a variety of challenges. These challenges include the delivery of healthcare to patients with greater multimorbidity and frailty syndromes, provision of increased social care in both volume and complexity, and increased expenditure on health and welfare programmes [2-4].

Whilst these demographic changes are a mark of the success of modern medicine, they nonetheless put pressure on health care systems designed for presentations of an acute disease or symptom [e.g. myocardial infarction; exacerbation of chronic obstructive pulmonary disease; acute abdominal pain]. Indeed, the current healthcare system was not designed for an ageing population with high rates of chronic long-term diseases and has been required to adapt extensively over its existence often with great upheaval [5]. This raises questions as to the sustainability of the health care system, which will require increased focus on preventative medicine [6], alongside a rethink about how we prioritise and support primary care [7].

The chapter that follows sets out the contribution made to some of these challenges from a body of my work published between 2012 and 2018. In so doing, this will demonstrate that the work meets the criteria required for a PhD by published work set out by Edinburgh Napier University in its Research Degrees Framework (2020) [8]. This specifically requires:

"…a published body of work that demonstrates independence, significance and originality."

My overall thesis contends that Scotland, similar to many other countries, is experiencing an increase in the prevalence of people with multimorbidity [9], and that associated care and health policy have to be adapted and developed to address the resulting challenges of increasing healthcare costs and utilisation [6,7,10]. Large top-down policy reforms such as integration of health and social care may play a role in addressing some of these challenges. However, the recent Nuffield Trust report highlights that there is little evidence to date that integration is making much progress on hard outcomes (hospitalisations, healthcare costs) and may be associated with underfunding of other important aspects of the care sector such as long-term care facilities [10].

However, this thesis argues that clinicians have a vital role to play in enabling sustainable healthcare in this current climate. This may be achieved by delivery of judicious prescribing, implementation of clinical practice guidelines through the lens of the Ariadne principles [11] and supporting patients to remain at home through the delivery of local and national initiatives. The Ariadne principles provide a framework which may guide care delivery in the context of multimorbidity, based around realistic treatment goals [11]. These are further described in section 1.5. It is clear that wider policy change will be required to improve outcomes for patients with multimorbidity, but change will be required at every level including at the individual consultation level.

The examples presented in the six studies [12-17] that form my body of work provide a critical analysis focusing on three clinical areas relevant to multimorbidity including clinical practice guidelines [12,13], drug prescribing [14-16] and hospital readmissions [17]. These clinical areas are associated and closely linked with important themes of patient centred care, treatment burden and deprescribing.

The narrative that follows provides a summary of the published work and outlines my specific contribution to this body of work. The originality and significance will then be outlined by providing additional context and engaging with those issues that are facing Scotland's health and social care system in the context of demographic change. The impact of the work and pertinent developments since publication will be described, alongside the limitations of the work. I will then consider the next steps in moving forwards and expanding my body of work.

The next section will provide a more detailed overview of the six studies which form the basis of this PhD by Published Work.

1.2 Summary of papers

The problem of multimorbidity in primary care is well documented and my thesis discusses the significant implications of multimorbidity on the day-to-day delivery of primary care. I am a practising General Practitioner [GP] in Scotland, who has developed research interests and performed clinical research during my undergraduate MBChB, academic foundation training programme and general practice training. Motivation to use clinical research to directly influence and impact the delivery of general practice was the driver that has resulted in over 9 years of research and several publications including 6 first-author peer-reviewed papers. These papers use different methodologies, have important findings and highlight original and independent thought within the field of multimorbidity. My experience, career aspirations and research methods training are included in Appendix C and D and my full CV is included in Appendix E. Table 1 provides details of my first author papers, and key points relating to both research methods and findings. The table outlines the range of methods that I have employed to answer key questions relating to the care of older patients experiencing multimorbidity and their clinical management.

Table 1. Published Papers which form basis of the PhD by Published Works

	Reference for the Paper	**Paper type and key findings**
Paper 1 [12]	Hughes LD. ***Using Clinical Practice Guidelines in Multimorbid Older Patients – A Challenging Clinical Dilemma***. Journal of the American Academy of Geriatrics 2012**.** 60:2180-1 Available from: https://doi.org/10.1111/j.1532-5415.2012.04223.x	***Case Report.*** * This case report illustrates that there remain practical challenges in applying clinical practice guideline recommendations * Concerted action is required to develop guidelines that are more aligned with the complicated clinical, social and psychological needs of multimorbid older adults.
Paper 2 [13]	Hughes LD, McMurdo MET, Guthrie B. ***Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to older people with multiple co-morbidities***. Age and Ageing 2013; 42:62-69 Available from: https://doi.org/10.1093/ageing/afs100	***Content Analysis using Hypothetical Patient Vignettes****.* * The use of clinical practice guidelines in health-care services has helped to reduce practice variation, deaths, and hospitalisations. * Clinical guidelines are known to be limited in their focus on single diseases and the evidence which these guidelines are based upon apply only to subsets of the population. * The study showed that the explicit adherence to clinical guidelines for two hypothetical patients with physical and mental health comorbidities led to complex treatment regimens with a significant risk of adverse drug reactions. * Future guidelines should provide practical examples of how patient-centred care can be achieved.
Paper 3 [14]	Hughes LD, Hanslip J & Witham MD. ***Centrally Active Prescribing for Nursing Home Residents-how are we doing?*** European Geriatric Medicine 2012 3 (5) p. 304–307. Available from: https://doi.org/10.1016/j.eurger.2012.04.008	***Single Centre Nursing Home Study.*** * Patients with dementia residing in nursing homes have a high prevalence of pain syndromes, insomnia and depressive disorder. * Centrally active drug prescribing in the community for nursing home patients remains high and may be associated with patient risk. * Patients with severe dementia were statistically more likely to be prescribed psychoactive medications. * Importantly, despite being exposed to significant levels of psychoactive drug prescribing this patient group may be under-treated for pain syndromes.

Table 1 (Continued). Published Papers which form basis of the PhD by Published Works

	Reference for the paper	**Paper type and key findings**
Paper 4 [15]	Hughes LD, Raitt N, Riaz MA, Baldwin SJ, Erskine K & Graham G. ***Primary Care Hypnotic and Anxiolytic Prescription - Reviewing Prescribing Practice Over 8 Years.*** Journal of Family Medicine and Primary Care. 2016 5(3): p.652-657 Available from: https://doi.org/10.4103/2249-4863.197312	***Single Centre General Practice Study*** * Reduction of benzodiazepine prescribing has been the basis of focused and financially incentivised work due to concerns around both drug dependence and tolerance. * This single centre study reported that, although benzodiazepine prescribing was significantly reduced over the study period, the prescription of other hypnotic agents increased during the same period. * The study highlighted the challenges with incentivisation strategies which may have unintended consequences, alongside a broader concern regarding the medicalisation of insomnia.
Paper 5 [16]	Hughes LD, Cochrane L, McMurdo MET & Guthrie B. ***Psychoactive Prescribing for Older People – What difference does 15 years make?*** International Journal of Geriatric Psychiatry. 2016;31(1):49-57 Available from: https://doi.org/10.1002/gps.4288	***Descriptive Epidemiology Study*** * Total psychoactive drug prescribing increased between 1995 and 2010 in Tayside, with differences evident between classes of drug. * The increase in psychoactive drug prescribing was significantly more in patients in lower socioeconomic groups. * The availability of new psychoactive drugs, safety concerns and economic factors may help explain these increases.
Paper 6 [17]	Hughes LD & Witham MD. ***Causes and correlates of 30-day and 180-day readmission following discharge from a Medicine for the Elderly Rehabilitation unit.*** BMC Geriatrics 2018. 18:197 Available from: https://doi.org/10.1186/s12877-018-0883-3	***Descriptive Data Linkage Study*** * Readmission after discharge from hospital is common, with 5.6% and 23.2% of geriatric patients being readmitted at 30 days and 180 days respectively after a period of inpatient rehabilitation. * Most readmissions of older people after discharge following inpatient rehabilitation occurred for different reasons than the original admission to hospital. * Patterns and predictors for early (30-day) and late (180-day) readmission differed, suggesting the need for different mitigation strategies.

The studies reported in Papers 1 and 2, highlighted the challenges for clinicians in managing patients with multimorbidity, given that current care delivery is often linked to clinical practice guidelines [12,13]. The studies, using a case report [12] and two hypothetical clinical vignettes [13], demonstrated some of the practical challenges around managing patients with multimorbidity including the difficulty in achieving patient-centred care [PCC] (where an individual's specific health needs and desired health outcomes are the driving force behind all health care decisions and quality measurements), risk of drug interactions and increasing treatment burden (the workload of healthcare and its effect on patient functioning and well-being). These are further described and discussed in sections 1.5.2 and 1.5.4 respectively.

The studies reported in Papers 3-5, examined the important themes of prescribing and polypharmacy associated with multimorbidity in three different settings [14-16]. The study reported in Paper 3 involved the analysis of centrally active drug prescribing in a nursing home in Dundee, reporting high rates of centrally active drug prescribing but under-treatment of patients for pain syndromes [14]. The study demonstrated that the challenges associated with managing patients with complex multimorbidity and frailty may lead to patient harm.

The study reported in Paper 4 assessed trends in anxiolytic and hypnotic prescribing during an eight-year period in a GP practice using routinely available prescribing data in the context of financial incentivisation to reduce benzodiazepine prescribing [15]. Significant reductions in benzodiazepine prescribing (mandated in local and national primary care guidelines) were achieved alongside a significant increase in non-benzodiazepine hypnotic prescribing (which was not mandated at that time). The complex interplay between incentivisation strategies and the core objectives of improved care delivery for patients with multimorbidity is an important consideration as new approaches to integrated care are developed and delivered.

The study reported in Paper 5, analysed regional psychoactive drug prescribing for older patients in Tayside comparing rates of psychoactive drug prescribing between 1995 and 2010 [16]. The study reported that psychoactive drug prescribing significantly increased between 1995 and 2010 for the population over 65 years old in

Tayside. Furthermore, it was found that individuals in lower socioeconomic bands were more likely to experience an increase in psychoactive drug prescribing (both single agent and combination psychoactive prescribing). This may represent a combination of higher rates of mental health diagnoses, alongside reduced access to non-drug interventions for mental health [16].

The study reported in Paper 6, provided a focused analysis of the geriatric population, multimorbidity and hospital readmission rates [17]. This study analysed routinely collected, linked clinical data on admissions to a single inpatient rehabilitation facility over a 13-year period: data included demographics, comorbid disease, admission and discharge diagnosis codes, length of hospital stay, and the number of medications on discharge. Most readmissions of older people after discharge from inpatient rehabilitation occurred for different reasons to the original hospital admission, suggesting it is essential to step away from a single disease focus in the design of both hospital avoidance and chronic disease management programmes [17]. The results of this study suggest that more multi-faceted approaches, such as care coordination, developing community healthcare programmes, and improving access to social care, may offer promise in terms of readmission mitigation.

1.3 Independence of My Work

One of the three requirements for a PhD by publication at Edinburgh Napier University is that the work is independent. Little if any contemporary health research is a solitary endeavour but rather requires teams, each bringing their subject or methodological expertise to enable work that robustly answers the research question posed.

My work has been no different. As can be seen from Table 1, each research study involved a team of experts that I brought together with the intention of drawing on their knowledge and skills. Importantly, I conceived the original research questions that formed the basis of the studies and subsequent publications. I brought the teams together and took key decisions after consultation with members. As will be outlined, some of the work resulted from funding I sought and for which I took forward successful applications. The teams themselves resulted from developing working relationships with senior academics in fields where I had a clinical interest (general practice and geriatric medicine). Through a combination of opportunistic exposure through undergraduate medical education and seeking out individuals in areas of clinical interest, I contacted them regarding research opportunities. This was helpful, as scholarship opportunities were highlighted and I could target research groups to work with on clinical topics of interest. Other groups, such as the research group which published Paper 4 [15], came together naturally through working relationships and demonstrated that not all research needs to come from established research groups.

Working within research teams has been an excellent experience, and I have developed as a researcher having been supported by colleagues. Throughout the development of the papers summarising research projects, I was involved in selecting which journals to submit work to and at times there were disagreements about this. For example, the study reported in Paper 2 [13] was submitted to the British Medical Journal, and although it received two very positive reviews, was felt not to meet the high standard of the journal. There were some in the research team who felt that it was always too optimistic to submit the paper to such a high-impact journal but it was agreed by all authors to submit after a balanced discussion. As the first author, I led the management of submissions and manuscript preparation, which at times was challenging due to the busy roles of the team members. I have been privileged to work with a variety of highly skilled and supportive academics and clinicians in the studies reported in these six papers.

The study reported in Paper 1 [12] was developed, written and published as part of my general practice medical student placement[1]. I was struck by the challenge of delivering care to patients in 10-minute slots, and it made consider the feasibility of current care models with increasing complexity of patients and healthcare interventions. Despite all the caveats associated with case reports, the paper

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[1] Paper 1 was not developed or submitted for any other academic qualification (e.g. MBChB).

demonstrated some important concepts which were relevant to many patients that I was seeing in general practice. More importantly, on a personal level, it started my own learning in the multimorbidity research field, obtaining patient consent for research, academic writing and the peer-review process.

During this period, I successfully applied for a funded summer studentship and had the opportunity to work with Professor Guthrie (Professor of Primary Care) and Professor McMurdo (Professor of Ageing & Health), experts in the field of general practice and geriatric medicine respectively, which led to the study reported in the Paper 2 [13]. After a discussion about different clinical topics, it was felt that multimorbidity would provide a useful research area. After reviewing several areas within the field of multimorbidity, it was agreed that we would aim to build on Boyd's work from 2005 regarding US guidelines [18] and place it into a British context which had never been done previously. Hypothetical clinical patient vignettes were constructed, which negated a requirement for ethics, using multimorbidity combinations commonly present in the Scottish population. I led the review of all the National Institute of Health and Care Excellence [NICE] guidelines, drafted the paper and revised it following supervisor feedback. I also led the article submission process and made efforts to address peer-review comments before obtaining further feedback from the supervisory team. The overall process was hugely educational, as it was my first primary research publication.

The study area which led to research reported in Paper 3 [14] was identified during my part-time job working in a nursing home. I was recognising a disconnect between analgesia prescribing and patient diagnoses when administering patient medications. After preparing a draft paper for submission, I sought support and guidance from two senior clinicians in geriatrics to help place some of the findings in context and this led to several changes in the paper in preparation for an academic submission. This guidance on aspects of the paper enabled a more focused message to be delivered, alongside suggestions for journal publication. They both provided support in responding to some peer-review feedback. The process was a further example of identifying clinical research areas through direct clinical exposure and experience.

During my academic foundation post, I worked in a GP practice in Arbroath, and during a GP Partners meeting, there were discussions around financial incentives for local prescribing optimisation work. I always had an interest in the effectiveness of financial incentives, in particular around the long-term efficacy and cost-effectiveness of the approach, and therefore suggested a review of relevant prescribing, which was the basis for the study reported in Paper 4 [15]. I designed and performed the analysis, drafted the manuscript and critically revised the manuscript following peer review. I shared findings, received feedback from colleagues at the practice about the paper and revision, and was aided in disseminating the findings to the local and regional GP network demonstrating some of the challenges. There were challenges around data-collection through the GP computer system VISION (Cegedim, London), which required pharmacy support. Importantly, a full debrief with the primary care team to shape future practice was arranged and subsequent non-published work by current GP Partners has shown improvements in non-benzodiazepine prescribing.

The study reported in Paper 5 [16] was commenced after I successfully applied for a further funded summer studentship, having already approached Professor Guthrie and Professor McMurdo regarding research opportunities in geriatric medicine around psychoactive prescribing. During the project I met Lynda Cochrane a senior statistician who provided both experience and significant training in statistical analysis. She was invaluable in starting to improve my understanding of core statistical concepts, which are key to high-quality research. There were numerous avenues to explore which were offered as part of the studentship, but I selected drug prescribing work as it was a common area of challenge in primary and secondary care placements. I developed the idea around study selection, with support from the supervisory team about exclusion and inclusion criteria and what was possible with the data sets available. I led the writing of the paper and redrafting based upon supervisor feedback and prepared the paper for submission to the journal. My writing was certainly improving in terms of how to structure academic publications. This was the largest data set I have worked with and gaining familiarity and experience with SPSS (IBM, New York USA) and Excel (Microsoft, Washington) was invaluable. The study reported in Paper 5 [16] has contributed to the literature on psychoactive prescribing in older patients and how this has changed over time, with citations in a recent clinical review on antipsychotic drug prescribing [19], and in work analysing the relationship between psychoactive prescribing and hospital length of stay [20].

During my academic foundation job, I worked within the Ageing & Health Department with Professor Witham who is an inspirational academic geriatrician and developed and delivered the study reported in Paper 6 [17]. I had a varied experience of clinical and academic training and support with shaping research questions using existing datasets. An aim of the project was to integrate social care data, but this proved not to be feasible due to the quality of the data available. I received support in performing and interpreting Cox-regression which I had not undertaken previously. The paper was jointly developed and written with my supervisor, and I learned a great deal including how to shape the narrative within a paper. I also realised how long it can take from starting a research project to getting the work published. Paper 6 [17] has been cited over 40 times and has been referenced in papers researching ways to develop transitional care from hospital to community [for example 21,22].

The role I played and my contribution to each paper is fully reported in the declarations section, with a summary in Table 2.

Table 2: Contribution of the candidate for each of the six papers which form the basis of PhD Publication

	Reference for the Paper	Author Contributions
Paper 1	Hughes LD. ***Using Clinical Practice Guidelines in Multimorbid Older Patients – A Challenging Clinical Dilemma***. Journal of the American Academy of Geriatrics 2012**.** 60:2180-1 https://doi.org/10.1111/j.1532-5415.2012.04223.x (Last accessed 24th December 2023) [12]	Lloyd Hughes identified the patient and clinician providing care, recognised the issues highlighted by the case, collected the data and wrote the paper.
Paper 2	Hughes LD, McMurdo MET, Guthrie B. ***Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to older people with multiple co-morbidities***. Age and Ageing 2013; 42:62-69 https://doi.org/10.1093/ageing/afs100 (Last accessed 24th December 2023) [13]	Lloyd Hughes and Bruce Guthrie co-conceived the study and conducted the review of the guidelines. Lloyd Hughes led the writing of the paper, in conjunction with Bruce Guthrie and Marion McMurdo.
Paper 3	Hughes LD, Hanslip J & Witham MD. ***Centrally Active Prescribing for Nursing Home Residents-how are we doing?*** European Geriatric Medicine 2012 3 (5) p. 304–307 https://doi.org/10.1016/j.eurger.2012.04.008 (Last accessed 24th December 2023) [14]	Lloyd Hughes designed the study, collected all the data and performed the data analysis. Lloyd Hughes led the writing of the manuscript, with Jennifer Hanslip and Miles Witham involved in re-drafting, and revised the paper following reviewer comments.

Table 2 (continued): Contribution of the candidate for each of the six papers which form the basis of PhD Publication

	Reference for the Paper	**Author Contributions**
Paper 4	Hughes LD, Raitt N, Riaz MA, Baldwin SJ, Erskine K & Graham G. ***Primary Care Hypnotic and Anxiolytic Prescription - Reviewing Prescribing Practice Over 8 Years.*** Journal of Family Medicine and Primary Care. 2016 5(3): p.652-657 https://doi.org/10.4103/2249-4863.197312 (Last accessed 24th December 2023) [15]	Lloyd Hughes designed the study, performed and interpreted the data analysis, wrote the manuscript and critically revised the manuscript. Neil Raitt, Muhammad Riaz, Sarah-Jane Baldwin, Gail Graham and Kay Erskine were involved in data collection, and interpretation of the data alongside revision of the paper following reviewer comments.
Paper 5	Hughes LD, Cochrane L, McMurdo MET & Guthrie B. ***Psychoactive Prescribing for Older People – What difference does 15 years make?*** International Journal of Geriatric Psychiatry. 2016;31(1):49-57 Available from: https://doi.org/10.1002/gps.4288 (Last accessed 24th December 2023) [16]	Lloyd Hughes and Bruce Guthrie conceived and designed the study. All authors were involved in data acquisition. Lloyd Hughes, Lynda Cochrane and Bruce Guthrie were involved in the data analysis and interpretation. Lloyd Hughes led drafting of the manuscript, with all other authors significantly involved in critical revisions prior to submission. All authors were involved in revision of the paper following reviewer comments.
Paper 6	Hughes LD & Witham MD. ***Causes and correlates of 30 day and 180-day readmission following discharge from a Medicine for the Elderly Rehabilitation unit.*** BMC Geriatrics 2018. 18:197 Available from: https://doi.org/10.1186/s12877-018-0883-3 (Last accessed 24th December 2023) [17]	Lloyd Hughes and Miles Witham co-designed and performed the analysis, co-wrote the manuscript and both critically revised the manuscript following peer review. Both authors agree to be accountable for all aspects of the work.

1.4 Significance of My Work

The body of work which forms this thesis has contributed to the literature in an original and significant way.

The studies reported in Papers 1 and 2 [12,13] have reported a clinical area that has received a significant research and policy focus over the last 10 years. The limitations of the applicability of clinical guidelines and the feasibility of their delivery in the era of multimorbidity was important to highlight. The study reported in Paper 2 [13] has been very extensively cited (589 times according to Google Scholar on 4th January 2024) by researchers publishing in several different areas of multimorbidity research including healthcare utilisation [23], health psychology and behavioural implications of multimorbidity [24], quality of life for patients with multimorbidity [25] and polypharmacy [26,27]. The research [13] has been cited by 12 systemic reviews **[**28-39], including one Cochrane review on interventions to deliver appropriate polypharmacy which has greater than 1000 citations [30]. Cochrane reviews are crucially important pieces of research, which influence patient care and policy and my work being used as part of the justification for the review is significant. The studies reported in Papers 1 [12] and 2 [13] argued that clinical practice guidelines need to be more patient-centred and coordinated. This is a theme developed further by the NICE guideline on multimorbidity published shortly after this work [40] which was chaired by Professor Guthrie (one of the co-authors). These developments are particularly crucial with the Covid-19 pandemic, which has stretched primary care systems with significant risk to mental and physical health for patients with multimorbidity [41].

The study reported in Paper 3 [14] demonstrated that judicious prescribing is crucial for nursing home residents, and a focus on appropriate prescribing is important for clinically relevant patient outcomes (pain management). The research has been highly referenced and contributed to broader work on analgesia management in patients with dementia [42-44]. This research has had local and regional impact by shaping aspects of the way psychoactive prescribing is started and monitored. Further work is underway in several sites to establish the impact of these changes on clinical care and clinically relevant prescribing outcomes. Extending this, the research reported in Paper 4 [15] has been impactful by demonstrating the importance of considering the broader implication of incentives in delivering care outcomes. For patients with multimorbidity, this is particularly important as there may be a greater risk of unintended consequences. The research reported in Paper 4 [15] has been cited in studies analysing the prevalence and management of sleep disorders [45,46], and other structural aspects of primary health systems which may influence prescribing practice [47]. The research had a local impact and highlighted the importance of research to working GPs as the GPs initially thought they had achieved significant improvements due to benzodiazepine reductions. Performing and sharing research findings, even on a small scale, is an integral part of healthcare improvement.

The research reported in Paper 5 [16] reported increasing psychoactive prescribing for older people in Tayside and considered some of the causes of this. Judicious prescribing is important to mitigate risk and maximise benefits in older patients, and this paper also commented on social determinants of health. The research reported in the paper has been cited 9 times, including a systematic review [19], and has shaped local research workstreams on psychoactive prescribing in high-risk patient groups defined by the Scottish Index of Multiple Deprivation.

The study reported in Paper 6 [17] has been cited over 40 times and provides a significant contribution to the literature by demonstrating that generalised susceptibility to illness in patients with frailty and multimorbidity means that in-patient rehabilitation alone does not significantly reduce readmission rates. Given that the causes of readmission are varied, it is likely that multi-dimensional interventions, improvements in care transitions and integrated health and social care are required to impact readmission rates. I am involved in several local projects building on this work to target improvements in readmission rates from our community hospitals.

Information on Altmetrics [48], including citations and comparisons to similar research papers, of the six research projects reported in the six papers are noted in Table 3. There are limitations to citations and impact factors calculated for journals

[49], but they do provide some indications as to the recognition of the work by the research community.

Table 3. Published Papers which form basis of the PhD by Published Works Dimension Scores

	Reference for the Paper	Citations and Altmetric Information [48]
Paper 1	Hughes LD. ***Utilizing Clinical Practice Guidelines in Multimorbid Older Patients – A Challenging Clinical Dilemma***. Journal American Academy of Geriatrics 2012**.** 60:2180-1 [12] Dimensions Badge: https://badge.dimensions.ai/details/id/pub.1009939099 Last Accessed 8th January 2024	4 Dimensions hasn't been able to calculate what an expected number of citations for this publication based on its field might be yet.
Paper 2	Hughes LD, McMurdo MET, Guthrie B. ***Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to older people with multiple co-morbidities.*** Age Ageing 2013; 42:62-69 [13] Dimensions Badge: https://badge.dimensions.ai/details/id/pub.1022674321 Last Accessed 8th January 2024	368 Compared to other publications in the same field, this publication is extremely highly cited and has received approximately 74 times more citations than average.
Paper 3	Hughes LD, Hanslip J & Witham MD. ***Centrally Active Prescribing for Nursing Home Residents-how are we doing?*** European Geriatric Medicine 2012 3 (5) p. 304–307 [14] Dimensions Badge: https://badge.dimensions.ai/details/id/pub.1030743756 Last Accessed 8th January 2024	6 Compared to other publications in the same field, this publication is highly cited and has received approximately 1.54 times more citations than average.

Table 3 (continued): Contribution of the candidate for each of the six papers which form the basis of PhD Publication

	Reference for the Paper	**Citations and Altmetric Information [48]**
Paper 4	Hughes LD, Raitt N, Riaz MA, Baldwin SJ, Erskine K, Graham G. ***Primary Care Hypnotic and Anxiolytic Prescription – Reviewing Prescribing Practice Over Eight Years.*** Journal of Family Medicine and Primary Care. 2016 5(3): p.652-657 [15] Dimensions Badge: https://badge.dimensions.ai/details/id/pub.1013159726 Last Accessed 8th January 2024	8 Compared to other publications in the same field, this publication is highly cited and has received approximately 1.68 times more citations than average.
Paper 5	Hughes LD, Cochrane L, McMurdo MET & Guthrie B. ***Psychoactive Prescribing for Older People – What difference does 15 years make?*** International Journal of Geriatric Psychiatry. 2016;31(1):49-57 [16] Dimensions Badge: https://badge.dimensions.ai/details/id/pub.1043984624 Last Accessed 8th January 2024	7 This publication has received about as many citations as you might expect, compared to the citation performance of other publications in the same field.
Paper 6	Hughes LD & Witham MD. ***Causes and correlates of 30-day and 180-day readmission following discharge from a Medicine for the Elderly Rehabilitation unit.*** BMC Geriatrics 2018. 18:197 [17] Dimensions Badge: https://badge.dimensions.ai/details/id/pub.1106385120 Last Accessed 8th January 2024	31 Compared to other publications in the same field, this publication is extremely highly cited and has received approximately 9.5 times more citations than average.

1.5 Multimorbidity – a challenge associated with ageing populations

This thesis and the research reported in six papers focus upon multimorbidity [12-17] with particular themes being around patient-centred care, deprescribing and treatment burden. The challenges of managing patients with multimorbidity have, and continue to be, a major part of my work as a GP. Reflection on the management of multimorbidity underlie much of the body of work on which this submission rests. Therefore, this section focuses on multimorbidity and why it represents such a challenge for healthcare services, especially for GPs, and so provides insight into the motivation behind this body of work.

The term multimorbidity was first mentioned in the literature over 40 years ago [50], with the last 10 years particularly seeing a significant increase in the focus given to the topic both clinically and within the research context [51]. Multimorbidity, defined as the co-existence of two or more chronic conditions within an individual [52,53], is now the norm in ageing populations with this group of patients being inherently heterogenous [54]. Multimorbidity differs from comorbidity, which is an index condition of primary interest with additional associated conditions, and refers to the joint presence of multiple, potentially interacting chronic health conditions where one condition is not more central than another [51,52].

Since the initial publications regarding patients with multimorbidity and, in particular over the last few years, there has been reflection on the utility and patient perception of the terminology [55,56]. Indeed, a taskforce on multiple long-term conditions led by the Richmond Group of Charities reported that patients did not feel that the term multimorbidity was acceptable to describe their condition and lived experiences [57]. A recent BMJ opinion paper identified a move towards the term multiple long-term conditions, which is advocated by the National Institute for Health and Care Research [NIHR] strategic framework [55]. Khunti et al reported that the term multiple long-term conditions is perceived as less fatalistic for patients and has more clinical relevance [55]. Presently multimorbidity remains commonly used within the medical literature, with 71 PubMed indexed publications published in the first 8 days of 2024, but this may change over time as the awareness of patient perception of the term multimorbidity is more widely recognised. Negotiated use of medical terminology, balancing patient and clinician experience and understanding of terms, is important [56,58] and there have been recent examples of such debate within the context of frailty [59] and geriatric medicine more broadly [60].

Multimorbidity itself partially represents the success of chronic disease management and diagnostics, with patients with chronic physical diseases and cancer receiving significant improvements in medical and pharmacological interventions and associated outcomes over the last 20 years [54,61,62]. The studies reported in Paper 1 and 2 [12,13] discuss chronic disease guidelines, recognising that most patients seen by GPs have chronic conditions. The study reported in Paper 3 [14] deals with patients residing in a nursing home, a group of patients who demonstrate the implications of increasingly successful medical interventions for acute disease presentations and increasing life expectancy.

Multimorbidity provides significant challenges to the structure of healthcare services, which are often speciality or disease-focused in nature. There is considerable evidence suggesting that the current disease-based approach to managing patients with multimorbidity is associated with a variety of poor outcomes including inadequate preventative care and access to rehabilitation services [63], repeated referrals for specialist care [64] and increased healthcare costs [65]. The study reported in Paper 6 [17] provides some analyses regarding the impact that frailty and multimorbidity have upon hospital readmissions after in-patient rehabilitation.

The healthcare needs of patients with multimorbidity, particularly those in lower socioeconomic groups and with mental health diagnoses, can be complex with different specialities focusing upon competing priorities (which may or may not be patient-centred), demanding self-care regimes, polypharmacy and challenges in coordinating such care regimes [66]. The study reported in Paper 5 [16] reporting that increases in psychoactive prescribing for older patients have not been equally distributed across socioeconomic groups demonstrates the significance of these challenges for clinicians. There is work highlighting that patients with multimorbidity can be considered more at risk of adverse patient safety events [67], with mixed physical and mental health multimorbidity associated with the highest risk of patient safety incidents [68].

Multimorbidity as a health issue is most commonly managed in primary care systems in countries where GPs act as the gatekeeper of secondary care services [11]. Indeed, GPs with generalist skills are well placed to attempt to manage and support patients through the variety of medical presentations, symptoms and psychosocial challenges associated with multimorbidity alongside providing a degree of coordination of care [11]. GPs are felt to be in a position to provide PCC, the fundamental characteristics of which is care that explicitly involves the patient in decision-making around treatment regimens and where the adaptation of care is based upon the patients preferences, context and condition [69,70].

1.5.1 Ariadne Principles: how to handle multimorbidity in primary care consultations

The Ariadne principles were developed in 2014 through consensus of 19 experts from North America, Europe and Australia, recognising the challenges and conflicts for GPs managing patients with multimorbidity [11]. These preliminary principles aimed to support GPs handling primary care consultations for patients with multimorbidity [11]. The principles provide a lens for clinicians to deliver care, and to work with patients to establish realistic treatment goals and develop a strategy to achieve them. The resulting framework guides and supports clinicians make clinical decisions, rather than provide specific recommendations. With the principles and framework developed by clinical experts in high-income countries with well-developed primary care systems, extrapolation of the framework directly to low- and middle-income nations is challenging. This is particularly important, as developing nations are also experiencing increasing numbers and prevalence of people with multiple long-term conditions [51].

Figure 1 provides a pictorial representation of the process of ongoing multimorbidity management for patients in primary care [11]. The agreement and sharing of realistic treatment goals by clinicians and patients is at the core of the Ariadne principles which can be seen at the centre of the diagram. These are developed and agreed after a process resulting from three components which are seen leading off from the centre of the diagram:

(i) a thorough interaction assessment of the patient's conditions, treatments, constitution and context (necessary starting point for presenting and continuing problems);

(ii) the prioritisation of health problems which take into account the patient's preferences (in particular most and least desired outcomes);

(iii) individualised management which realises the best options of care in diagnostics, treatment and prevention to achieve the goals.

The focus upon realistic treatment goals as the core component of the principles fit more broadly with health policy initiatives, such as *Realistic Medicine* in Scotland [71]. *Realistic Medicine* aims, through making changes throughout the Scottish healthcare ecosystem, to encourage shared decision-making between patients and clinicians with an associated personalised approach to care. *Realistic Medicine* also aims to reduce healthcare variation, reduce waste, improve risk management, and encourage service innovation [71]. For example, pragmatic discussions between clinicians and patients around investigations and expected benefits of interventions may empower patients to make decisions which involve less invasive treatments and are more conservative representing shared-decision making (e.g. a watch and wait approach for prostate cancer in an 85-year-old).

By definition the Ariadne principles encourage shared decision making and a personalised approach to care, and therefore may be a good fit for clinical consultations for patients with multimorbidity. The principles, and *Realistic Medicine,* by focusing upon realistic treatment goals from an individual perspective and policy perspective respectively, may support healthcare systems address health variations. This may be achieved by improving access to care for patients at risk of under-use of healthcare (under-treated patients) whilst simultaneously addressing the opposite challenge of over-use of healthcare (over-treated patients) [71,72]. There are similar programmes, such as '*Choosing Wisely'* in England which focus on reducing the use of inappropriate interventions [73] and 'minimally disruptive medicine' which seeks to advance patient goals for health, healthcare and life whilst minimising the burden of treatment that healthcare often imposes [74-76].

Overall, the Ariadne principles are valuable in providing a framework for clinicians to use when managing patients with multimorbidity, with some limitations which will be discussed later in this chapter. This framework has direct relevance for the body of work on which this thesis is based [12-17].

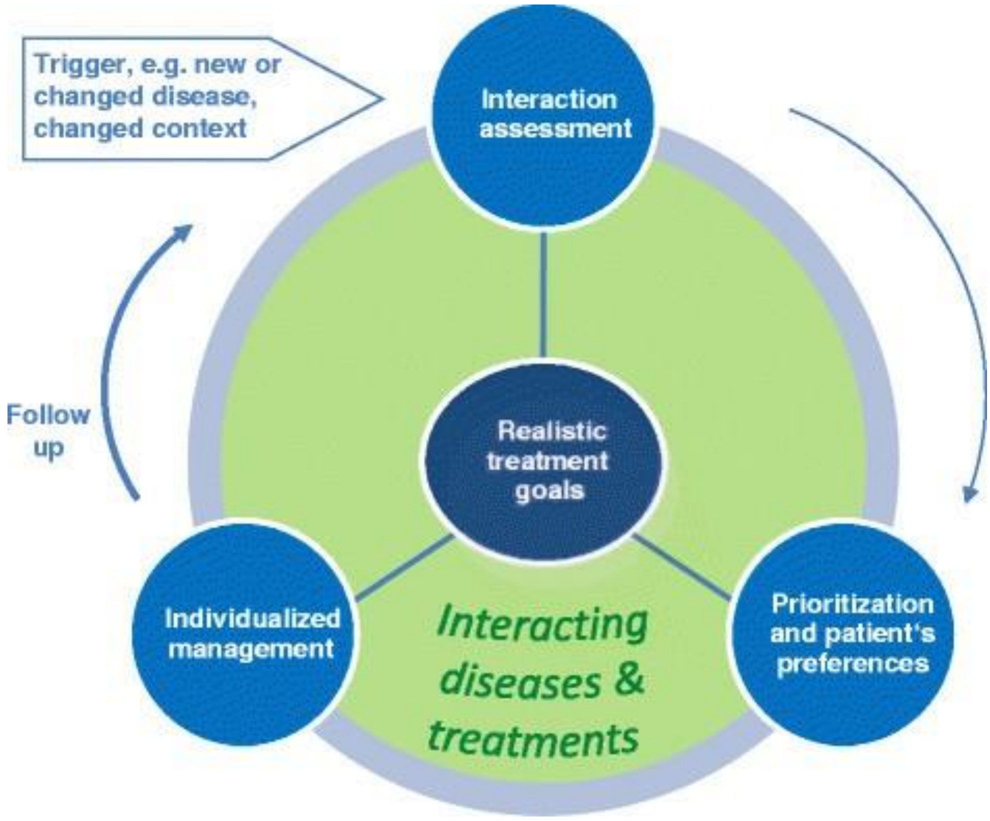

Figure 1. Ariadne Principles for Primary Care Providers Managing Patients with Multimorbidity [11].

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The authors work on which this thesis is based, consider all aspects of the Adriadne principles [12-17]. Research on clinical guidelines [12,13], psychoactive prescribing in a nursing home [14] and hospital readmission after geriatric in-patient rehabilitation [17] all explicitly outline the importance of individualised management (e.g. considering what chronic disease targets are achievable and desirable for a patient), prioritisation of patient preferences (e.g. what symptom(s) are the primary concern, and as such which disease should be prioritised for focused treatment and/or referral) and interaction assessment (e.g. delivery of judicious prescribing with minimal risk of iatrogenic harm in nursing home setting). In particular, the authors work discussing hospital readmission after in-patient rehabilitation links to realistic treatment goals, as this group of patients had considerable frailty and increased risk of decompensation of a variety of chronic diseases.

Cross-sectional research on anxiolytic / hypnotic prescribing [15] identified that focusing upon systems to deliver prescribing improvement may lead to unintended consequences. With patients with multimorbidity being almost 15 times more likely to be prescribed an anxiolytic / hypnotic medication [77], ensuring that an interaction assessment forms part of a patient-provider interaction remains pertinent. Finally, demonstrating that psychoactive prescribing in Tayside for patients over 65 [16] increased between 1995 and 2010 may mean that prioritisation of patient preferences alongside interaction assessment will be increasingly important (e.g. are patients willing to continue psychoactive medications associated with increased risk of cognitive impairment or electrolyte disturbance as they age if symptoms are well controlled?).

The Adriadne principles sensibly avoid specific recommendations, but merely provide a framework to guide and support care decisions made by GPs. The potential for such principles is theoretically profound, but a degree of caution is required before extrapolating that these benefits will be achieved, given the challenges within busy clinical environments and limited resources in primary care [78]. Indeed, the principles are clearly valid when considering the interactions of many patients with multimorbidity with GPs, but the reality of being able to deliver such a patient-centred approach is likely to be small. Delivery of the Adriadne principles may involve longer consultation times and are likely better suited once a targeted group of patients are identified as most likely to benefit from the intervention. GP assessment of particularly complex patients, or indeed cluster-based analyses to identify particularly complex patients at risk of negative outcomes, may be a way to target this approach to the right patient cohort in primary care. For example, if a report can be provided to practices about specific patient disease clusters which are at particularly high risk of negative health outcomes, GPs may proactively prioritise their clinical review and management. Such approaches may be used to extend work reported in Paper 3 and 6 [14,17], by identifying particular patient groups such as those with a higher risk of experiencing pain syndromes in nursing homes or experiencing post-hospitalisation syndrome after a period of rehabilitation for multi-faceted primary care interventions.

The framework of the Ariadne principles has been used in clinical research in the context of multimorbidity and polypharmacy [79]. In 2022, a pragmatic cluster-randomised clinical trial [RCT] comparing an intervention (delivery of training and clinician interviews regarding problem-based learning, constructivism and the Ariadne principles) to usual care was published. The authors reported improvements in medication appropriateness at 6- and 12-month follow-up and measures of PCC, although the benefit was marginal. The cost-effectiveness and sustainability of such an approach remains unclear, taking into account the impact of this upon other important parameters such as treatment burden, adverse drug reactions and disease-specific measures (e.g. HbA1c).

There are broader limitations to the Adriadne principles. Firstly, there is increasing agreement around the approaches to care and policy which may improve healthcare delivery and outcomes for patients with multimorbidity [7,28,29,40]. The evidence base is much more limited with regards to implementation, and these principles will be challenging to implement as they primarily focus upon fundamentally changing clinician behaviours. It is unclear as to how the outcomes of realistic treatment goals can be readily measured or how evidence of their efficacy can be demonstrated. The design, delivery and evaluation of interventions for patients with multimorbidity will be crucial to identify what parts of these principles have particular value.

Secondly, there is a risk that moving the focus towards the consultation and process of agreeing realistic treatment aims may lead to perverse clinical outcomes. A 1998 trial which assessed the effect of additional training on practice nurses and GPs in PCC in relation to newly diagnosed type-2 diabetes, found that clinicians placed a greater focus on the consultation process with improved outcomes in communication, greater treatment satisfaction and wellbeing [80]. However, these benefits can be at a cost of worse diabetes related clinical outcomes [80]. Walking this tight rope will provide a challenge for those designing interventions.

Thirdly, given that it is unrealistic to deliver this framework within all consultations for patients with multimorbidity a degree of selection will be required to identify groups of patients who have the most to benefit from it. The process and means by which this is achieved will be important to consider in order to reduce the risk of unintended exacerbation of health inequalities and to ensure the equitable allocation of healthcare resources.

Fourthly, shared decision-making is essential to the delivery of quality and PCC for people with multimorbidity and is at the centre of the Ariadne principles. This process enables individuals to make and revisit medical decisions by balancing and evaluating the trade-offs of the benefits and burden within their lived experience [81]. However, the ability to engage in shared decision-making is not equal between individuals. Patients who are incapacitated acutely due to illness / accidents, develop neurodegenerative diseases or those with intellectual disability need additional consideration when shared decision-making is planned. This may include involving caregivers or family members who are closely linked with the individual and use of decision-making aids where feasible to maximise the engagement with the person at the centre of the decision. These processes can be associated with useful outcomes [82,83]. For example, physician communication and use of shared decision-making behaviours with surrogate decision makers for incapacitated patients at high risk of death or severe functional impairment in the intensive care unit were associated with greater trust in the treating physician [82]. Similarly, a systematic approach to shared decision-making for children with disabilities promotes family and clinician collaboration, and can address gaps between child/family values, understanding of choices and priorities for care and those of the clinician [83]. Ongoing research regarding how shared decision-making could be operationalised for people with multimorbidity is required [84].

However, despite these limitations the Adriadne principles in my view provides a useful basis to consider an approach to support patients with multimorbidity in primary care. Determining the best methodology to selecting patients who will benefit from the approach, and developing and testing interventions to establish effectiveness and efficacy of the principles will provide the next challenge.

The following short sections will summarise three core concepts which are relevant to this PhD by Published Works thesis: PCC, deprescribing and treatment burden.

1.5.2 Multimorbidity & Patient-Centred Care

PCC has been reported as encompassing five conceptual dimensions: the biopsychosocial perspective, patient-as-person, sharing power and responsibility, therapeutic alliance and doctor-as-person [85]. PCC is growing in prominence, and the Institute of Medicine has identified PCC as a key aspect of high-quality care [86] with PCC practices associated with improvements in care quality [87], decreased healthcare utilisation [88] and improved patient concordance with treatments [89].

PCC consultation methodologies include components such as *the patient's narrative* (patients spontaneous description of the problem, including their ideas, concerns and expectations [90]) and *collaboration* (shared decision making between clinician and patient [91]).

The authors work on clinical practice guidelines [12-13], explicitly discusses the challenges of clinicians delivering PCC concurrently with clinical guideline recommendations. The work demonstrated that UK clinical guidelines for common chronic diseases do not adequately consider PCC. Indeed, the general statements provided to clinicians to consider the importance of PCC in their practice are not particularly helpful. Research which formed the basis for Paper 3 [14], reported prescribing practice which may under-treat pain syndromes for patients with dementia with a potential adverse impact on patient quality of life. PCC has been adapted to develop a variety of interventions for patients with dementia [92], with a 2022 systematic review including 30 studies, reporting that delivery of patient centred interventions generally leads to improvement in patient behavioural and psychological symptoms of dementia and cognitive function (with the effect size differing between interventions) [93]. Despite the role of such interventions, their implementation will likely be stifled by a variety of financial, staffing and political pressures within the social care sector which I discuss in an editorial for the *British Journal of General Practice* [94].

The authors work reported in Paper 6 [17] identifies that readmission to hospital is common even after in-patient rehabilitation where patients have undergone comprehensive geriatric assessment (CGA). CGA is a process of care, which involves a multidimensional holistic assessment of an older person which considers health and well-being, to formulate a plan to address issues which are relevant and of concern to the older person (and their family or carers where relevant) [95]. CGA is goal-orientated and patient centred in its approach [95,96]. PCC in the context of hospital discharge planning is pertinent, and this extends to the reasons and context of hospital readmission [95]. PCC can be delivered in a wide variety of ways, from CGA to one-on-one consultations in primary care using the Ariadne principles.

The potential that PCC may have for patients with multimorbidity has been identified and has been the focus of clinical research. Such studies have included the multi-component patient centred 3D trial (based on dimensions of health, depression, and drugs) which did not report improvements in patient quality of life [97], a patient-centred multidimensional assessment program for patients with ≥ 3 admissions within 12 months in Italy which reported reductions in admissions and emergency department visits [98] and a patient-centred prescription model of care which improved prescribing (by measures of potentially inappropriate medications and drug burden index) and medication adherence [99]. Despite some positive clinical trials looking at PCC, as described for hospital readmission [98] and prescribing [99], larger trials which are more multi-dimensional in nature have not reported statistically significant results [97]. With the impact of Covid-19 reported to have a significant impact on the delivery of PCC [100], the design and delivery of trials of complex interventions that take PCC into account continue to be important and inform how health systems can adapt and implement programs for patients with multimorbidity to achieve the benefits of PCC.

Although the PCC approach is difficult to argue against from an ethical standpoint, there are some challenges associated with the implementation of PCC and associated interventions which should be considered by policymakers and commissioners [101]. For example, the CADRES study randomised patients to PCC, usual care or dementia-care mapping interventions and reported higher rates of falls in the PCC group alongside the benefits of reduced agitation for patients with dementia [102]. Thus, PCC may lead to choices which are associated with increased risk but are closer aligned to patient values [102]. There is also conflicting data about the cost-effectiveness of PCC interventions [101,103-105] and the sustainability of clinician engagement in PCC [106].

The papers which form the basis of this thesis [12-17] do not clearly discuss and explore the patient voice and lived experience, which may have enabled exploration of domains particularly relevant for PCC. Qualitative methods and mixed methodologies may be a useful approach in future work to explore these important domains.

1.5.3 Multimorbidity & Deprescribing

Polypharmacy, commonly defined as the prescription of 5 or more medications daily [107], is commonly associated with multimorbidity and is associated with adverse drug reactions, patient safety events, increased costs and iatrogenic harm [67,108,109]. Despite guidelines often recommending alternatives to medications or advising caution, it remains inevitable that patients will end up on several medications with an increased cost of care [108]. This is not necessarily detrimental, but ensuring optimal prescribing is an area of increasing focus in terms of patient safety, sustainability and improved efficiency [109,110]. There are challenges to this as some of the definitions in this area are not clearly defined. For example, a recent 2023 scoping review reported that the usefulness of 'inappropriate polypharmacy' as a single definition is of doubtful use presently due to extensive heterogeneity [110]. Several research studies were excluded from the review alongside limited grey literature inclusion, but the identification of limitations surrounding definitions is key. Indeed, defining multimorbidity has been a priority for research leaders to enable comparison between studies [111].

"Deprescribing" is a process of medication withdrawal supervised by a health professional with the goal of managing polypharmacy and improving outcomes is well defined [111]. This process is linked to PCC and treatment burden, as the goals of deprescribing will differ between patients and may change for an individual depending on the circumstances of the consultation and symptoms experienced.

The complex intervention of deprescribing can take many forms, with a recent evidence synthesis reporting 34 context-mechanism-outcome configurations describing the knowledge of tailored prescribing [112]. These were reported under eight headings relating to organisational, health-care professional and patient factors, and interventions to improve prescribing [112]. Context-mechanism-outcome configurations are a proposition stating what it is about an initiative that works, for whom and in what circumstances. The authors concludes that deprescribing requires attention to providing an enabling infrastructure (such as developed IT systems), access to data (risk and benefit of treatment cessation), tailored explanations and trust between clinicians and patients [112]. Such developments would support patient-centred deprescribing, supporting individualised management and interaction assessments which are both Ariadne principles.

Managing patients living with multimorbidity, and delivery of judicious prescribing through deprescribing is an uncertain process. The 'fear of change' in relation to deprescribing is an important consideration in patients with multimorbidity and may lead to clinicians performing fewer deprescribing interventions [112]. Supporting clinicians overcome barriers such as patient engagement in the process, and multiple prescribers / providers of care will require more practical guidance and high-quality data about the risks of stopping certain medications. Furthermore, supporting the identification of patients who have most to gain from these interventions (e.g. patients with multimorbidity, polypharmacy, frailty, multiple prescribers due to medical complexity etc) is pertinent [112,113]. In relation to the Ariadne principles, placing patients realistic treatment goals at the centre of discussions regarding deprescribing may be helpful in framing of the consultation.

Improving the coordination of prescribing within health systems to support deprescribing and mitigate the risks of uncontrolled polypharmacy has been proposed as an approach for high-risk patients with multimorbidity [109]. These groups may include nursing home residents and those over 65 years with mental – physical health multimorbidity, which were groups of interest in research reported in Papers 3 and 5 [14,16]. My research reporting on clinical practice guidelines [12,13], highlighted that although guidelines were helpful at recommending medications or interventions to be commenced they were much less effective at providing advice about deprescribing.

More broadly, since the publication of research reported in Paper 4 regarding hypnotic and anxiolytic drug prescribing [16] primary care pharmacists are much more involved in polypharmacy reviews and proactive pharmacy interventions and support GPs significantly in this work. The broader change in the roles of different healthcare providers is an important area to consider as the healthcare system develops.

1.5.4 Multimorbidity & Treatment Burden

Treatment burden, in terms of all healthcare interventions and activities, is an emerging concept for patients with multimorbidity [114]. Increasing treatment burden can complicate the patient’s condition by impairing the patient’s ability to adhere to recommended medications and interventions with an associated increased risk of hospitalisation as well as impacting the quality of life of the patient [114]. This is an important consideration as patients develop realistic treatment goals with their clinician.

Treatment burden has been defined as a patient's perception of the aggregate weight of the actions and resources they devote to their healthcare, including difficulty, time and out-of-pocket costs dedicated to healthcare tasks such as adhering to medications, dietary recommendations and self-monitoring [115]. It is natural that with increasing multimorbidity there is a risk of increasing treatment burden for patients, and this should be considered as part of the broader treatment recommendations and primary care management of chronic disease. A systematic review of qualitative data isolated components associated with treatment burden, including financial burden, lack of knowledge, diet and exercise, medication burden and frequent healthcare reminders of their health problem [116]. GPs and integrated primary care systems may be well placed to address these components. The Ariadne principle framework for patients with multimorbidity may be used to support patients through interacting diseases and treatments to make decisions around their treatment goals.

The authors work on clinical guidelines [12,13] explicitly considered treatment burden in terms of increasing medication, intervention and self-care recommendations. Patients with multimorbidity were at risk of increasing treatment burden when guidelines were followed, without any clear guidance or advice within the published guidelines about how to consider treatment burden. Treatment burden was an important consideration as part of research published in Paper 3 [14] on nursing home prescribing, with older patients exposed to medications with associated harms. Research reported in Paper 4 [15] and 5 [16] reporting increasing psychoactive prescribing suggests that treatment burden in context of medications, commonly identified as a significant factor for patients [117], is an important consideration for patients with multimorbidity. Treatment burden is an important consideration for patients with multimorbidity, and the influence that it has upon patients' realistic treatment goals and care decisions can be explored using the Ariadne principles.

Indeed, high treatment burden is relatively common for patients with multimorbidity, and as such clinicians should aim to minimise this where feasible [118]. Treatment burden is more likely to impact more vulnerable patients with increased risks of hospitalisation or requirements for care [118] thus potentially increasing healthcare inequity. There is evidence that improved patient experience is associated with lower treatment burden [119], but at the present time there remains limited clear guidance about how to safely prioritise the reduction of treatment burden for patients with multimorbidity.

1.6 Chapter Conclusion

The current healthcare landscape faces a variety of challenges, including delivering health and social care to an ageing population, and increasingly complex healthcare treatments and interventions alongside a backdrop of perpetual fiscal challenges [2,10,51]. These challenges have become even more pressing as health systems attempt to remobilise after Covid-19.

Therefore, the delivery of PCC has become more pressing. This may be delivered at the policy and systems level, but also within individual consultations between patients and clinicians and may support mitigating treatment burden and supporting deprescribing. This is not to suggest that further macro level research and policy change is not to be explored but that clinicians can be supported to improve care for patients with multimorbidity through consultation level approaches alongside this.

The Ariadne principles are a useful framework to consider the body of work which forms this thesis, with individualised management, prioritisation of patient preferences and interaction assessments all pertinent to my published work. My research has limitations, in particular due to the lack of the patient voice but does identify and explore important clinical areas within multimorbidity and identifies other areas for future research.

This chapter has introduced my work, and the independence and significance of the work. Multimorbidity, and the important themes associated with my work of PCC, deprescribing and treatment burden have been defined and explored by drawing upon a broad range of academic literature and evidence. These themes will continue to be explored throughout the thesis.

Chapter 2 discusses the research methodologies used in the research which form the basis of the 6 publications of the PhD by Published Works, ethical considerations for the studies alongside outlining the role of reflexivity throughout this process.

Chapter 2

Research Methodologies
&
Reflexive Practice

2. Research Methodologies and Reflexive Practice

2.1 Introduction

The six publications on which this narrative is based use and demonstrate a range of research methodologies. These include a clinical case report [12], clinical guideline analysis using patient vignettes [13], observational cross-sectional studies [14,15,16] and observational case-control study [17]. Each of these has strengths and limitations which will be outlined in the following section.

More broadly, the chapter will detail some of the ethical considerations of the author's work which were often only briefly touched upon within the published papers. Finally, reflexivity is considered and how this has been incorporated by the author within the research process.

2.2 Research Methods

The author's first publication was a case report, which identified the real lived experience of a patient with multimorbidity [12]. The case demonstrated several important concepts relevant to the field which was developing at that time and provided an opportunity to shape more comprehensive work. A case report approach provided an insightful means of exploring the issues of applying clinical guidelines to patients who have multimorbidity, providing clinical evidence of the limitations of clinical guidelines that was used to develop further research questions. In addition, the case report provided an opportunity to write and prepare an academic paper at an early stage of my undergraduate degree.

The medical research genre of case reports and case series declined significantly over the second half of the 20th century, with increasing focus on research articles which developed increasing statistical rigor and complexity [120]. However, there remains a value in the narrative provided by case reports and this is reflected in the establishment of the *Journal of Medical Case Reports* in 2007 and a recent increase in the space that high-impact journals leave for case report publications since the late 1990s [120,121]. The development of the CARE guideline for case report writing has aided the standardisation of the genre and therefore the reliability of case reports [121].

There remain merit in the publication of case reports, including identifying new observations, generating hypotheses and the ability to perform in-depth narrative case studies which can provide an understanding of essentially human phenomena. Indeed, the author has used case reports to identify changes in the clinical manifestation of fibromyalgia in patients with Alzheimer's disease [122,123] that has provided the basis for developing a small prospective longitudinal cohort study. Case reports also provide a useful approach for identifying and discussing rare disease presentations, complications or responses to therapeutic interventions [120,121].

There are extensive limitations of case reports, including that they cannot generate information on rates, ratios, prevalence or incidence as case reports or series are not selected from a representative sample. Furthermore, there is publication bias towards positive outcomes, emphasis on the rare, and the risk of overinterpretation. Case reports are also lower on the hierarchy of the evidence pyramid, a system of rating evidence when grading recommendations based upon the probability of bias [124], as they are often biased by the author's experience and lack of control of confounders which was the case in my case report [12]. Despite this, they continue to have a role in research and certainly the author's work [12] using this method was an appropriate way to demonstrate some of the individual challenges patients with multimorbidity may face. Indeed, the case report [12] identified some limitations in the clinical practice guidelines and demonstrated a need for clinical practice to change to reflect the complexities of patients with multimorbidity.

The authors work on clinical practice guidelines used a selective analysis with patient vignettes to interrogate the extent that NICE clinical guidelines address patient comorbidity, patient centred care and patient compliance to treatment recommendations [13]. When designing this study [13], it was clear we required to focus upon commonly occurring long-term conditions affecting patients, alongside those conditions which are commonly associated with multimorbidity. The NICE guidelines selected were for type 2 diabetes mellitus, secondary prevention in people with previous myocardial infarction, osteoarthritis, chronic obstructive pulmonary disease and depression (two guidelines including one for managing depression in people with chronic physical problems) [125-130]. The majority of people with these conditions will have significant comorbidity (71% of people with diabetes are multimorbid, 92% with coronary heart disease, 82% with osteoarthritis, 83% with COPD and 64% with depression) [131]. All six guidelines were published within 5 years of the study to ensure they were reflective of current clinical practice.

Our patient vignettes were developed to be representative of a patient who would be commonly found on a GP practice list, and therefore increase the applicability of the findings. The ability of vignette studies to desensitise sensitive topics, alongside directing elements to a specific part of a complex process has been reported [132,133]. The latter is particularly relevant for multimorbidity, which involves numerous complex processes from a patient, healthcare provider and health system level. For example, diagnostic uncertainty and reasoning in multimorbidity was explored using eight video case-based vignettes which differed in type of morbidity, field of medical specialism and relatedness of underlying diseases [134]. Clinicians viewed these videos before generating potential diagnoses, with the paper reporting increased sensitisation and training regarding multimorbidity (particularly common co-morbid conditions) is pertinent due to a high rate of under-diagnosis [134].

The approach that was opted for has limitations, including the critical feedback that we developed patient vignettes and conditions to demonstrate that clinical practice guidelines were associated with driving polypharmacy, and treatment burden. We considered approaches which used real patients and involved a larger number of clinical practice guidelines but it was felt that the research question could be adequately answered in the form published. On reflection, it was felt that using real patients would not enhance the utility of the research when compared to patient vignette, as the approach would have similar limitations in relation to bias.

Consideration was also given of using up to ten clinical practice guidelines, a combination of European and UK guidelines and more than two patient vignettes. The importance of the paper was to demonstrate that clinical guidelines for common conditions do not adequately take into account multimorbidity. During a meeting of the research team, it was felt that a focus upon UK guidelines would enable a clear message of the paper and there was extensive variability of the development and implementation of European wide guidelines. Furthermore, by using two vignettes which between them had five commonly occurring chronic diseases which are strongly associated with the development of multimorbidity [131], the challenges of managing patients with multimorbidity with clinical guidelines could be identified. Increasing the number of conditions included or the number of vignettes would not significantly enhance the validity or generalisability of the findings. Furthermore, the two patient vignettes both had mild to moderate disease states rather than severe disease states to reflect that the challenges of clinical guidelines are not limited to the most complex and unwell patients with multimorbidity. Despite inevitable limitations, the value of the case report [12] and vignette study [13] was demonstrated with valuable insights into the challenges of clinical guidelines for patients with multimorbidity.

Research on prescribing and hospital readmission [17] were all observational studies which included cross-sectional [14,15,16] and case-control designs [17]. Subjects were chosen from an available population of potential relevance to the study question(s) and eligibility criteria. This process required the data collection and analysis in two studies [14,15], and the analysis of large population datasets which had already been collected [16,17].

In the single-centre nursing home research, all patients resident in the nursing home were eligible for inclusion as the research question was focused on centrally active prescribing for patients in a nursing home environment [14]. In the single-centre general practice research reporting hypnotic and anxiolytic drug prescribing over time [15], eligibility criteria were focused on any patient who received an acute or repeat hypnotic or anxiolytic drug prescription over the course of 12 months. Hypnotic and anxiolytic medications were defined in line with the 2012 edition of the British National Formulary [BNF] [135].

Psychoactive drug prescribing for older people (defined as 65 years old and over) was explored using community dispensing prescribing data [16]. Similar to previous work, psychoactive medications were defined in line with BNF chapters [135]. Patients were selected for inclusion if they had received a psychoactive medication in the 3 months prior to the two cross-sectional time points (31st March 1995 and 31st

March 2010] and would include acute and repeat prescribing given that the aim of the work was to review psychoactive drug prescribing differences between 1995 and 2010 in Tayside. Causes and correlates of 30-day and 180-day readmission was researched using a database of 4449 patients within a medicine for the elderly dataset within NHS Tayside. Patients and associated demographic and clinical characteristics were included in the analysis if they were readmitted to hospital within 30 days, a standard marker used to judge healthcare system effectiveness [21,22], and 180 days. The latter was chosen as a readmission at this time point is less likely to be related to the initial period of in-patient rehabilitation and may represent other geriatric syndromes such as frailty or post-hospitalisation syndrome [95]. The inclusion criteria enabled us to explore the reasons for readmission to acute care facilities in a cohort of older people discharged from inpatient rehabilitation after an acute illness. We were able to report that most admissions for older people after a period of in-patient rehabilitation occurred for different reasons than the original hospital admission and that patterns of predictors for early and late readmission differed.

Cross-sectional and case-control studies are relatively inexpensive to conduct especially when using already available datasets. Cross-sectional studies provide an indication of prevalence alongside studying associations between multiple exposures and outcomes [136]. Understanding prevalence provides an indication as to the degree that an issue is found in a population. This will inform the potential impact of an issue upon health systems. The results of cross-sectional studies may influence and inform hypotheses which may form the basis for a more complex intervention, but a fundamental limitation is that they report associations rather than causation based on the data. Furthermore, cross-sectional studies cannot be used to study behaviour over time as they measure data at a discrete time point. Longitudinal cohort studies would be an approach to detect changes in the characteristics of a target population at both the group and the individual level over a period of time [137].

Case-control studies are an efficient design for less common outcomes such as readmission [138]. Case-control studies enable researchers to analyse multiple risk factors for an outcome of interest at one time and may enable early identification of associations worthy of further study. There are some limitations, such as the fact that the control group are commonly recruited through convenience sampling, leading to a risk of bias as the control group are not representative of the general health of the population. However, the risk of bias can be mitigated through matching of patient characteristics.

Given that observational cross-sectional methods provide an indication of prevalence alongside associations between multiple exposures and outcomes, it was an appropriate method to explore the prevalence of hypnotic and anxiolytic drug prescribing practice in a GP practice in Paper 3 [15], psychoactive drug prescribing in a Dundee nursing home in Paper 4 [14], and differences in regional psychoactive drug prescribing between 1995 and 2010 in Paper 5 [16]. The datasets used in these research projects were selected as they were able to answer the research question(s) formed as part of each programme of work. A further advantage of using routinely collected clinical data, is that the data could be analysed and interrogated quickly using SPSS v22.0 (IBM, New York USA). This was of particular importance when tight deadlines were provided for short-term funded research studentships and an academic foundation doctor post.

All four of these publications [14-17] have generated exploratory hypotheses ready to be tested in more robust future designs such as longitudinal cohort design or RCT. For example, Paper 3 highlighted that patients with severe dementia may be under-treated for pain syndromes alongside overall high rates of psychotropic drug prescribing [14]. A longitudinal cohort study of nursing home residents could be an approach to establish changes in pain manifestation, treatment alongside psychoactive drug prescribing more broadly over the course of a patient's dementia diagnosis and illness.

There are several limitations associated with observational studies. One of the fundamental limitations of cross-sectional studies is that you cannot make causal inference, which from a policy perspective is of fundamental importance. For example, I was unable to explain why patients with more advanced dementia were more likely to be under-treated for pain [14] but could postulate some potentially relevant factors (e.g. challenges in accurate assessment of pain due to cognitive deficits, staff awareness of tools used to assess pain in dementia, and clinician concern around adverse drug reactions of analgesia). More broadly, sometimes the identified associations may be challenging to explain. For example, in Paper 6 which reported research on readmission after geriatric rehabilitation [17], older age was associated with a reduced risk of readmission in contrast to several other studies. The four observational studies [14,15,16,17] have reported several clinically relevant associations, but the research has not been able to report causation and as such as provided the basis for further research (using different methodologies) to achieve this. Finally, retrospective studies, such as case-control studies, may have a degree of recall bias or selection bias but the dataset used for readmission work did not rely on patient recollection [136-138].

A limitation of all the research which forms my body of work, is that there has been minimal patient engagement in the research. Since the publication of my initial study in 2012, patient and public involvement and engagement [PPIE] has become much more prominent within clinical research, and upon reflection spending time becoming aware of PPIE opportunities within the locality would have been useful. Indeed, PPIE in research has become a key component recommended by grant award bodies and is specified in government policies [139]. There is an increased literature which explores the consultation, collaboration, and co-production processes of clinical research and how this can involve patients and members of the public [140]. Benefits of PPIE may include rates of enrolment in clinical trials [141] and better designed trials which target important symptoms or outcomes relevant to patients or communities [142]. The Covid pandemic has also shaped PPIE in clinical research, with the online environment potentially providing an opportunity to extend PPIE [143].

Increasingly, guidance exists to help researchers plan and conduct meaningful PPIE at both national and international levels [144]. This includes the NIHR [145,146] in the UK and the Patient-Centred Outcomes Research Institute in the US. The central focus that PPIE now has within clinical research compared to when the author published his initial work can be evidenced by the fact that the Patient-Centered Outcomes Research Institute in America was only formed in 2009. Furthermore, a recent Medical Research Council (MRC) publication regarding clinical research about complex interventions, of relevance to multimorbidity research, identified six core elements one of which was ‘How can diverse stakeholder perspectives be included in the research?’ [147]. Subsequently to the author’s publications, PPIE is now recognised as a core attribute of clinical research, particularly around complex interventions. However, despite this, reporting of PPIE in study reports is often minimal, usually concentrating discussion around the process of how PPIE was obtained rather than its impact [144].

PPIE could have played more of a role in studies published by the author. For example, research on primary care prescribing [14] could have particularly benefited from PPIE by considering the broader contexts for GP prescribing in the locality (e.g. high rates of polysubstance use, poverty, housing crisis, high rates of chronic pain) alongside shaping the research programme to make it more patient-centred. Indeed, current research and quality improvement in this area has been focused on prescribing but PPIE may have led to prioritisation of research into psychosocial factors which are relevant to prescribing. Practically, this may have used patient forums which meet monthly (organised through the GP cluster model) as a basis for initial discussions. Alongside identification of patient centred outcomes, this may have supported dissemination of the work to the locality.

PPIE is part of multimorbidity research in the form of advisory groups, such as the Multimorbidity Mechanisms and Therapeutics Research Collaborative in London, to help shape the research process (planning, delivery, dissemination) and monitor progress of the project, and assist in dissemination of research findings. There is increasing evidence that PPIE and patient research partnerships is feasible in patients with significant illness and debility, rather than patients with mild to moderate disease [148]. The MRC framework identifies stakeholder engagement as an important part of PPIE in complex interventions. This needs to occur at each stage of the clinical research programme to support identification of patient valued outcomes and priorities to help shape an intervention with better opportunity for improvement in health. Other relevant considerations include considering the context of the delivery of the intervention, development of programme theory, identification of key uncertainties, and refinement of the intervention prior to economic considerations [147].

In my nursing home prescribing research [14], I may have been able to achieve PPIE if I had more time and collaboration with colleagues as part of the research process. A significant challenge was balancing time to engage with broader stakeholders with resource constraints. Recent work has identified that people living in nursing homes with dementia, can be actively involved in clinical research through PPIE and the resources and approaches to achieve this are clearer than in 2011 when the work was commenced [149,150]. Approaches to develop PPIE, may have been in the form of a caregiver reference panel, and/or service user forums which have been used in other research programs [151]. PPIE will be an active consideration of research moving forwards. PPIE was not really considered in the context of other clinical studies using pre-existing datasets, but stakeholder engagement may support future secondary analyses of data by identifying patient valued outcomes of interest and potential benefit. Future research performed by the author will always consider PPIE as a core part of the clinical research process.

Delivery of meaningful PPIE is not easy to achieve [148,152]. Recent research has published lessons learned from PPIE in the context of multimorbidity research [152]. The Canadian Aging, Community and Health Research Unit reported five lessons for researchers which included: 1) actively finding patient partners who reflect the diversity of older adults with multimorbidity, 2) developing strong working relationships with patient partners, 3) providing education and support for both patient partners and researchers, 4) using flexible approaches for engaging patients, and 5) securing adequate resources to enable meaningful engagement [152].

Within my future research looking at universal outcomes for patients with frailty for example, PPIE would provide an opportunity to really explore the study and design it in a manner which would prevent research waste and answer questions relevant to both patients and clinicians. However, PPIE will take time and effort to establish and integrate into a clinical research programme.

2.3 Ethical Considerations

As with all research, there have been ethical considerations within the body of work which forms this PhD by Published Works. These have been considered and addressed in different ways. They have been briefly touched upon within the published papers, but some of the specific aspects of the considerations are detailed here.

The case report published in Paper 1 [12] involved taking individual consent for the patient in question, and explaining the rationale and process involved. It was my first experience of taking informed consent for research, and I used a standardised form to complete this process and to enable a clear discussion with the patient. Written informed consent is a basic principle of medical practice and research, and provided an opportunity for the patient to discuss any questions or queries about the proposed case report and to understand the rationale for what I was intending to produce. There is evidence that patients understanding of the basic components of informed consent is limited [153], and patients' provision of consent may be related to the respect and/or rapport they have with a clinician or being overwhelmed rather than the rationale for the research [154]. Moving forwards, taking consent over time may be a consideration for research which involves interventions (to allow time for patient to consider the information) and recognising the impact that a therapeutic relationship has upon consent may influence which individual seeks consent from the patient.

Research which was published in Paper 2 [13], given its nature and methodology, had fewer ethical concerns and did not require ethical approval. It was a discussion paper that set out issues and concerns around using clinical guidelines and involved no primary data collection. No ethical declaration is required for such papers. That said, there is clearly a responsibility in writing such pieces to carefully consider the way in which contentions are put forward, to ensure that they are not over-reaching and genuinely reflect the results of the prepared manuscript. This is something to which the author and co-authors gave careful consideration.

The single centre nursing home prescribing study reported in Paper 3 [14] required active consideration of the ethics of data collection, and analysis at an early stage. Indeed, there were several meetings about the nature of the data collection with the senior management team within the private provider, which involved fully explaining the rationale and benefit to the patients in the home. This process helped shape the research questions and proposal, and close working with the senior management team led to the provision of time for me to record and analyse the data, alongside presenting the findings to the nursing home and local GP practices. Formal ethical approval was deemed unnecessary after provisional discussion with the care home provider and University of Dundee as it involved routinely collected anonymised healthcare data. There continues to be debate between ethical approval for clinical audit and clinical research, and there are often grey areas [155]. This process highlighted that early engagement with ethical considerations is important to reduce delays, improve the quality of research and of course protect patients. More broadly, considering the evolving ethical context of clinical research is important as processes associated with ethical approval have changed significantly over the last 10 years.

Paper 4 [15] required data collection, with anonymisation, to establish the prevalence of hypnotic and anxiolytic drug prescribing. Such searches are performed regularly in routine clinical practice to shape and review individual and practice performance, but it remained important to formalise this through the practice and local NHS Trust. After some provisional discussions, it was confirmed that no formal ethical approval was required. Given the findings reported in this paper, it made me consider how research conclusions with negative outcomes for patients or sub-optimal practice can be communicated in a helpful and supportive manner. Open and non-judgemental communication of core findings and suggested next steps went down well and led to the practice changing the approach towards the issue. The potential conflict of interest when working in the same place you are performing research must be considered in the context of this particularly given researchers have an ethical duty to their participants.

Research published in Paper 5 [16] and 6 [17], used previously collected and safely secured databases for the analysis. Ethical approval was already achieved for the overall dataset at the point of commencing the study with a shorter focused approval process for specific research proposals and associated individual safety protocols for accessing data in a Safe Haven. However, when there were considerations to amend the underlying dataset (such as linking additional individual–level prescribing data to the dataset used in research on hospital readmission) this would have required significant changes and further ethical approval. After careful consideration, this was not progressed as it was felt that it was not cost effective and that additional research questions could be answered from other available data sources. Ensuring that data is used for a clear purpose with benefit to patients is crucial, and not just because it can be used. The requirement for further ethical approval or review when studies or the way data is used are amended remains an important safeguard.

There is a broader debate presently about the adequacy of the Ethics Review Committee (ERC) in patient data protection and storage in the era of big datasets. There have been several examples of concerning practice, such as the 2015 case where the NHS legally provided Google DeepMind with 1.6 million pieces of identifiable and sensitive data without ethical oversight or patient consent [156]. There are calls to reform aspects of the ERC to reduce weaknesses related to the scope of ERCs (currently around protection of individual interest) and their functional weaknesses (skills, composition and the operational activities of ERCs) which could include clearer guidelines on the ethics of large datasets [157]. This is clearly an area for researchers to reflect carefully on the work they are taking forward, to carefully review their own approaches to addressing key ethical concerns, and to draw on user involvement to inform their work. For example, patients with multimorbidity may bring a different independent set of perspectives (focused on symptoms due to disease, functional impairment, quality of life, access to care etc) when considering ethical approval for studies looking at interventions for this patient group.

2.4 Reflexivity as part of PhD by Published Works

Reflexivity is the process of engaging in self-reflection about who we are as researchers, how our subjective views and biases guide and inform the research process, and how our worldview is shaped by the research we do and vice versa [158,159]. Reflexivity is a process which, unlike reflection, actively acknowledges one’s own beliefs, bias, and judgement systems before, during and after the actual research process with a greater potential to influence and guide the research process in real-time [160]. Although typically reflexivity has been associated with qualitative research

[161], there is an evolving body of literature which considers how reflexivity may be a useful tool in quantitative research [160,161].

Although often informally done, reflexive practice has been an important aspect of my own role as a researcher. My awareness of these issues has increased over the course of my research journey since 2012. For example, both single centre research programmes reported in Paper 3 [14] and Paper 4 [15] were very much driven by myself and this had its challenges. As outlined in section 2.3, ethical consideration for Paper 3 [14] involved multiple conversations with different stakeholders and it is likely that the study in its current form would now require formal ethical approval. A larger research team at the outset of the programme may have supported this process at an earlier stage. Furthermore, dissemination of research findings may have been more extensive had there been more time in between research programmes. My personal focus during this busy period of undergraduate training was on further research completion and publications, which is only part of the role of an academic. Sharing and disseminating research is a fundamental aspect of clinical research, and indeed research more broadly [162,163], and on reflection this could have been enhanced through submitting work to regional and national meetings and conferences (e.g. Scottish British Geriatrics Society Annual Meeting or the RCGP Annual Conference). Subsequent research reported in Paper 5 [16] and Paper 6 [17] has been more collaborative which supported the development of research skills and improved dissemination of research findings. Indeed, I presented key findings from both Paper 5 [16] and Paper [17] locally (within NHS Fife and NHS Tayside) and nationally (Royal Society of Medicine, London) and this was actively encouraged and supported as part of the overall research process. This learning experience has fundamentally changed how I will approach future research endeavours.

Considering the body of work which form this thesis and broader research I have performed to date, I have been aware of my own political, ideological and personal agendas. The impact these have upon individual research programmes may be very small, but active consideration of them is important. For example, in research published in Papers 3 and 4 [14,15] I considered how I would react and proceed if there were findings that would be challenging for colleagues to accept or demonstrated sub-optimal practice. Given I was working within each of the single centres at the time of the studies with close working relationships with staff members, this needed to be considered at an early juncture and involved discussions with stakeholders.

As a researcher I have often worked within the realm of traditional ethics, which may not fully address the subtleties of some larger datasets and challenges in obtaining informed consent from participants. However, at an early juncture the *Good Clinical Practice* training programme encouraged considering participant understanding of the rationale for data collection (particularly for those who cannot consent) and potential problems associated with data collection techniques even when formal ethical approval was not required. *Good Clinical Practice* is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human participants administered within NHS Scotland health boards with oversight from NHS Research Scotland. These considerations led to pre-registration of the formal approach for data collection in research published in Paper 3 [14] and Paper 4 [15]. Having the data collection operationalised at the outset was helpful from a practical level, but also encouraged active consideration of the ethics of decisions to adjust these processes (e.g. will the research still achieve its outcomes and provide benefit to the study population?).

During formal statistical training delivered as part of funded studentships, the assumption that numerical data is entirely objective was challenged by exploring how datasets could be manipulated based upon the use of statistical methods and sampling. This led to the encouragement of recording and saving journal field note summaries of core analyses and justifications for exclusion or inclusion of certain groups, to mitigate any risk of unconscious bias influencing the analysis of the data. This was a useful process which also helped communication with others in the research team(s) regarding the analysis and interpretation of data.

The challenges of confirmation bias, where researchers place more weight on findings during interpretation that support a hypothesis rather than those that challenge it [164], was something which was considered as I have started to publish papers and developed themes within my work. During the process of preparing this

PhD by Published Works, I have become aware of the value of positionality statements in supporting reflexivity in my work [165] but also some of the challenges with such approaches, and the degree to which they have utility [161]. Being clear about ones viewpoints, biases and agendas may aid the development of research proposals and publications through active awareness and recognition of relevant conflicts [161]. The development of steering groups is another approach to providing oversight for a programme of research.

The research published in Papers 5 [16] and 6 [17], is based on larger datasets and broad reflexive questions were touched upon throughout the work but particularly for data analysis and interpretation. These included considering any silent assumptions in the dataset and whether analysis of the dataset could reproduce inequalities [160]. Significant time was spent understanding the datasets at the start of the project, characterising typical presentations, and the original purpose of the data collection. Some of these considerations were made as an individual but others within wider research team discussions about research progress.

Alongside the individual research programmes, reflexivity has aided the development and writing of this thesis. Before, during and after the development of the thesis narrative, I considered my personal motivations, conflicts of interest, methods used in my published work and data collection and introspection in relation to the data analysis and interpretation. This process has been helpful in identifying and developing the narrative, noting that wide system change is needed to address patients with multimorbidity, but also that change is needed at the individual consultation level. The Ariadne principles [11] are a sensible construct to consider the macro and micro level changes that are needed to develop multimorbidity management and place my work in context of these principles.

More broadly, these considerations have aided identification of important limitations of the body of work such as the fact that the published work is ‘top-down’ and involves interrogation of existing data with limited PPIE and patient perspectives (see Chapter 2.2) and stimulated development of future research questions (such as GP-decision making and risk management around patients with multimorbidity).

Reflexivity has provided a useful process for me personally as I have led, contributed to and published clinical research. Efforts to actively identify and address (where possible) researcher bias throughout the research process has been of real value.

2.5 Chapter Conclusion

This chapter has outlined the research methodologies which have been used in the research which form the basis of this PhD by Published Work, alongside consideration of the ethical considerations for the work which were briefly touched upon within the publications. Furthermore, it has considered how reflexivity has aided the author develop and guide his future research endeavours. In particular, I have become more collaborative in my approach to research and have been more aware of the wider remit of the role of a clinical academic.

Chapter 3 outlines the broad clinical, research and policy challenges associated with multimorbidity. An important component of this PhD by Published Works is that it is original, and hence it is addressing gaps in the literature. In particular, the influence of an ageing population on multimorbidity, the need for strong primary care systems and the relevance of multimorbidity in the wider efforts to deliver sustainable and realistic medicine are considered.

Chapter 3

Multimorbidity – Clinical, Research and Policy Challenges

3. Multimorbidity – Clinical, Research and Policy Challenges

3.1. Introduction

Multimorbidity is associated with a broad array of significant challenges to healthcare, and the increasing prevalence and incidence of multimorbidity have implications for clinical practice, clinical research and healthcare policy [7,52,54]. This chapter will consider each of these areas, alongside drawing on the contribution of my research towards the understanding of these areas. It will argue that a focus on sustainability and strong primary care systems remain a core component of the delivery of effective healthcare to patients with multimorbidity. The latter includes supporting and encouraging practioner level interventions alongside broader health policy initiatives.

3.2. Clinical Challenges

The importance of the subject area covered by my research is underlined by the implications of multimorbidity upon patients' lives, the increased prevalence of multimorbidity now evident internationally, and the resulting implications for primary care professionals. Multimorbidity is associated with worse health outcomes, including decreased quality of life [166], higher mortality [167], psychological distress [168] and longer hospital stays [169]. With the increase in the prevalence of multimorbidity, a significant part of GP consultations and workload relates to patients with multimorbidity. For example, in general practice consultations, one study reported that patients with multiple chronic conditions accounted for over 50% of all GP consults [170]. The current structure of primary care, often with short consult times, means that the interplay between different conditions and competing patient and clinician priorities may be challenging for GPs to manage [171]. The prevalence of mental health problems increases linearly with increasing numbers of physical conditions, with individuals with comorbid physical and mental health particularly poorly served by the current model of primary care [172,173].

GP consultations involving the assessment and management of discordant conditions are increasingly common e.g. a 75-year-old man presenting with increasing pain from hip osteoarthritis, high blood pressure requiring medication titration, poor glycaemic control in diabetes, and worsening symptoms associated with prostatic hyperplasia [173-175]. In such cases, unifying treatments are limited and treatments for some conditions may worsen symptoms of another condition. The study reported in Paper 3 demonstrated one example of these challenges, with GPs commonly being requested to manage patients residing in nursing homes [14]. This group of patients have a high level of frailty and managing symptoms of pain can be challenging due to limited history from patients with cognitive impairment alongside the high risk of adverse drug interactions due to polypharmacy. The Ariadne principles of developing realistic treatment goals, which enable individualised management which consider the interaction of competing medications and/or interventions and prioritise patient preferences are particularly useful conceptually for this group [11]. There are inherent risks with both over and under-treatment of patients in nursing homes and finding the optimal approach can be challenging for individual GPs. The impact of this research has been demonstrated by being referenced as part of the justification of a systematic review reporting temporal trends in analgesia use in nursing homes [43].

The challenges for clinicians consulting and managing patients with multimorbidity are also associated with high healthcare costs [175,176]. Indeed, the annual costs of multimorbidity was reported in a 2022 systematic review and meta-analysis as between $800-$150,000, depending on disease combination, country and other study characteristics [175]. Despite some limitations regarding the standardisation of methods of data collection and cost prediction in different studies within the review, the study was timely reporting that certain diagnoses (such as mental health and cancer diagnoses) are associated with higher costs [175]. Efforts to identify combinations of conditions associated with higher costs alongside clinically relevant outcomes [e.g readmission, quality of life, treatment burden etc] may thus have dual benefit for health system sustainability and individual patients.

Developing approaches to support clinicians provide PCC to patients with multimorbidity is likely to be complex. For example, the use of a coalition of healthcare providers within the Camden Core Model (a care transition program) to support patients with high healthcare utility reported no significant difference in readmission between intervention and control groups [176]. The intervention, which involved intensive clinical and social components, excluded patients with cognitive impairment, those with complications of long-term disease with limited treatment options and uninsured patients which may have limited generalisability [176]. Furthermore, the RCT was also unable to discern whether there were improvements in other relevant measures such as patient satisfaction, engagement with care, treatment burden and prescribing measures. The nature of the challenges associated with delivery of clinical care for this group of patients makes designing, implementing and showing effectiveness of multi-factorial interventions difficult.

Recently health policy has influenced aspects of primary care with a particular impact on people with multiple long-term conditions. For example, continuity of care has long been identified as a fundamental component of general practice and has been crucial in the development of primary care systems over time [177]. Increased continuity of care is associated with improved quality of care, GP satisfaction, patient satisfaction, increased confidence in decision-making and the enablement of PCC [178,179]. These benefits can be of greater value for people with multiple long-term conditions, given the higher likelihood of healthcare contacts, polypharmacy, and hospitalisations [180]. Despite the benefits of continuity, government pressure to prioritise patient access to care arguably increases barriers to continuity of care [177]. A recent Modified Delphi stake-holder panel identified eight priorities for improving primary care access, with two addressing organisational structure targets (interdisciplinary primary care site leadership; clearly identified group practice management structure); four addressing process improvements (patient telephone access management; contingency staffing; nurse management of demand through care coordination; proactive demand management by optimising provider visit schedules), and two addressing outcomes (quality of patients’ experiences of access; provider and staff morale) [181]. This paper was from the USA and did not address how improved access should be funded but did draw on key areas which have been the basis of European work to improve and prioritise access [177,182].

One approach to improve access, especially in a climate of a shortage of GPs [177,183,184], has been expanded primary care teams (including physiotherapists, mental health nurses, paramedic practitioners, physician associates and nurse practitioners) [182]. This approach aims to ensure 'right person, right time' based healthcare, but for those with multimorbidity can further exacerbate fragmentation of care, make navigation of care more difficult, reduce PCC with team members working within their silo of expertise, alongside reducing patient satisfaction. The implementation of expanded primary care teams should not be 'one-size fits all' and should account for practice and population needs [185]. Addressing the complex nature of current difficulties in primary care is challenging, and continued research and effort is required to support continuity (e.g. Health Foundation and Royal College of GPs collaboration [186]) and consider how other policy approaches to address problems within primary care may impact people with multimorbidity.

Challenges associated with managing discordant multimorbidity are exacerbated in areas with higher rates of socioeconomic deprivation, with patients in these areas presenting with multimorbidity at an earlier age and more likely to have mental and physical health multimorbidity [187]. Socioeconomic inequality represents a significant public health challenge in the UK, with one in three premature deaths in the UK attributable to this inequality [187]. An early age of onset of multimorbidity is a clear indicator of the challenges facing preventative medicine and this is discussed in more detail in Chapter 4.3.

Multimorbidity, despite work exploring disease clustering, is generally accepted to be a heterogenous condition [40,51]. This has significant implications for the interventions required to address the impact of multimorbidity on patients and healthcare providers, with a single disease or symptom-focused interventions unlikely to be particularly efficacious. The studies reported in Paper 1 and 2 demonstrate that focusing upon single disease guidelines to optimise therapeutics for patients with multimorbidity is associated with complex self-care and treatment regimens suggesting that a pragmatic balance is required for care delivery [12,13]. The challenges of clinical guidelines in their current form are that it makes aspirational approaches to care such as the Ariadne principles very hard to deliver.

There are parallels with interventions developed to promote healthy ageing and mitigate the impact of frailty. These interventions cannot be overly focused on single measures as geriatric syndromes are also commonly heterogenous in their presentation and manifestation [26]. The impact of the studies reported in Paper 1 and 2 [12,13] on the broader literature is significant, with my contribution relevant to helping shape the development of clinical guidelines for patients with multimorbidity [40].

It can be challenging for GPs within a busy clinical environment to find the terminology of multimorbidity particularly helpful presently. Indeed, many patients with multiple conditions are not complex particularly when concordant, and other patients with single diseases may be complex. The relationship between multimorbidity and complexity is not linear in terms of disease count, rather it reflects the challenges of delivering generalist care which is personalised to the patient alongside the interaction between individual conditions. The individual GP is often well placed to recognise this complexity [188]. GPs may be in a good position to place the diagnoses and medications in context, to support patients identification of realistic treatment goals, individualised management and patient preferences in the clinic.

A guideline for patients with multimorbidity was published in 2016 [40], providing welcome advice for clinicians managing patients with multimorbidity. However, the guideline provides generic rather than specific advice due to the extensive heterogeneity that exists in this group of patients and, like the Ariadne principles, provide a framework to approach care delivery. An underlying challenge for clinicians remains that although there is evidence that clinical practice guidelines are associated with positive healthcare outcomes [189], they are generally developed within a single disease framework. Many disease guidelines do not consider the cumulative impact of treatment and therapeutic recommendations upon patients with multimorbidity or consider the availability of such interventions as demonstrated in the studies reported in Papers 1 and 2 [12,13]. For example, NICE guidelines recommended that a 75-year-old man with type-2 diabetes uncontrolled by diet and chronic obstructive pulmonary disease, be prescribed five medications as a minimum, with up to eight other drugs routinely recommended depending on the intermediate outcome control, symptoms and progression of the diseases [13]. He would be advised to routinely engage in six self-care and lifestyle alterations, with others recommended under some circumstances (e.g. complications associated with diabetes) [13]. The study reported in Paper 1 provided an example of a real-life clinical case that GPs will commonly encounter, with individual patient stories remaining an important part of the broader evidence base [12]. In this case, the fact that the patient came to the GP with frustration about clinical care decisions, was particularly important for onward discussion. The study reported in Paper 1 was often used as a basis for discussions around multimorbidity and GP decision-making in medical student teaching delivered as part of my teaching roles [12].

Polypharmacy is common in multimorbidity as clinical guidelines are more focused on starting treatments and provide limited guidance on when and how to stop treatment. Polypharmacy in the context of multimorbidity itself is recognised as an area of difficulty for patients and clinicians alike [54]. Following guideline recommendations for patients with multimorbidity can be associated with a significant treatment burden [12,13,190], as patients can be advised to attend multiple uncoordinated hospital and primary care appointments for single diseases, adhere to often complex medication regimes (whilst being aware of important side effects) and perform self-care recommendations alongside living their normal lives. The study reported in Paper 5 highlighted that psychoactive drug prescribing has increased in prevalence in older patients within Tayside from 1995 to 2010, with a particular increase in antidepressant medications [RR=2.5 (95% CI 2.41–2.59) $p<0.001$] and opioid analgesia [RR=1.21 (1.19–1.24) $p < 0.001$]. Changes in prescribing patterns were potentially influenced by changes in clinical guidelines (recommendation of antidepressants for moderate depression; reduction and cessation of hypnotic medications), and safety concerns (the withdrawal of thioridazine from the market influenced the reduction in neuroleptic drug prescribing) [16]. The impact of the work is clear, highlighting that prescribing practice changes over time for a variety of reasons, but these changes are unequally distributed across population groups.

PCC is valued by patients [69] and is increasingly an important component of healthcare employee practice [70]. However, the dimensions of PCC are broad and include patients’ preferences, information and education, access to care, emotional support, family and friends, continuity and transition, physical comfort, and coordination of care. These are valued differently by different patients meaning the type and manner of care delivery will differ significantly between patients and there are challenges with the measurement of PCC [191]. Unfortunately, clinical research focusing on PCC to improve clinical care for patients with multimorbidity has not been particularly positive to date [192,193].

More broadly, existing clinical guidelines are usually based on evidence from RCTs carried out in relatively narrow subsets of the population, which may not be representative of the patient population seen in general clinical practice [194]. There are broader challenges around the prioritisation of high internal validity at the expense of external validity, and limited follow-up times [194]. Given that the trial evidence is based upon a homogenous group of patients due to rigid inclusion and exclusion criteria, the drug/intervention may be useless for patients with multimorbidity with clinicians extrapolating that there ‘may’ be a benefit for this patient group.

Shifting towards the use of routine data, as in the study reported in Paper 5 [16], may help the future evidence base for patients not presently well served by RCTs. A systematic review of qualitative research highlighted that GPs reported three major challenges in delivering care to patients with multimorbidity [195]. These were (i) practicing without supporting evidence due to the limitations of the current evidence base, (ii) clinical uncertainty associated with the complexity associated with multimorbidity and (iii) working with a fragmented healthcare system designed around single medical specialities [195]. Addressing these issues would help address some of the challenges noted in the studies reported in Paper 1 and Paper 2 [12,13] in interpreting and implementing clinical guidelines for patients with multimorbidity in the community.

3.3. Research Challenges

The research reported in six original papers that meet the requirements for this PhD by Published Works contribute to the considerable research associated with multimorbidity, the response of GPs and wider health and social care policy. Over the last 15 years, there has been extensive focus on the epidemiology of multimorbidity, its measurement and its impact on physical and psychiatric functioning [51,193]. It is understood that multimorbidity is common, with prevalence likely to increase to 67.8% by 2035 from 54% in 2015 [196], with significant implications for healthcare systems in high and lower-middle income countries alike [51,52]. The association between deprivation and a higher incidence of multimorbidity, alongside associations with a variety of negative health outcomes (functional impairment, hospital admission etc.) has also become clear [51].

The widespread use and recording of chronic disease metrics in electronic systems within primary care across Europe and North America have aided the development of large datasets to answer pertinent research questions [197]. The studies reported in Papers 5 and 6 both interrogate large datasets to try and answer research questions surrounding psychoactive drug prescribing and the rate of hospital readmission together with the underlying causes [16,17]. The linkage and analysis of large representative datasets to develop actionable knowledge for clinicians remains the aim. These data can provide real-world real-time information about certain patient groups under-represented in clinical trials (e.g. patients with multimorbidity), with some data being monitored in real-time providing real potential for clinical research. There remain numerous methodological challenges to ensure high-quality complete data (missing or incorrect data), and some datasets require complex analyses with specialist expertise [198]. Some of these challenges have been experienced whilst developing for care home patient datasets in the UK [199].

In the study reported in Paper 6 together with my team, I aimed to link social care data with the geriatric hospital dataset but this was not possible due to significant data gaps and input errors [17]. For example, it would be apparent from National Health Service [NHS] data that a patient was a nursing home resident but the social care data would report they were receiving a twice-daily package of care as it had not been updated for 18 months. This was disappointing, as being able to interrogate the relationship between important social care measures (package of care, recent respite care etc.) and hospital readmission would have been extremely useful. Given that health and social care integration is becoming an increasing area of policy focus, it would be hoped that integration of health and social care datasets can be developed to help answer important research questions in this area alongside effective information sharing between health and social care. This was proposed as part of the 2021 Nuffield Trust report on health and social care integration [10], but there remain significant barriers to overcome at the present time [200]. Greater use of administrative data may well be able to continue developing an understanding of hospital readmission for geriatric patients in the study reported in Paper 6 [17]. This could involve looking at targeted sub-groups such as those residing in long-term care and interrogating any benefit of multi-faceted mitigation strategies such as the use of Hospital @ Home service or Enhanced Care in Care Home teams which have been developed across Scotland.

The Academy of Medical Sciences report [51] into multimorbidity recommended a standardised definition and classification system for multimorbidity. The definition of multimorbidity agreed by the report, was the co-existence of two or more chronic conditions, each one of which is either:

- A physical non-communicable disease of long duration
- A mental health condition of long duration or,
- An infectious disease of long duration

Data collection and the availability of certain data was an important limitation in some of my own work. For example, had the regional Scottish prescribing dataset, which forms the basis of research reported in Paper 5 [16], included detailed information on clinical diagnoses, social care use and hospital clinic attendance the scope of the questions posed could have been extended. The limitation of poor data collection and maintenance preventing effective integration of health and social care datasets in research reported in Paper 6 [17] has already been outlined. These challenges were identified as part of the Academy of Medical Sciences Report [51], recommending that multimorbidity research should have standardised data collection in order to standardise the evidence base and datasets [201]. Furthermore, combining different sources of data, such as administrative and research datasets, may increase the capture of relevant clinical information in this area [202,203].

The development of large datasets holds promise in interrogating relationships within the diverse group of patients with multimorbidity [204,205]. During the review of research for this PhD, the clear definition of aspects of the research projects and consideration of data integrity before analysis was very important and this remains so. For example, significant efforts were made deciding the definition of centrally active drug prescribing prior to data collection in the study reported in Paper 3 [14], definitions of psychoactive medications in studies reported in Paper 3 and 5 [15,16], selection of diagnoses for hypothetical patients in the study reported in Paper 2 [13] and the selection of appropriate and informative readmission time-points in the study reported in Paper 6 [17]. If some of the limitations of current administrative datasets are addressed, this may have significant implications in research areas such as readmissions, frailty and multimorbidity where interventions often need to be multi-faceted.

The Academy of Medical Sciences report was timely and hopefully will promote research which develops a better understanding of the challenge of multimorbidity, developing strategies that can enable clinicians and healthcare systems to improve clinical care for this heterogenous group of patients [51]. This complements the recommendations from the 2021 systematic review which suggested focusing upon the patient experience of care, optimising medications management and targeted support of health behaviours likely to benefit a variety of diseases [206].

A 2021 expert consensus reported a patient-centred framework for multimorbidity research to identify gaps in the research literature, with one particular core finding being the need to focus upon universal outcomes (functional status, quality of life and mortality) [207]. Figure 2 demonstrates the framework incorporates the concept of concordant and discordant comorbidity, and includes potential causes, interactions, and outcomes. Further research focusing upon gaps in study design (longitudinal studies to examine onset of multimorbidity), patient inclusion (studies of multimorbidity in rare diseases or under-served populations) and interventions were suggested as the priority moving forwards. There are inherent limitations to expert consensus publications but identifying universal outcomes as a way of focusing research outcomes on a heterogeneous population is a useful endeavour and may enable better comparison between studies and clinically relevant measurement for patients. Furthermore, universal outcomes are helpful to consider in relation to the Ariadne principles as patients may identify functional improvement or quality of life part of their treatment goals.

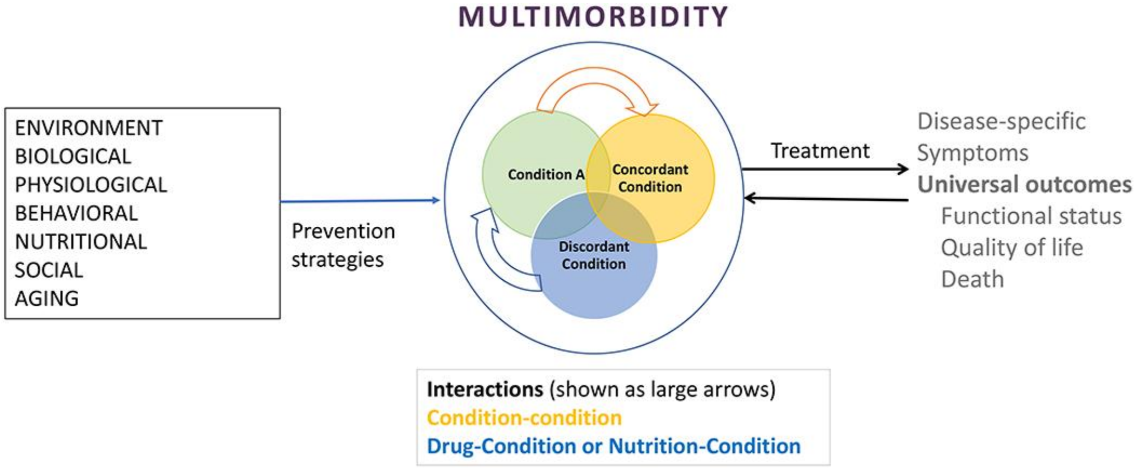

Figure 2: Conceptual model and research framework for multimorbidity, depicting relationships among causal factors, disease conditions and interactions, and outcomes of multimorbidity. [207]

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The transition from multimorbidity research findings to real change in the clinic has been slow. The challenges identified by my research such as polypharmacy and prescribing decision making remain as relevant now as when I commenced my research. For example, the study reported in Paper 1 and 2 [12,13] called for changes in the way clinical guidelines were developed and applied to patients with multimorbidity and, although there has been some change towards this, it has not filtered down to many GP clinics yet. In the context of these continued challenges, three core questions remain for clinicians:

1) What clusters of conditions should prompt prioritisation for clinical teams to target efforts to improve coordination of care?

The narrative presented in this thesis has focused on multimorbidity as distinct from simply the additional effects and treatment needs of the separate conditions. Clearly, different clusters of conditions will have their own specific implications. Understanding how clusters of diseases affect people and populations is key to the ideas developed within my published work.

Recent research in 2022 used sequence analysis to understand the sequencing of common chronic diseases that lead to multimorbidity [208]. There are limitations to this methodology as sequences were reconstructed from three diseases only (cancer, cardiovascular disease and diabetes), as more diseases would have produced more trajectory states and become more difficult to interpret [208]. Despite these limitations, the identification that patients who were older, less educated and lived in more deprived areas had accelerated trajectory of illness and higher admissions to hospital is pertinent. Thus, healthy ageing and policy targeting the social determinants of health and preventative medicine may need to be prioritised.

The Spanish Chronic Care Program started in 2011 has been working to improve the identification and management of complex chronic and advanced chronic diseases and developed an approach to characterise groups of complex chronic patients (using physical and social domains), who have a greater usage of primary and secondary care [209].

There is optimism that such work may be generalisable internationally, with work analysing UK, Canadian, American and Irish datasets reporting the presence of similar disease clusters and risk factors related to these conditions, albeit with different probabilities of occurrence [210]. Furthermore, there has been interesting work on English and Welsh NHS datasets, which has developed an understanding of the chronological development of multimorbidity [204,211]. Clustering and the temporal order of the cluster sequence are important, as rates of morbidity may vary significantly [191]. For example, in real and hypothetical patients within studies reported in Papers 1 and 2 information indicating which conditions should be targeted first in terms of outcomes would be helpful [12,13]. Should clinicians focus on depressive symptoms before hypertension management? Are outcomes different between patients who develop hypertension after a diagnosis of depression or for those who develop depression after a diagnosis of hypertension?

It is hoped that such work will be further refined and developed over time to enable GP practices to identify groups of patients who will benefit most from targeted interventions and make the most of finite primary care resources.

2) What are the processes for making clinical decisions in the context of fragmentary evidence for patients with multimorbidity?

Inevitably, the body of work presented by my research and associated six publications, and the wider academic work has considerable gaps which leaves clinicians with challenges in how to manage the complexities of multimorbidity.

There has been exciting British research which aimed to improve the utility of clinical practice guidelines for patients with multimorbidity [212]. The authors used three conditions (type 2 diabetes, depression and heart failure) to attempt to cross-link recommendations between guidelines to help identify potential interactions, making the guideline interface easier for clinicians to compare the effectiveness of recommended therapies and to note how long it takes treatment benefit to arise which may aid decision making for patients with limited life expectancy [212]. This work has taken forwards a key concept in research reported in Paper 2 [13], and similar work published in the United States [213]. This provides an example of the significance and impact of the published work.

If this work can be extended to other common physical and mental health conditions, this could really impact the delivery of guideline-based care in general practice. For example, a GP reviews a 76-year-old patient on 8 medications, with a past medical history of depression, hypertension, type 2 diabetes and osteoarthritis, in the clinic after an elevated blood pressure reading was noted in an annual review with the practice nurse. The GP feels increasing an anti-hypertensive agent may be indicated based on a case note review. An online reference providing guidance on interactions between different medications, and the time required for the patient to be on medication before benefit is experienced would be helpful for the GP to have a patient-centred discussion about management options.

These approaches may provide possible solutions to some of the challenges identified by my research such as fragmentation of care and polypharmacy associated with delivering guideline recommendations [12,13]. By extension, these approaches may also improve the delivery of safe psychoactive drug prescribing for nursing home residents [14], and those with mental health diagnoses [15,16]. For example, determining the numbers needed to treat for secondary prevention may be very helpful when prescribing for nursing home patients or early identification of clinically relevant drug interactions for physical-mental health multimorbidity. With research being targeted toward high-yield and clinically pertinent targets around multimorbidity, it is anticipated that interventions for primary care providers in the coming years may be able to make a real impact for patients with multimorbidity.

3) How do we helpfully distinguish multimorbidity from related concepts of frailty, and complexity?

Multimorbidity has several associated concepts, such as frailty and polypharmacy. Work has shown simultaneous presence, and interaction between multimorbidity and frailty [214], with other research reporting interacting relationships between polypharmacy, frailty and multimorbidity [215-217]. Throughout the period of research and research projects which led to the publication of my six papers, these were common themes which were discussed and explored in the context of each research project.

A significant difficulty remains regarding how these terms can be utilised to drive forwards clinically useful developments. Further research investigating the relationships between them remains important but is also needed to shape these concepts into helpful definitions for use ‘in the clinic’. For example, does a diagnostic note stating ‘frailty – severe’ on a patient electronic record change the clinical care provided by a GP and, if so, how? How can these terms be used to modify and personalise the clinical care provided to these patients to ensure meaningful outcomes? Such outcomes may be varied and could include patient experience, drug effects, hospital (re)admission or physical symptoms. Significantly, in research reported in Paper 3 the majority if not all patients reviewed by the GPs in the nursing home in Dundee would be coded as ‘frail’, but this on its own does not impact the care delivered [14].

The benefit of this approach can be considered through research reported in Paper 1 and 2 on guidelines [12,13] and Paper 6 regarding geriatric readmissions [17]. Providing evidence that for patients with multimorbidity, following guidelines per se may increase the treatment burden may prompt providers to adapt services to mitigate against this. For example, through the combination of congruent chronic disease clinics to reduce duplication of care or to arrange for more complex patients to be reviewed by clinicians rather than by other healthcare staff in chronic disease clinics. The studies reported in Papers 3, 4 and 5 all consider prescribing challenges in the context of multimorbidity [14-16], often driven as indicated by the author’s work by guideline recommendations [13]. Further work focusing on how the recommendations of the new multimorbidity guideline have been implemented and what barriers remain for the delivery of PCC may be opportunistic areas to extend the work discussed in this thesis.

Reporting that patients readmitted to hospital after geriatric rehabilitation were frail is not practice changing [17]. However, understanding that frailty itself means that patients are more likely to be readmitted at 30 or 180 days for a condition unrelated to their initial presentation is useful for systems change [17]. For example, developing responsive follow-up programmes and social care systems to support patients felt to be particularly vulnerable to readmission (e.g. patients with previous myocardial infarction, congestive cardiac failure, diagnosis of active cancer, and chronic obstructive pulmonary disease) may have a role in mitigating readmission rates after in-patient rehabilitation [17]. However, presently there seem to be no clear multimorbidity combinations for a cluster-targeted intervention approach which can reduce admissions and reduce associated secondary care costs [218].

The progression of research, to clinical and policy change, is an exciting area of possible development.

3.4. Policy Challenges

Multimorbidity has significant implications for healthcare systems, and health policymakers alike. The increasingly specialised care and interventions for specific chronic conditions are becoming more expensive, and not providing patient-centred sustainable healthcare for patients [192,219]. The priority of policymakers engagement in the solutions to this challenge is vital for a number of reasons.

3.4.1 Ageing Populations, Morbidity & Mortality

There is considerable debate about the relationship between ageing populations and morbidity in the literature. These relationships may actually increase the significance of some of research findings. Firstly, Gruenberg [220] proposed that with increasing ageing will come increasing morbidity. He argued that better medical care will reduce mortality associated with chronic disease complications, and therefore increase life expectancy, rather than reducing the incidence or rate of progression of chronic disease thereby increasing the period of time spent with ill-health associated with these diseases before death (“expansion of morbidity scenario”). Secondly, in contrast, Fries [221] contended that the time patients spent with significant morbidity could be compressed into the later years of life by achieving better health into older age (“relative compression of morbidity scenario”). This would involve significant and varied medical and biopsychosocial interventions to achieve a broader focus on healthy ageing [222].

Manton proposed a “dynamic equilibrium”, viewing mortality reductions as, at least in part, the result of reductions in the rate of chronic disease progression [223]. This scenario argues that with declining rates of chronic disease progression there will be delays in the occurrence of severe disease states, but there will equally be a redistribution where the rates of milder chronic disease will increase. Therefore, the proportion of time spent with serious disability will be reduced but the time spent with mild to moderate disability will be increased at an individual level. These competing visions are relevant to multimorbidity, with the dynamic equilibrium [223] and expansion of morbidity scenarios [220] proposing significant increases in the presence of chronic disease. There are reported differences between ageing populations and the influence on morbidity patterns between different developed countries [224-228], but it is clear that multimorbidity as a healthcare issue and hence of ideas developed in this narrative, is going to be of increasing importance in future years.

The impact of some of these theories of ageing, and predicted increasing rates of morbidity and chronic disease reinforces that multimorbidity is here to stay in the longer term. My work has indicated key issues with speciality guidelines [12,13], highlighted that recommendations aimed to be beneficial (e.g. to reduce benzodiazepine prescriptions) can have unintended consequences [15] and that patients with frailty and multimorbidity are vulnerable to readmission from multiple causes so clinical attention is required across all of their conditions to try and keep them in the community [17].

There have been several policy efforts to try and mitigate these challenges. In Scotland, the 2021 *'A Scotland for the future: opportunities and challenges of Scotland's changing population'* prioritises healthy living, aiming to increase healthy life expectancy and drive innovation for an ageing society [229]. The leading cause of death in Scotland presently is ischaemic heart disease and as such targeted preventative health measures have the opportunity to reduce morbidity as people age

[229]. This is reflected in the Scottish plan which involves increasing exercise and activity programmes, diet and weight management schemes and remobilisation of services after Covid-19. In England, *'Ageing Well'* is a theme within the NHS Long Term Plan [230]. The workstream aims to promote a multidisciplinary team approach to support older people living at home independently, provide NHS support to long-term care providers, and develop rapid community response teams to reduce hospital admissions [230].

In addition to understanding the impact of ageing and morbidity across countries, further details about the distribution of morbidity across different geographical areas are important for policy planning. For example, it is well documented that older patients are not evenly distributed across the UK with greater proportions in rural and coastal areas [231]. The study reported in Paper 4 [15] reported anxiolytic and hypnotic drug prescribing data in a relatively deprived practice population and it is likely that different results would have been reported in line with findings from research reported in Paper 5 if the work was performed in a different practice [16]. This may be extended to the study reported in Paper 3 [13] with the nursing home being located in a deprived area of Dundee. The relevance of the nursing home location on patient health (in the years prior to admission to the nursing home) may be mitigated as many people move significant distances to be admitted to a care home of their choice but the pressure on GP practices in these localities may influence the proactive nature of care provided.

Consideration must be given to the social determinants of health with an appropriate focus on multimorbidity burden. The relationship between social disadvantage and multimorbidity is complex [232], but it is clear that socioeconomically disadvantaged individuals have earlier onset and more rapid accumulation of multimorbidity resulting in widening inequalities into old age [233]. Furthermore, general practice, which is not funded to match the clinical need of practices, may actually increase health inequalities [234] and perpetuate the inverse care law (the principle that the availability of good medical or social care tends to vary inversely with the need of the population served). Reducing socioeconomic inequalities and improving preventative medicine should be considered an important feature of policies to address multimorbidity. Health inequality and multimorbidity is further discussed in Chapter 4 (4.3).

3.4.2 Sustainable Healthcare & Finite Resources

Patients with multimorbidity are responsible for more than half of all healthcare utilisation, with significant implications for Governments and policymakers [235]. Healthcare budgets are increasingly stretched, and there have been a variety of approaches across Europe to address this including service restructuring, centralisation and integration of health services, adjustments in salaries of clinicians and a focus on efficiency and quality within healthcare services [236]. Furthermore, there is rising awareness of the impact that an ageing population and the increasing prevalence of chronic disease may have on future expenditure due to reductions in the relative numbers of taxpayers and challenges upon the healthcare workforce in the years ahead [235,236]. These factors require mitigation and have led to sustainability becoming an important consideration for policymakers. Sustainability, defined as the capacity of a health service to deliver healthcare over time with consideration to future generations, is now considered a metric of quality in healthcare [237]. It incorporates a variety of important facets of health systems including quality improvement programmes, process and systems design, resource allocation and workforce planning issues across an integrated healthcare system [237-239]. As previously outlined, *Realistic Medicine* and other associated work-streams demonstrate that sustainability is an increasing part of the health policy landscape.

In the context of multimorbidity, these approaches to care are particularly important. For example, research reported in Paper 2 highlighted polypharmacy associated with clinical practice guideline implementation, with limited information regarding the value of these additional medications at an individual patient level [13]. Using research reported in Paper 3 as an example, GPs delivering more effective pain management to patients with dementia may add significant personal value and allocative value compared to other medications recommended by guidelines for secondary prevention [13].

The broad concept of *Realistic Medicine* has included efforts to improve prescribing by reducing inappropriate polypharmacy, implementing clinical practice guidelines through the lens of PCC, and supporting patients to stay at home alongside environmental sustainability initiatives. The Kings Fund has linked sustainability with a recommended important cultural shift, towards ‘shared responsibility’ for health rather than ‘personal responsibility’ [240]. Shared decision-making enables patients’ own preferences to be considered and may lead to conservative options being taken by patients as the fundamental value of an investigation or test may be seen differently between a clinician and patient [240]. For example, patients with advancing chronic kidney disease may choose conservative care rather than renal replacement therapy (i.e. dialysis), which may shorten their life but may improve quality of life and reduce costs associated with haemodialysis.

Reducing over-diagnosis and over-treatment is an important component of developing healthcare sustainability, and shared responsibility for health decision-making may be part of the way to achieving this [241-243]. The approach can also be used to develop PCC through goal setting [244] and has been instrumental in the development of the Chronic Care Model [245]. This work has been developed from the now 20-year-old Institute of Medicine report which recommended a change from ‘professionals controlling care’ to the ‘patient as the source of control’ with key components noted in Table 4 [246].

Table 4. Simple rules for the 21st-century health care system – Institute of Medicine [246].

Current Approach	**Recommended Approach**
Care is based primarily on visits	Care based on continuous healing relationships
Professional autonomy drives variability	Customisation based on patient needs and values
Professionals control care	The patient as the source of control
Information is a record	Shared knowledge and free flow of information
Decision-making is based on training and experience	Evidence-based decision-making
Do no harm is an individual responsibility	Safety is a system property
Secrecy is necessary	The need for transparency
The system reacts to needs	Anticipation of needs
Cost reduction is sought	Continuous decrease in waste
Preference is given to professional roles over the system	Co-operation among clinicians

One important way to reduce future healthcare burdens, and thus improve sustainability, is to improve the management of chronic conditions and those with multimorbidity [236,237]. Clearly the body of literature discussed in this narrative contributes to the consideration of how managing these complex clinical situations can be done more effectively.

Firstly, the development of clinical practice guidelines and protocols has had significant benefits in terms of standardising clinical care and improving outcomes [48,247,248]. Financial incentives have also been used to encourage practitioners to deliver an intervention or care standard, as has used data to provide an inter-practice comparison in target areas (e.g. antimicrobial prescribing rates) [249]. However, there are associated limitations when they are implemented without due consideration for multimorbidity [18,71]. Research reported in Paper 1 and 2 consider these challenges specifically [12,13]. Future guidelines should support shared decision-making between patient and provider [11] and improve the utility of clinical practice guidelines outlined previously [18,71]. Furthermore, clinicians should continue to have a crucial role in working with patients to deliver treatment through the lens of PCC. Agreeing and working towards realistic treatment goals is a salient part of this approach, in line with the Ariadne principles.

Secondly, training for clinicians specifically for patients with multimorbidity is potentially an important area albeit with a limited evidence base at present [250]. The Royal College of GPs has made efficient management of multimorbidity a clinical priority and are funding research and targeting quality improvement to attempt to understand the barriers to providing holistic care to patients with multimorbidity in primary care, alongside showcasing best practice exemplars and highlighting the importance of effective multimorbidity management for GPs [250,251]. Future research extending findings from the author's current work may consider using financial incentivisation strategies to deliver sustainable healthcare and patient-centred consultations. The role that financial payments for performance have upon prescribing were discussed in research reported in Paper 4 [15] and exploring their role further in delivering safe and sustainable multimorbidity care would be clinically helpful.

Secondary prevention of multimorbidity, such as targeted management of diabetes to avoid chronic kidney disease, vascular disease or hypertension to reduce the risk of stroke has been proposed, with some evidence to suggest that this may be both clinically beneficial and cost-effective [252,253]. Although it is likely that particular combinations of concordant conditions will offer greater opportunities for cost-effective interventions for unifying risk factors, there remains a risk that focusing upon individual diseases in patients with multimorbidity may exacerbate some of the broader challenges already touched upon, including inappropriate polypharmacy, fragmentation of care alongside not being responsive to the increasing need to adopt a patient-centred [12,13].

Alongside secondary prevention, primary prevention through interventions targeting health behaviours, such as exercise [254], has been shown to be effective and safe for patients with multimorbidity. A recent systematic review reported greater improvements in physical activity and weight loss when specific behaviour change techniques were utilised, which may have utility for policy makers [255]. However, it should be noted that the small number of studies matching the inclusion criteria did lead to inconsistency in estimates of the meta-analyses. Furthermore, the majority of the patients included in the meta-analyses were of white ethnicity, of higher socioeconomic status with a limited range of conditions and this reduces the generalisability of the systematic review findings [255].

Pain syndromes and mental health comorbidity in patients with moderate to severe dementia are often undertreated due to communication difficulties, highlighting that efficacious prescribing for patients with multimorbidity does not simply mean a reduction in medications but rather every medication must add genuine value to the patient in terms of risk reduction, symptom relief or patient safety. Research reported in Paper 3 contributed to the field, primarily by highlighting that within one unit patients may experience overtreatment of one symptom (behavioural and psychological symptoms of dementia) whilst also being undertreated for another symptom (pain) [14]. The concurrence of over and undertreatment is especially important in patients with dementia, with the literature being clear that pain syndromes are often under-recognised [110,256,257] and that neuropsychiatric symptoms associated with dementia may be treated early and potentially inappropriately with psychotropic medications [18-19]. Building on this work to improve prescribing for this group of patients continues to be an area of research and policy focus [258] and an area that I continue to research as a GP.

3.4.3 Financial Incentives, Socioeconomic Factors & Strong Primary Care

The body of work on which this submission of work founded is a demonstration of my belief in the importance of primary care in the lives of people, especially so in the context of ageing populations and its implications for multimorbidity.

To deliver effective healthcare to patients with multimorbidity, there are several areas of policy that should be considered. These include the role of financial incentives, which has been a core policy to drive forward health improvement for some time, alongside the implications of socioeconomic factors upon care delivery and outcomes. A well-resourced multi-disciplinary primary care system continues to be important for the delivery of coordinated care for patients, linking into secondary care systems, whilst preventing negative healthcare outcomes such as hospital readmissions [259].

Using community-based prescribing data in research reported in Papers 4 and 5, the author highlighted challenges with utilising financial incentives to improve prescribing practice [15], and that older patients in more deprived socioeconomic groups were more likely to experience increased rates of psychoactive drug prescribing over time [16].

Financial incentives to improve prescribing and reduce costs have significant limitations [260,261], and for heterogenous patients with multimorbidity, careful consideration is required prior to implementation to avoid perverse outcomes for certain patient groups [262]. There has not been enough evidence generated to suggest that financial incentives have improved primary care as a whole [262]. The research extended previous data that clinicians prioritise targets if financially incentivised by commissioners, which may come at a cost (such as reduced continuity of care) [262,263]. It would be challenging to see how financial incentives could be used to promote more qualitative measures, such as the Ariadne principles.

In work published following the publication of this work, researchers reported that the Quality and Outcomes Framework (the payment framework for UK-based general practice, Scotland opted out in 2016) (QOF) is associated with difficulties for patients with multimorbidity including multiple payments, with sums paid not reflecting the actual workload of practices managing these patients [264].

In a population data analysis, research presented in Paper 5 [16] reported an increase in psychoactive drug prescribing in Tayside over 15 years, and a disproportionate increase experienced by patients in lower socioeconomic groups reflecting the importance of social determinants of health. Indeed, one of the leading drivers of multimorbidity [265] and polypharmacy [266] is socioeconomic disadvantage alongside increasing age. However, although poverty can be considered a risk factor for mental health disorders [267,268], the relationship is far from simple as it is not causal and can be bidirectional [269]. Higher prescribing rates may reflect limited access to non-pharmacological therapies which may be addressed with concerted efforts [269], alongside GPs working in deprived areas seeing depression in the context of challenging life circumstances as a problem which is insolvable leading to an inverse care law in the management of depression [270]. Integrating services within areas of high deprivation such as mental health counselling services, social advice services and broader healthcare support may reduce some of the variation in healthcare provision and outcomes for patients with multimorbidity and improve sustainability.

Finally, supporting patients at home through local and national initiatives (e.g., hospital at home [271], rapid response social care services [272]) and preventing avoidable hospital admissions and readmission is another crucial facet of the promotion of sustainable healthcare for patients with multimorbidity and a key policy aim of UK governments. This requires robust primary care systems, with the four core primary care functions (first contact, comprehensiveness, coordination & continuity) being strongly associated with better quality services, lower costs, less inequality in healthcare and better population health [273-275].

There have been a variety of disease management and care coordination programmes to improve the quality and delivery of care and the management of patients at home. Indeed, team-based care (in particular, teams including pharmacists and mental health specialists) and smoothing the transitional points between primary and secondary care have been identified as areas that can reduce unwanted hospital admissions [276] although the effectiveness of these approaches is mixed [277]. There is evidence that integration of healthcare may enable patient access to services and improve patient satisfaction with services [278].

The author's research presented in Paper 6, reviewed hospital readmissions in a geriatric patient population after a period of in-patient rehabilitation [17]. The paper concluded that with an increasing prevalence of multimorbidity, particularly among those at increased risk of readmission, it is essential to step away from a single disease focus in the design of both hospital avoidance and chronic disease management programmes. It was significant that older patients undergoing in-patient rehabilitation have a generalised susceptibility to illness meaning that readmission rates were high and more commonly were due to a different reason than the initial admission to hospital. The current challenge remains that the delivery of uniform interventions is unlikely to yield significant reductions in readmission for older adults with multimorbidity due to their heterogeneity and may in fact lead to perverse outcomes due to disease-disease or disease-treatment interactions [279]. The impact of research into readmission after geriatric rehabilitation [17] is that multi-faceted interventions, which include the Hospital @ Home model of care, are important to develop and assess to see whether hospital readmissions can be mitigated. Hospital @ Home programmes can be considered a 'step-up' service (patients admitted to the service from the community) and/or 'step-down' service (patients discharged from hospital setting to community under Hospital @ Home care) with the latter having potential for multifactorial discharge assessment in a patient's home environment [280]. These community-based interventions will require well-staffed and funded primary care services for them to connect to the wider healthcare ecosystem. The author is involved in developing a Hospital @ Home service in Perth City to try and deliver these exact improvements.

A series of systematic reviews published in 2016 reported that there are data that education/self-management, exercise/rehabilitation and telemedicine may help to reduce unplanned hospital admission in selected patient populations [281]. However, in a similar vein to multimorbidity, clear strategies for reducing unplanned hospital admission [281], readmissions [282] and healthcare utilisation [283] remain elusive for complex patients with multimorbidity. This is despite the patient group being at particularly high risk of both [281-286]. For patients with multimorbidity and frailty syndromes, there is a greater likelihood of decompensation of individual disease processes, interactions between prescribed treatments (e.g. acute kidney injury and dehydration secondary to increased doses of diuretics for a patient with heart failure) and a higher risk of developing a post-hospitalisation syndrome, defined as an acquired transient period of vulnerability following in-patient admission [287].

There is no doubt that multimorbidity places significant challenges on both primary care and secondary care systems. My work has focused on several specific areas, including prescribing practice, financial incentivisation and hospital readmissions. Future work looking at multi-faceted interventions to enhance judicious prescribing practice, appropriately incentivisation and support for primary care providers to deliver preventative care and minimise hospital readmission is vital to explore broader health system change to improve care delivery for patients with multimorbidity. Healthy and sustainable general practice and primary care systems remain a core component of the delivery of healthcare to patients with multimorbidity [249,272], with practitioner-level interventions (delivery of patient-centred consultations) and larger policy interventions (implementation of primary care networks) being part of this vision. Continuous and real-time assessment of such interventions, where feasible, should be subject to regular review and research to target interventions which provide value to the healthcare ecosystem.

3.5. Chapter Conclusion

This chapter has reflected on the issues with which the body of literature used towards this submission for PhD by Published Works has contributed to understanding potential ways forward for primary care. It has demonstrated the originality of that work in tackling key gaps in knowledge. Given the implications of ageing populations for primary care, addressing those gaps is key to ensuring a sustainable primary care system. The likelihood is that these issues will only become more pertinent in the future, and hence the multimorbidity literature is going to become increasingly pertinent. My work is of course not the last word, and this chapter has also reflected on contemporary initiatives that have developed over the time since my research has been published, to which my work contributes, and that future work will build on.

Chapter 4 will explore multimorbidity through a primary care lens, consider how the Ariadne principles relate to the author’s published work and consider health inequality and its relationship with multimorbidity.

Chapter 4

Multimorbidity in Primary Care

4 Multimorbidity in Primary Care

4.1 Introduction

Over the last few decades, there has been a steady increase in prevalence of a variety of chronic diseases and multimorbidity with the majority of these patients being managed primarily within primary care [288,289]. Many health services, models of care and clinical practice guidelines are not designed to take into account competing diseases and treatment interactions for patients with multimorbidity as they navigate their longitudinal care [7,11,36]. Reorientation of the health system towards patient centred frameworks, such as the Ariadne principles [11], alongside greater consideration of other measures such as functional status or quality of life are vital [264].

Achieving this will be challenging and require change at a microscopic level (e.g. patient – clinician interactions in a consultation towards realistic treatment goals) alongside broader macroscopic level change (e.g. embedding patient centred care within primary care led chronic disease clinics).

This chapter explores the context in which my work sits, specifically multimorbidity, the Ariadne principles and health inequalities. Firstly, the chapter will outline PCC and value-based healthcare in the context of the Ariadne principles, whilst indicating how my work is aligned to the Ariadne principles. Secondly, the chapter will discuss the relationship between multimorbidity and healthcare inequalities and how my work considers this relationship.

4.2 Multimorbidity: through a primary care lens

Many GP consultations involve patients with multiple long-term conditions [170], and patients with multimorbidity have increased mortality and morbidity [166-169]. This can be seen as a challenge or an opportunity, whereby a reorientation of current clinical practice may lead to improvement of clinically relevant measures for patients. Indeed, supporting decision-making for patients with multimorbidity was the core purpose of developing the Ariadne principles in 2014 [11]. The need for an individualised, patient-centred approach to care means that a single multimorbidity pathway will be elusive, with treatment and interventions ranging for curative to palliative in their scope. Within primary care, the consultation between clinician and patient may have a therapeutic dimension in addition to any referral or prescription [290,291]. It is for this reason that a framework which supports clinician multimorbidity decision-making has potential value at a consultation level as demonstrated in Table 5.

Table 5 summarises how work published by the author relates to the core components of the Ariadne principles published by Muth et al in 2014 [11]. As shown, the Ariadne principles provide a supportive framework that puts into context the commonalities across the body of my work that links to multimorbidity and the role of primary care.

Table 5: The Ariadne Principles and Relationship to my Work

Ariadne Principles **[11]**	**Relationship to my Work**
Realistic Treatment Goals	**Paper 2 [13]:** demonstrated that UK clinical practice guidelines do not clearly support clinicians in the identification of realistic treatment goals or PCC outside generic statements. **Paper 3 [14]:** described the undertreatment of pain within a nursing home. Potentially identifying key realistic treatment goals for patients would help GPs prioritise clinical assessment and treatment. **Paper 6 [17]:** identified readmission after discharge from hospital is common even after in-patient rehabilitation. Proactive frailty care identifying realistic treatment goals may optimise medical treatments and support mitigation of readmission risk.
Interaction Assessment	**Paper 1 [12]:** described the impact and interaction of clinical guideline recommendations for an individual patient. **Paper 2 [13]:** demonstrated that UK clinical practice guidelines do not clearly consider the interactions between different conditions or treatments when making recommendations. **Paper 6 [17]:** reported that some clinical characteristics are associated with 30-day and 180-day readmission. These characteristics may be used to prioritise consideration of patients at high risk of disease-disease and disease-treatment interactions.

Table 5 (Continued): The Ariadne Principles and Relationship to my Work

Prioritisation and Patient Preferences	**Paper 4 [15]:** demonstrated of the limitations of using financial incentives to improve prescribing**.** Incentivising clinician action to prioritise PCC may be hard to achieve, and broader policy change would likely be needed. **Paper 5 [16]:** described an increase in psychoactive drug prescribing in Tayside that was more significantly seen in lower socioeconomic groups. Understanding patient preference, in part through understanding their concerns, is crucial to supporting judicious prescribing. **Patient 6 [17]:** demonstrated that hospital readmission is common and can be challenging to predict in older patients with multimorbidity with competing interactions. Supporting patients in the community requires identification of their priorities and preferences, to enable anticipatory care plans and clinician decision-making to take these into account.
Individualised management	**Paper 1 [12]:** described how the delivery of individualised management for long-term conditions was of benefit for the individual. **Paper 3 [14]:** reported the importance of identifying the undertreatment of pain syndromes in older patients with dementia. Individualised management of dementia care may help support the identification of symptoms of key importance, recognising that some patients may be at a much higher risk of iatrogenic harm than others. **Patient 6 [17]:** demonstrated that hospital readmission is common and difficult to reduce. Discussing the risk of hospital readmission with patients in a proactive way may support make individualised management plans. For example, does a patient wish to be admitted again acutely or could other options be explored?

The Ariadne principles represent an approach to refocus and align primary care management of patients with multimorbidity to one which is more patient-centred [11]. Such approaches should be considered in the context of increasing limitations associated with the biomedical model of care for patients with frailty [292] and multimorbidity [293].

For such a patient-centred approach to be implemented in the truest sense, high-value and team-based care will be needed given the multifactorial challenges facing healthcare systems for patients with multimorbidity [294]. Firstly, value-based healthcare aims to increase the value that is derived from the resources available from the population reducing overdiagnosis, overtreatment and undertreatment [72]. This concept has particular relevance for patients with multimorbidity, as a recommendation for an intervention based on a clinical guideline may have no value to the individual patient’s experience. A challenge in the assessment of value-based healthcare remains that is the discriminatory ability to differentiate between high-value care and low-value care for individuals. Presently to measure the outcomes of value-based healthcare providers measure population-specific outcomes [295], efficiency data [296], and clinician experience of providing care [297]. Further work is required to support the ability to differentiate between high-value and low-value care at a service, process and individual level.

Secondly, team-based care is needed to integrate and coordinate the management of long-term chronic disease for patients with multimorbidity (especially when concordant). Team-based care has been shown to improve chronic disease management for hypertension, diabetes and dyslipidaemia in a US retrospective observational electronic health record study [298]. This study had several weaknesses, such as a narrow definition of team-based care and the database not being nationally representative [298]. However, the demonstration that team-based care was associated with improved performance in terms of disease diagnosis, prescriptions, monitoring and disease control is an important finding and has been extended by other studies [298,299]. Primary care is well suited to team-based care, but it remains uncertain to date how these approaches deliver in terms of clinically relevant multimorbidity patient outcomes.

The four components of the principles will be discussed, in relation to my work [12-17] and recently published data. Placing my published work into the framework of the Ariadne principles has been a useful way of placing my work in context, alongside considering new avenues for future research.

Realistic Treatment Goals

GPs managing patients with multimorbidity commonly find that newly presented problems may be complicated by the existence of other conditions or prescribed medications. Early identification of what is important to the patient is a useful framing tool for this, which may influence management directly (by not prescribing a certain medication) or indirectly (focused counselling around certain side-effects the patient is worried about).

One of the inherent limitations of the Ariadne principles is that it remains challenging to demonstrate that the frameworks implementation improves clinically relevant outcomes. The implementation of the framework would also likely be varied depending upon the setting and nature of the research. The flexibility of a framework may have clinical utility but does lead to challenges within research domains. For example, there could be several ways that realistic treatment goals could be established with a patient (within normal clinical practice; as part of a multimorbidity or chronic disease clinic; using patient information forms). Furthermore, different members of the healthcare team could be involved in this process.

There has been recent work reporting an integrated model of goal-orientated shared decision-making which supports realistic treatment goals [300]. The framework, using three steps, proposes a way to identify patient goals alongside supporting them to be achieved through using a goal board to visualise the result [300]. Embedding goal setting into a model of shared-decision making may provide an operational approach to address the challenges associated for patients with multimorbidity, although further testing of the model is required [300]. Goal setting should be considered a prerequisite for decision-making for many people with multimorbidity [301], but clear evidence that the approach leads to improvements in outcomes is lacking presently. Overall, the approach has intuitive sense but limited data to showed improved clinical outcomes. For example, a 2022 scoping review and concept analysis reported that future research on goal-orientated care for patients with multimorbidity should focus on how and what goals are set by patients, how this knowledge is translated into work processes by healthcare teams alongside establishing the process of evaluation of goal-orientated processes of care [302]. A concept analysis does not provide a quality assessment of included papers, but the paper delivered an appropriate approach to outline the key components of goal-orientated care for patients with multimorbidity [302].

The author's work in 2012 [13] demonstrated the limitations in clinical practice guidelines in relation to PCC and realistic treatment goals. Other research published in Paper 3 [14] and Paper 6 [17], outline potential opportunities for the identification of realistic treatment goals. Proactive frailty programmes which support the identification of key goals of care, may improve pain management for patients with dementia (perhaps by adding as part of annual reviews). In relation to hospital readmission, if a patient prioritises home-based care over all else after a recent admission with hypotension and falls, then GPs may reduce the tightness of hypertensive control and glycaemic control thereby reducing the risk of hypotension and hypoglycaemia respectively. Realistic treatment goals are therefore relevant and are actively considered within the research which forms the basis of this thesis [13,14,17].

Shared decision-making is a joint process in which a healthcare professional works together with a person to reach decisions about care [303]. With advanced multimorbidity, the uncertainty of specific management decisions increases and shared-decision making is a way of working through this [304]. 'Total Uncertainty' was identified as a shared experience in a thematic synthesis across five domains which affected patients, carers and health professionals. The themes of 'appraising and managing multiple illnesses'; 'fragmented care and communication'; 'feeling overwhelmed'; 'uncertainty of others' and 'continual change' may be useful to consider in the context of identifying realistic treatment goals and subsequent action plans to achieve or maintain it [304]. As identified in the author's work published in Paper 1 [12] and Paper 2 [13], clinically useful recommendations for shared decision making with a strong evidence base are limited. Furthermore, a recent thematic analysis of 4 focus groups (2 with patients ≥65 years old and 2 with GPs) questioned the current use of shared decision-making in current general practice [305]. The authors reported an incorrect perception that most clinicians are already effectively implementing shared decision-making needed to be addressed, and that training in the communication of uncertainty and recent multimorbidity guidelines should be a priority [305]. NICE have developed various patient decision aids and tools to support clinicians deliver shared decision-making since the publication of my previous work [303], and the Royal College of General Practitioners is also developing training programmes in shared decision-making [306].

There are of course multiple barriers to deliver PCC [69,93], with recent work identifying the greatest perceived barrier being individual physician-patient interactions within consultations [307]. This work extends other data [288,290,291], which suggests potential value in considering the consultation as a means to address aspects of shared decision making and PCC for patients with multimorbidity.

Interaction Assessment

A variety of interactions are important to consider with regards to patients with multimorbidity. These include disease-disease interactions [e.g. poorly controlled diabetes leading to accelerating chronic kidney disease], disease-treatment interactions [e.g. anti-muscarinic medication for urinary symptoms are associated with cognitive dysfunction] and treatment-treatment interactions [anticoagulation for atrial fibrillation and antiplatelet treatment for ischemic heart disease] [288]. The agreed response to these interactions will differ between different patients, their level of function, frailty status and social context.

The Ariadne principles propose consideration of these interactions as part of a comprehensive assessment, prioritising review of complex medication regimes (through deprescribing and polypharmacy reviews), symptom burden and consideration of their direct impact on the patient and active monitoring for psychiatric symptoms such as depression and anxiety [11].

Interactions in the context of patients with multimorbidity has been considered in the context of the author's work. Research reported in Paper 1 [12] describes the impact that individual recommendations had upon the individual patient, whilst research published in Paper 2 [13] demonstrated the limitations of clinical practice guidelines in providing clinicians with useful information about interactions which could likely be anticipated.

The latter is essential, as drug-drug interactions between recommended drugs for different conditions are common and of clinical relevance [308]. There has been work using epidemiological data, which has demonstrated the ability of guideline recommendations to compare absolute benefit of long-term preventative treatments, inform decision-making around interactions alongside cost-effectiveness [212]. Despite the importance of some of these findings, the usability of guidelines in their current form to support rapid consideration of interactions remains very limited.

The authors work on hospital readmission published in Paper 6 [17], reported that some clinical characteristics are associated with 30-day and 180-day readmission, which will likely include different clinically relevant interactions. These characteristics may be used to prioritise patients at higher risk of readmission, and active consideration of interactions which may be associated with hospital readmission. Indeed, the MoPIM (**Mo**rbidity, **P**otentially **I**nappropriate **M**edication) multicentre prospective cohort study reported that different clusters of conditions (osteoarticular, psychogeriatrics, minor chronic disease and cardiorespiratory) had differing relationships between potentially inappropriate prescribing and adverse drug reactions [79,309]. There may be challenges in the reporting of potentially inappropriate prescribing and adverse drug reactions due to reporting differences between clinicians [310] but determining relationships between multimorbidity clusters and clinically relevant interactions (such as primary care consultations [311] or clinical trajectories [312]) may support targeted improvements in healthcare processes.

GPs use management reasoning in the context of multimorbidity [313], demonstrating that GPs keep their patients in mind throughout the consultation process [314]. The wide variety of treatment options available to clinicians can be perceived as challenging alongside the interactions between different conditions and treatment, meaning that the focus of consultations moves towards maintaining balance between evidence-based care, patient priorities and quality of life [313]. However, a recent qualitative review reported limited information is available regarding GPs clinical reasoning processes for patients with multimorbidity whilst commenting that GPs often underestimate their clinical reasoning skills [315]. It is likely that clinical reasoning will be key for patients with multimorbidity, due to the variety of interactions and heterogeneity of patients. Contextual considerations are a key area of future work and might profitably focus on GPs clinical reasoning and its potential relationship with other parameters such as PCC and deprescribing.

Prioritisation and Patient Preferences

Patients with multimorbidity can have competing symptoms and conditions to manage, and this requires prioritisation by the patient and healthcare provider alongside consideration of the patient preferences. The Ariadne principles outline that patient prognosis and currently active medical conditions should be taken into consideration, given that patients may swing between disease-specific symptoms (e.g. breathlessness in asthma) to generic (e.g. tired all the time) and the aim of treatment may change from curative, preventative to palliative over time. Furthermore, treatment goals should not be considered fixed, and should be regularly reviewed in a timely fashion to review progress and response to medications or interventions. The nature and duration of this review of progress and response remains undefined, given the individual context of each patient. Clinical guidelines are not well placed to deliver this nuance [12,13,18], and therefore interpretation and implementation of recommendations requires careful clinical judgement.

The Ariadne principles recommend taking time to clarify patient preferences by understanding their concerns, but this can be very hard to do in short consultations placing more importance on relational continuity. However, there is evidence from a systematic review that tools used in clinical care could improve identification of patient priorities and needs, and support partnership working between patients and practitioners [316]. The variety of tools identified, may form part of broader multi-disciplinary patient care, and could be collected by others in the team [317]. It remains important to note that clinical decision tools should be considered to support decision-making rather than replace it. Research published in Paper 6 [17], may demonstrate a useful example of where these tools could be used. Upon preparation for discharge after in-patient readmission, identification of important preferences for treatment would support GPs deliver important interventions such as deprescribing and reducing treatment burden. Furthermore, it may support the implementation of anticipatory care planning which is designed to anticipate, avert, or delay future functional decline through early identification of at-risk individuals [318,319].

Research published in Paper 5 [16] describing increased psychoactive prescribing for patients over 65 demonstrates that mental health, alongside physical health, social functionality and preventative care are all important domains for patients. Patients with mental health conditions may find that their psychiatric symptom burden changes over time, and this burden may impact their physical health significantly. Addressing hypertension may be harder when a patient is clinically depressed for example. Regular refocusing of patient priorities as new diseases develop or social context changes will be important in this context.

The call for primary care systems to be realigned to better reflect the experiences and perspectives of patients with multimorbidity by the Ariadne principles [11] has been reinforced by a recent integrative review of the qualitative literature [320]. The review focused upon literature that reported the perspective of people with multimorbidity, identifying 29 studies for inclusion [320]. The review reported five categories of experience and perspectives important for patients with multimorbidity: (i) care that is tailored to my unique situation; (ii) meaningful inclusion in the team; (ii) a healthcare team that is ready and able to address my complex needs; (iv) supportive relationships and (v) access when and where I need it. Furthermore, the review outlined the important role that patients have as partners in the design and evaluation of primary care services strengthening the case for PPIE in multimorbidity related research.

The patient voice is important when considering prioritisation in healthcare, primarily as there is a well documented disparity between clinician and patient prioritisation [18], with research on this area requiring PPIE. As discussed in Chapter 2, the lack of patient involvement in the papers submitted in this thesis and analysis of top-down data is a limitation of the body of work. PPIE will be a key component of future work focusing upon prioritisation and preferences of patients with multimorbidity.

Individualised Management

The Ariadne principles propose that an individualised management plan can arise after the identification of patient preferences and prioritisation and interaction assessment, which takes into account realistic treatment goals. The balance between the proposed benefits of treatment / interventions and the risks, and how these fit the individual patients biopsychosocial context needs careful planning and can support implementation of PCC. With a variety of modifying factors, interactions and limited evidence to support decision-making, the balance between benefits and risks will likely change over time. Clinical reasoning and patient prioritisation will therefore play a crucial role in the agreed management. Other domains such as patient resilience [321], and frailty [25,214] may be relevant to include as part of this process.

It should be stressed that for many patients with multimorbidity, the complexity of this decision may be limited. A robust 80-year-old with atrial fibrillation may clearly benefit from being started on anticoagulation, and the time taken to compute these competing domains may be brief. The degree of flexibility offered by the Ariadne principle framework is a strength from an operational perspective.

Work on prescribing in nursing homes [14], identifying undertreatment of pain syndromes in patients in dementia, highlights the risk of undertreatment in this patient group. The Ariadne principles may be applied to support individualised management for older patients with dementia in nursing homes, particularly around important symptoms, to support judicious prescribing. Such prescribing may involve medications being commenced (e.g. analgesia or bone protection) and being stopped (e.g. medications for secondary prevention of cardiovascular disease) depending on the individual context.

Similarly, the Ariadne principles may be applied to support patients at risk of hospital readmission. Preventing hospital readmission is challenging due to it being associated with a wide variety of variables [17]. However, the individualised management around hospital admission, preferred place of care and priorities of treatment may help prioritisation of care needs for an individual. It may be that supporting closer collaboration between primary and secondary care for complex patients when agreeing individualised management plans, may be an important area of potential benefit [322].

There has been interest in developing clinical tools which may support clinicians track and manage patient with multimorbidity symptoms, which often form the basis of individualised management. Such tools offer a way for review appointments to provide some data points to be discussed, and reflected upon, with reprioritisation of symptoms to be performed as required. The SymTrak-23 [Symptom Tracker] program, has been demonstrated to be a feasible way to monitor symptoms of older adults with multimorbidity in primary care [323] with a shorter version (Sym-Trak-8) demonstrated to be reliable in older adults where treatment response is felt to be a concern [324]. SymTrak-23 was developed to target the most prevalent and disabling symptoms and functional impairments experienced by older adults, including SPADE symptoms (sleep disturbance, pain, anxiety, depression, [low] energy/fatigue) as well as impairments related to mobility, cognition, and vision or hearing. However, there remains no evidence that these tools have been integrated into clinical practice or improved patient outcomes. Future work which explores the role that such tools may have to support individualised management is required.

4.3 Health Inequality & Multimorbidity

Health inequalities refer to the systemic, avoidable and unfair differences in health outcomes which can be observed between populations, between social groups within the same population or as a gradient across a population ranked by social position [325]. The factors which make up the root causes of health inequality are a complex balance of social, environmental, economic and cultural determinants of health. Health policy in Scotland aims to address the fundamental causes (such as poverty, marginalisation and discrimination), prevent the wider environmental influences (equity in access to services and opportunities for work) and mitigate the individual experience and effects of inequality [326]. Indeed, improvements in health life expectancy, well-being, morbidity and mortality are all part of broader Scottish Government strategy [326].

There is considerable evidence that socioeconomic, psychosocial and behavioural determinants of health are associated with the development of multimorbidity [327,328]. Lower education level [329,330] and socioeconomic deprivation (measured by household income, total household wealth or household area [331]) is associated with increased prevalence of multimorbidity [329-331] and the development of multimorbidity at an earlier age [200]. These factors may also influence the associated challenges of polypharmacy [332-333]. My cross-sectional work highlighted a greater likelihood of older patients in more deprived socioeconomic groups being prescribed psychoactive medications [16]. More recent work supports these findings, demonstrating that excessive polypharmacy [defined as 9-20 medicines] is associated with living in a deprived neighbourhood [332] and that patients with lower levels of education had greater polypharmacy, even when controlling for disease burden [333]. This is important because primary care in areas of higher deprivation is not well placed to address the impact of extreme polypharmacy, mental-physical health multimorbidity and challenging psychosocial dynamics on health [334,335]. The disproportionate impact of the GP workforce shortage on deprived areas remains a major policy challenge [336].

The relationship between lifestyle factors, such as smoking and alcohol consumption, and many chronic diseases are well documented [336]. Such relationships often exacerbate health inequalities [326,336]. The development of multimorbidity has been associated with a suite of lifestyle factors such as smoking status, decreased physical activity, high alcohol consumption, obesity and a poor quality diet [337,338]. Supporting patients to make healthy choices with regards to lifestyle factors, in particular factors associated with a multitude of individual chronic diseases such as obesity and smoking, are likely to be of benefit for patients with multimorbidity [328]. Future research investigating approaches to support the delivery of preventative and public health interventions for patients with multimorbidity will be important.

Other psychosocial factors, such as adverse childhood experiences [339,340] and a feeling of lack of control over an individual's life (the extent to which people believe what happens in their life is determined by factors outside their control) [330] have also been associated with the development of multimorbidity and mental-physical multimorbidity. These factors are more commonly experienced by individuals in lower socioeconomic quintiles and may be associated with challenging multimorbidity clusters [341] and lower levels of patient engagement in their care [336]. Improvements in patient engagement in healthcare decisions, and indeed in clinical research, is a clinical area which has potential to improve outcomes and relevance of research as discussed in Chapter 3.

Health inequality is of very significant importance when considering patients with multimorbidity at the individual level. Reflecting on my work on clinical practice guideline recommendations [12,13], different patients within different contexts will likely benefit from different approaches to managing their chronic disease. For example, an older patient with carer responsibilities for a spouse may not wish to travel far for rehabilitation after a heart attack or may be very averse to taking medications where sedation is a side effect. The development of an individualised plan for patients with chronic disease, in line with the Ariadne principles, that considers their clinical conditions and treatments and social context may be helpful for GPs in supporting patient-centred decision-making but is challenging to deliver in daily general practice.

The Cambridge Multimorbidity Score (CMS) is a validated score which assigns a 'score' to 20 conditions based upon the impact of a patient being diagnosed with a condition on their healthcare usage [342]. The CMS may enable the identification of patients who may benefit from prioritisation of an individualised management plan, in keeping with the Ariadne principles. Chronic pain, COPD, alcohol problems, anxiety and depression, cardiovascular disease and diabetes contribute to 64% of the burden of disease in the most deprived decile, compared with 49% in the least deprived decile [343], further extending the potential impact of GP workforce challenges in areas with high deprivation [344]. The identified conditions which form the basis of the CMS are chronic in their nature, and it is likely that there will be periods where one or more of these conditions will take precedence for the patient at the individual level (e.g. harmful alcohol consumption after a bereavement or after recent hospitalisation with a heart attack). Taking time to recognise and identify this is likely to be helpful in improving health outcomes [78,345].

For individual clinicians, a patient with chronic pain, significant anxiety, poor diabetes control and ischaemic heart disease is challenging to manage in 10-minutes unless there is a very narrow consultation focus. Attempting to identify realistic goals for the patient, prioritise patient preference (What symptoms/condition impact her the most at the time of the consultation?) in order to develop an individual management plan whilst considering interactions between treatments or social context remains harder still. Future research may consider how to best operationalise the implementation of the Ariadne principles and how their impact is measured.

Healthcare inequality remains a key aspect of focus for health policy makers and is known to be associated with significant harm for patient populations [325,326]. The 2023 Health Foundation Report '*Leave no one behind: The state of health and health inequalities in Scotland'* identified numerous barriers to policy implementation [345]. The report identified that health inequality continues to increase across Scotland, and there is a significant risk that tight fiscal decisions may further exacerbate all these challenges [345]. The prevalence of drug-related deaths, inequalities in the health and developmental experiences of infants and children, and health and socioeconomic outcomes of young and middle-aged men were all identified as particular groups of concern [345]. Policy and governmental efforts to address and improve care for patients with multimorbidity must include preventative healthcare and broader societal factors to deliver improvements in clinical and social outcomes. Furthermore, health and social care needs to be easier to access for high-risk groups with a move away from the concept of ‘hard to reach patients’ to ‘easy to access healthcare’ [346-348].

4.4 Chapter Conclusions

This chapter has considered multimorbidity, the Ariadne principles and health inequalities. It has been demonstrated how my work sits in relation to the Ariadne principles, alongside critiquing the framework and identifying some broad research gaps. Furthermore, the importance of health inequalities in relation to multimorbidity has been established and how the body of work on which this thesis is based has engaged with this relationship. Finally, future research and policy efforts focused towards preventative and public health measures has been isolated as an area of future research to improve outcomes for patients with multimorbidity and reduce health inequality.

Integration of health and social care has been an approach across health systems to try and improve access and effectiveness of primary care services, improve chronic disease prevention and management, and population health and health promotion. Chapter 5 show how my papers have and are contributing to this key element and will explore health and social care integration in relation to multimorbidity and consider the broad challenges of implementing health policy reform within primary care systems which are commonly complex and poorly understood [349].

Chapter 5

Integrated Care – Attempting to Address Care Fragmentation

5. Integration of Health & Social Care – Attempting to Address Care Fragmentation

5.1 Introduction

The increasing prevalence of multimorbidity has led to a variety of healthcare challenges for primary and secondary care systems. Some of these challenges include fragmentation of care provision and poor coordination of care [64,350]. As a result, health systems across the world over the last few decades have made efforts to integrate health and social care systems which have taken a variety of forms (e.g. primary care networks, integrated care systems) [10]. Over the last decade, health and social care integration has become a major component of health policy focus, primarily driven by an ageing population and increasing prevalence of multimorbidity [10,170].

This chapter aims to draw on themes identified within my published work whilst placing this in the context of the health and social care integration agenda and considering what this means for practitioners. An element of the thesis linking my research argues that although integration of care may provide some opportunities for enhancing care provision, it will not be a panacea for complex patients (i.e. patients with complex multimorbidity, frailty etc). Indeed, GPs even as part of longstanding integrated care systems still require a range of responses to deliver high-quality care for the extensive varied health and social needs of their primary care patients [351,352].

5.2 Integration of Health & Social Care

Integrated health systems have the opportunity to improve access to healthcare, quality and continuity of clinical and healthcare services, alongside improving efficiency [353]. Integrated care has been defined by Leutz as, "*the search to connect the healthcare system (acute, primary and skilled) with other human service systems (long-term care, education and vocational and housing services) to improve outcomes (clinical, satisfaction and efficiency)"* [354]. Although this is a commonly used definition, a review of the literature in 2009 isolated nearly 175 definitions and concepts relating to the integration of care [355]. Integration of care can arise in different ways, including organisational integration (e.g. coordination of structures and governance across organisations), functional integration (e.g. alignment of non-clinical support and back-office functions), service integration (e.g. coordination of services at the organisational level) and clinical integration (e.g. coordination of care into coherent processes) [10,356,357]. Indeed, different healthcare systems may target integration at different system levels depending upon clinical and social needs within the locality.

5.2.1 Integration of Health and Social Care in Primary Care

Primary care is a key component of a health system which is patient-centred and more integrated [247,358], as these systems can provide a degree of care coordination (through referrals to public sector secondary care systems), long-term 'cradle to grave' healthcare, free at the point of access of care and capitated budgets for specific practice populations [272,359]. However, there are numerous barriers which limit the ability of primary health care systems to deliver integrated care including differing health priorities between different clinical areas and providers, conflicting organisational objectives and activity-based incentivisation schemes [360]. Experience to date shows that while integrated care has significant support, implementation in the complex sphere of healthcare is challenging and clear evidence of benefit is limited at best [10,361,362]. The manner in which integration service changes are implemented and reviewed to establish clinical effectiveness, sustainability and efficacy are also limited [10].

In Scotland subsequent to the majority of my publications, geographical groupings of GP practices (referred to as clusters) were introduced to replace the QOF alongside developing a whole new way of working for primary care in 2016 [363]. As the National Framework for Quality and GP Clusters in Scotland 2017 made clear [364], the programme involves the implementation of values-driven quality improvement and learning, within and across practices, alongside the broader role of integrating and developing primary care within the wider health service. Work assessing their progress 2 years after their formation reported that although the cluster model was functioning, there was a feeling it was too early in terms of perceived impact [362].

The body of work which forms the basis of this PhD by Published Works, relates to aspects of care integration and together forms a coherent voice in relation to this important aspect of health and social care development. Indeed, the promotion of PCC [12,13] and independence in the community [17], and reducing care fragmentation [13] are all relevant to integrating health systems and multimorbidity.

Within the author's work locality, there are a variety of quality-related work streams, some of which look at the integration of health and social care teams for patients at high risk of hospital admission, such as Enhanced Care Support in Angus, Enhanced Care Home Team in Dundee and Local Integrated Care Service in Perth. These work-streams bring together social care providers from the respective Health & Social Care Partnerships, and clinical providers (GPs / district nursing / allied health professionals) within the NHS Board to deliver targeted intervention. Such programmes may help address some of the challenges identified in my six publications including causes of hospital readmission [17], disproportionate increases in psychoactive drug prescribing rates [16], and nursing home prescribing [14].

Although such programmes have not been delivered without challenges, collaborative working between GP clusters and the wider healthcare ecosystem has facilitated some of this change. Focused research within GP cluster groups on these programmes may identify the efficacy of such work upon patients with complex multimorbidity or frailty. This data may help drive forward appropriate and effective local approaches to supporting patients in the community. The author is currently planning future work with the University of St Andrews and the local GP Cluster on these areas.

5.2.2 Integration and Person-Centred Care

Firstly, the promotion of PCC and independence in the community for older patients was explored in work which analysed hospital readmission in the study reported in Paper 6 [17]. The originality of the work, focusing upon geriatric rehabilitation units where theoretically there has been more time to optimise discharge planning compared to acute hospital discharge, contributes to the literature by indicating that time alone in a rehabilitation setting is not associated with significant reductions in hospital readmission rates.

People should be a partner in their care alongside healthcare professionals [357], and by understanding the causes and correlates of hospital readmission for older patients we can more accurately develop mitigation strategies to promote patient independence. Such efforts may enable interventions to reduce hospital readmission and improve sustainability within the hospital system. Frailty syndromes and multimorbidity involve diverse symptoms and lived experiences for patients, and developing communities with resilience with responsive primary care systems is important as part of the broader patient journey [365,366]. Collaboration between social care providers, secondary care healthcare providers and community healthcare teams to enhance the patient experience at the interfaces of care (e.g. admission to hospital, transfer to the rehabilitation unit, discharge) remains an admirable ambition. Integration of social care remains a particular challenge [10], and intensive focus on integration processes will be unable to overcome inadequacies in staffing, funding or inequality within the healthcare ecosystem [361,367].

Subsequent to the publication of the study reviewing geriatric readmissions [17], within the geriatric rehabilitation centre, multi-disciplinary teams now regularly include the attendance of social work team members. This has anecdotally improved patient discharge planning, identification of patient-centred outcomes, communication of delays of care to in-patient teams, and aided the prioritisation of care for in-patients by social work teams. More broadly, there is research specifically looking at care transitions from hospitals to the community in order to reduce hospital readmission [368], and work published in 2023 which reported lower hospital readmission, greater use of primary care and improved continuity with a GP-led service (MidMed) for patients with moderate to severe frailty identified by electronic frailty index [369]. The latter Scottish study reported lower risk of hospital readmission/A&E reattendance, greater use of primary care and improved continuity of care for patients managed by a full-time GP with a special interest in frailty and multimorbidity [369]. The intervention involved this individual providing primary care modified CGA and direct patient care to patients with frailty and multimorbidity only. Although the study was a pilot programme in Midlothian, Scotland [369], it provides a very useful framework for considering primary care approaches to manage patients with frailty and multimorbidity. Such approaches may support identification of realistic patient treatment goals, delivery of coordinated multi-disciplinary care alongside mitigating treatment burden and supporting deprescribing.

Research presented in Paper 1 through a single-case report [12], demonstrated integrating guideline recommendations and clinical care provision whereby a GP enabled the patient [John Smith] to experience PCC which recognised his own personal priorities. The paper noted that at a micro-level some of the broader policy change is achievable to implement and can benefit individual patients in a significant way. Increasing the integration of community services through the Scottish GP contract will ideally make the implementation of various community services easier.

5.2.3 Care Fragmentation

Secondly, the studies reported in Paper 1 and 2 demonstrate the potential risks of care fragmentation, the very antithesis of integrated care, that clinical practice guidelines can have upon healthcare [12,13]. This is a crucial concept to understand in the context of ageing populations and increasing multimorbidity.

Being able to integrate guideline recommendations, and coordinate care recommendations would go some way to recognising people as partners in care and enable GPs to support patient decision-making, but achieving this will require investment in primary care digital systems [40,212]. Digital healthcare solutions may provide an opportunity to integrate care for patients with multimorbidity, and provide choice for patients about the manner in which their care is delivered but require more focused studies on outcomes for patients with multimorbidity [370,371].

More broadly, financial incentives for GPs that are indexed to various measures of performance have been used for years to achieve disease-focused targets, and have been associated with improvements in quality of care [372] and implementation of quality improvement programmes [373]. However, they may have unintended consequences, particularly for those with multimorbidity as indicated in the study reported in Paper 4 [15]. The potential impact of implementing financial incentives for patients with multimorbidity is increasingly recognised, with the author being involved with discussions within Fife about the incentivisation of safe psychoactive drug prescribing practice through the GP cluster model. These discussions included outlining the findings of the study reported in Paper 5 regarding the disproportionate increase in psychoactive drug prescribing, demonstrating the local impact of the work [16].

For patients with multimorbidity, nuanced patient-centred discussions are needed regarding what chronic disease target is appropriate for them in the knowledge that targeting one chronic disease metric may worsen another – this does not fit well with the financial incentive model [374]. GPs have reported a decrease in person-centred care and reduced continuity of care since the QOF was introduced to incentivise GPs to achieve nationally agreed targets [375]. Other research from the same group highlighted that financial incentives linked to specific treatments can negatively change the nature of the clinic visit, and lead to clinician resentment of the programmes and the lack of engagement in service reforms [374,376]. There has been recent work looking at financial incentives in relation to encouraging the provision of person-centred integrated care [377]. A Dutch expert consensus group has proposed a payment model combining person-centred bundled payments with shared savings payment model and pay-for-performance components [377]. The paper provides a hypothetical funding model, with such work providing the basis for targeted work to adapt, develop and research financial incentives to maximise their benefits and mitgate risks. Furthermore, the implementation of the Ariadne principles may be a useful avenue to explore as part of this broader interface between health policy and primary care delivery.

Other sections in this thesis have highlighted some of the efforts to integrate guidelines for different chronic diseases [212], alongside efforts to make the evidence base more reflective of patients commonly seen by GPs with multiple chronic diseases.

5.2.4 Care Collaboration

Thirdly, the study presented in Paper 3 highlighting the presence of significant psychoactive drug prescribing within a nursing home whilst undertreating patients for pain was a significant finding with relevance for the primary care system [14]. Presently the vast majority of care home residents are managed primarily by GPs, with the British Medical Association highlighting concerns about the sustainability of some of these arrangements due to workforce capacity and capability concerns [377]. Indeed, there are concerns that although GPs are well placed to deliver care home initiatives as they are well connected to the broader healthcare commissioning system, limited capacity may limit meaningful engagement to deliver quality improvement in care homes [377].

Some of the benefits of integration of GP care delivery and GP commissioning of care may be limited by further reorganisation of the healthcare system with the move towards integrated care systems from clinical commissioning groups in England. However, the role of the GP remains important for this patient group. GP interactions with nursing home residents, staff and family members have been identified as crucial in how the quality of healthcare is interpreted, particularly around medication management [378-380].

Integrating efforts to improve aspects of nursing home care have been shown to be better when NHS staff are provided with time to develop relationships with care home providers and are integrated with other specialists relevant for the management of this patient group (e.g. old age psychiatry, geriatric medicine) and have nursing home medicine recognised by commissioning organisations [378-380]. The author has been working in Perth (as a GP with Special Interest in Geriatrics) developing closer working relationships between old age psychiatry, GPs and community geriatrics. One of the aims of the approach is to deliver safe and appropriate prescribing for nursing home patients building upon the study findings [14].

System-wide governance will be required to drive forward systems change in this area and will require collaboration between private and public care providers as performance frameworks and agreed ways of working are developed. However, rather than focusing upon further organisational and systems reform, a concerted effort is needed to shift the focus to staff behaviours/values, incentives, training, skills and resources alongside digital solutions to care delivery to actually move towards an integrated health ecosystem [10]. Furthermore, health systems must be better at measuring integration and system change, agreeing on standardised measures to enable this and communicating the current evidence base [372]. This will enable an accurate evidence base to be developed and best practice shared. Such an approach will avoid repeated pilots of small-scale studies, avoid investment in approaches known to be ineffective and ensure focus upon aspects of change that actually lead to improvements in care.

Finally, regional prescribing research reported in Paper 5 demonstrated increases in psychoactive drug prescribing, disproportionately affecting patients within lower socioeconomic groups [16]. These prescribing rates were considered reflective of higher mental health diagnoses rates, alongside higher prevalence of pain syndromes (e.g. osteoarthritis) in patients within lower socioeconomic groups. Clearly, prescriptions may form part of a patient management plan for these conditions, but the embedding of poverty-aware practice into healthcare systems [381] and improving access to mental health services [382] are all pertinent to addressing this health inequality. Integration of social care is being seen as a way to address the inequity of health and social care outcomes, and specific programmes such as pharmacy and mental health service integration into primary care teams may help access to mental health care and pharmacotherapy [383].

There is a relationship between multimorbidity and polypharmacy partly driven by guidelines [12,13,18], and the integration of healthcare systems may provide an approach to support prescribers deliver appropriate prescribing. Furthermore, integration may improve access to evidenced-based non-pharmacological options for chronic disease management and support patients in self-care. Such integration can be on a macro-level (e.g. broad regional commissioning for multi-disciplinary obesity management programmes) or micro-level (e.g. community pharmacy collaborating with GP clusters to deliver focused polypharmacy reviews). The GP Cluster Model of care introduced in Scotland has prescribing as a core part of quality improvement through collaborative working. However, there are concerns that limited access and availability of data analytics, clinician capacity and quality improvement expertise may limit the potential of GP clusters to deliver desired change in the context of integration and prescribing [384]. Investment in developing capacity for quality cluster leads, and further research looking at specific areas such as polypharmacy, high-risk prescribing or long-term care prescribing [385] is required.

The author is keen to explore through further research, management and clinical work whether broader systems changes have been noted to have an impact on clinically relevant outcomes.

5.3 Chapter Conclusion

Ageing populations, increasing multimorbidity, and biopsychosocial complexity are increasing the pressure on healthcare systems [10,51,228,361]. Integration of health and social care systems has been proposed as an avenue to explore improvements in care for many years, but evidence of improvement in patient outcomes is limited across different healthcare systems [10,355,360]. In Scotland, the GP cluster model of care may provide an opportunity for primary care-based research looking at the quality of care provision and integration of care components for patients with complex multimorbidity, mental and physical health multimorbidity and prescribing for high-risk patient groups.

The body of published work that forms this thesis has outlined that development of PCC through optimisation of clinical guidelines [12,13], and identifying causes and correlates for geriatric readmission [17] may provide important insights into the increasingly integrated healthcare ecosystem.

There have been considerable changes to the health policy landscape since this work was published such as the GP Cluster model of primary care delivery, and this is something which is pertinent to consider in future research.

Chapter 6 considers how the field of multimorbidity has changed since my work has been published, alongside some of the limitations of the work. That will provide an opportunity to consider what the next steps are in moving forward and expanding that body of work. The chapter will also consider my own personal learning throughout the period of research.

Chapter 6

Multimorbidity – A Changing Landscape

6 Multimorbidity – A Changing Landscape

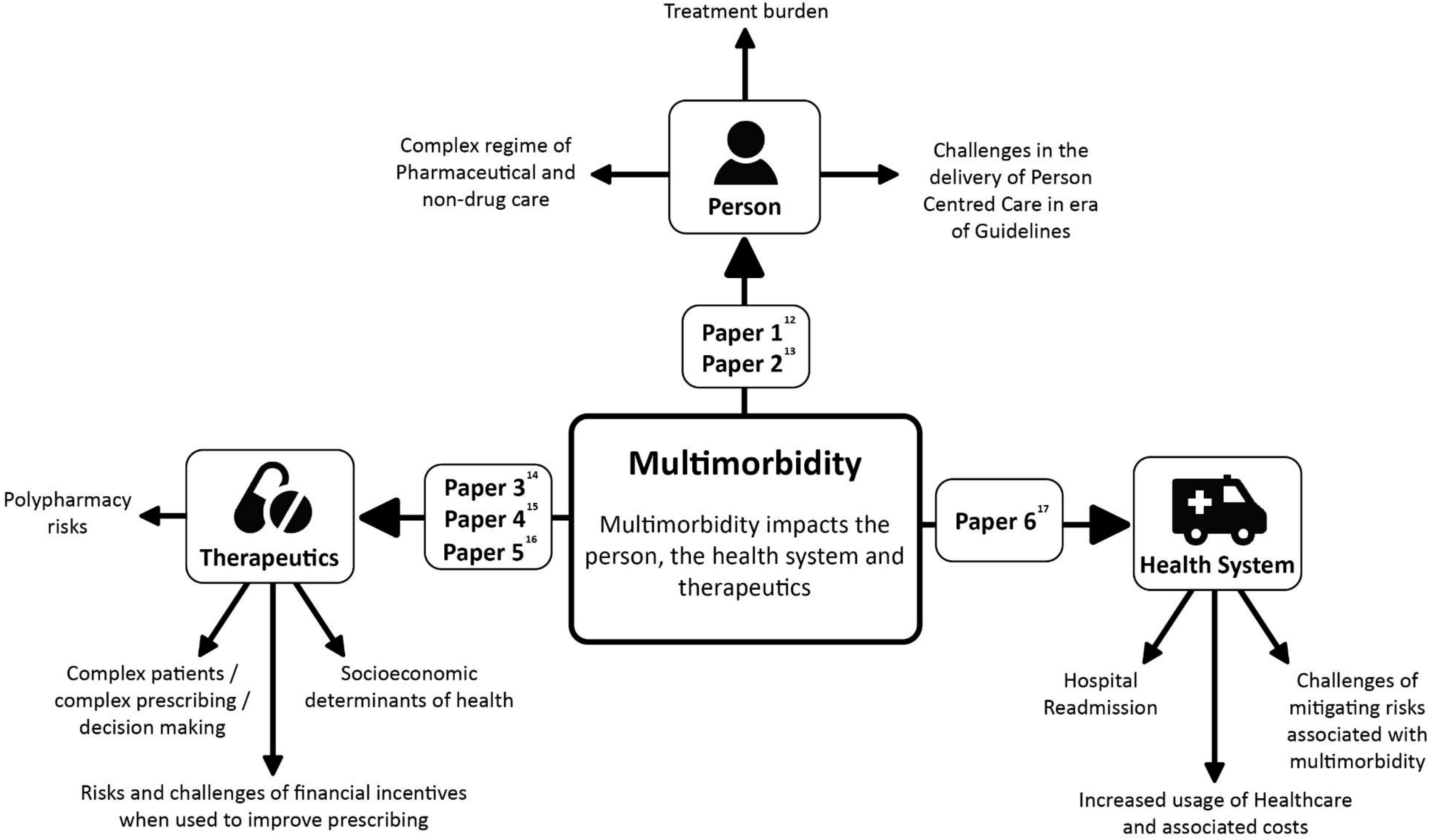
6.1 Introduction

Knowledge never stands still. Since my first published paper in 2012, the research and clinical field in multimorbidity has evolved extensively. For example, the studies reported in Papers 1 and 2 discussing the challenges of managing patients with multimorbidity with clinical practice guidelines in their current form [12,13] predated the NICE multimorbidity guideline in 2016 [40] and the publication of the Academy of Medical Sciences report on multimorbidity [51]. Understanding is always moving on whether building on what has gone previously or shifting understanding of what was previously accepted.

Despite the time-period which has elapsed since initial publication, the six research studies which form the basis of this thesis still have clear clinical implications for individuals with multimorbidity, healthcare systems and for prescribing practice. Key clinical implications of the studies will be identified in the subsequent sections, with figure 3 summarising key clinical implications of my published work. The significance of the studies has been discussed in section 1.4.

The shifting landscape of multimorbidity and primary care has implications for considering the limitations of the work that underpins this PhD by Published Works. In considering the changing context within which that work sits, this chapter will also reflect on the limitations of the work and key areas for future research.

Figure 3: Clinical Implications of Published Work



6.2 Guidelines for Multimorbidity

The 2016 NICE multimorbidity guideline [40] provided important recommendations for clinical practice including suggesting pragmatic assessment for frailty alongside formal assessment of treatment burden and a patient-focused management plan for their long-term conditions. This built upon the foundations of some of the findings of the studies reported in Paper 1 and 2 [12,13]. These studies highlighted fundamental challenges for clinicians when using clinical practice guidelines to deliver chronic disease care, including the limited ability to be patient centred alongside implications for individual patients [12,13]. Guideline based care may drive increasing complexity of drug and non-drug treatment recommendations, referrals and treatment burden for people with multiple long-term conditions. These implications are more pertinent in the context of the use of financial incentives to drive forward improvements in chronic disease management. The NICE multimorbidity guideline was an approach to address some of these challenges together.

It can be argued that the NICE multimorbidity guideline primarily offers pragmatic and patient-centred advice rather than specific ‘what to do’ statements but this reflects the limitations of the available evidence base [386]. That said, the guideline has highlighted the importance of multimorbidity as a distinct and important clinical entity to address, alongside the salience of communication between healthcare providers and associated care coordination [386-388]. Shifting towards integrating guideline recommendations where possible and considering the impact of a patient's conditions on their quality of life are now considered best practice [40,386,389]. This may support GPs, in line with Ariadne principles, to agree realistic treatment goals and individualised management with patients.

The publication of the NICE multimorbidity guideline has provided the impetus for further research within the field by identifying areas with limited clinical data upon which to base practice [390,391]. Such areas include improving our understanding of clusters of diseases which have the worst prognoses [392] and ascertaining the benefits and risks of starting and stopping long-term medications in patients with multimorbidity [212]. Furthermore, establishing how can we measure and research treatment burden for patients with multimorbidity remains important to develop and assess interventions to improve patient experience and quality of life [393,394]. These areas hopefully will enable GPs to target groups of patients most likely to benefit from interventions (such as polypharmacy review, and frailty screening) alongside supporting prescribing decisions for patients with multimorbidity or frailty.

A Spanish 2022 retrospective observational study, using the EpiChron cohort (1.3 million people), reported that the clinical profile of multimorbidity clusters in the oldest adults varied significantly by age and gender [395]. In particular, clusters in octogenarians exhibited conditions that were associated with high morbidity and importantly a degree of preventability [such as dyslipidaemia and diabetes] [395]. This may be of relevance for GPs as they see octogenarians in clinic, with the Ariadne principles helpful in identifying realistic treatment goals and patient preferences to support a pragmatic approach to the implementation of preventative primary care. The limitations of observational studies have been outlined in Chapter 2, but they do provide important insights into the prevalence of multimorbidity clusters.

As indicated in the Ariadne Principles, establishing patient preferences and priorities for care and treatment remains a crucial part of the delivery of PCC and was reported as an area of challenge in initial studies considering the limitations of guideline-driven clinical practice [12,13,18]. However, a recent systematic review reported scant evidence of tools that clinicians can use to identify patient preferences and priorities. There have been efforts to develop this area, including an evidence map of health-related preferences for older patients with multimorbidity from 152 studies (57,093 total patients) [396]. The evidence map was developed using an iterative approach, to develop and identify the clusters alongside a sensitive approach to the search to identify relevant studies (including unpublished studies). Addressing some of the limitations surrounding patient preferences to enhance the ability of PCC provision is ripe for future research and development.

Recent work has also used individual-level participant data (IPD) from industry-sponsored clinical trials to highlight that this approach may be able to provide a means to investigate treatment effects on patients with multimorbidity [397]. IPD reviews are a specific type of systematic review that involves the collection, checking and re-analysis of the original data for each participant in each study.

The IPD review authors concluded that although patients included in these trials had lower rates of multimorbidity than people in the community (approximately half the rate), a substantial number of trial participants had a high level of multimorbidity [397]. This IPD data may provide a useful resource to be able to clarify whether trial conclusions can be extrapolated to patients with multimorbidity. The authors called for future trials to become more representative of multimorbidity, alongside calling for trialists to report the prevalence of multimorbidity and the range of comorbidities among trial participants [397]. This is an important area for recognition given the diversity of the Scottish population. Such approaches could complement efforts to improve the implementation of guideline recommendations, by improving the generalisability of the evidence which forms the basis of these guidelines. The limitations of industry-sponsored clinical trials, such as susceptibility to reporting bias, must be considered in such IPD research [397].

6.3 Polypharmacy & Multimorbidity

There have been considerable changes in the research surrounding polypharmacy and psychoactive drug prescribing in the context of multimorbidity subsequent to the publication of studies reported in Papers 3, 4 and 5 [14,15,16].

These three studies have important clinical implications regarding drug prescribing and multimorbidity. Firstly, individuals with multimorbidity associated with complexity (such as those living in nursing homes) are associated with both the harms of over-prescribing and under-prescribing [14]. In addition, communication and cognitive difficulties make SDM and PCC harder to implement regarding prescribing. Secondly, financial incentives and targeted programmes of work to address single areas within prescribing may be well meaning but can be associated with unintended consequences [15]. Well planned and implemented programmes of work are required to target certain high-risk prescribing areas, with active consideration of what consequences may be. Thirdly, changes in prescribing rates are associated with a multitude of different factors but socioeconomic determinants of health remain relevant not only for patients developing multimorbidity at an earlier age [9] but also for the associated negative sequelae of multimorbidity such as higher rates of mental health diagnoses [46,155] and psychoactive drug prescribing [16].

A 2019 systematic guideline review and expert consensus reported the current evidence in relation to the best clinical management for patients with multimorbidity and polypharmacy using the Ariadne principles for managing multimorbidity as a framework [398]. The authors reported guiding principles alongside specific recommendations and tools providing actionable support for clinicians [398]. A major challenge in implementing the review recommendations was reported to be single disease-focused healthcare models, and speciality structured health services [398], similar to the themes identified by the author's earlier work on clinical practice guidelines [12,13].

More broadly, existing guidelines on multimorbidity (diagnosis-based) and polypharmacy (treatment-based) were produced separately, despite reporting similar themes and the authors suggested the future integration of these ure [398,399]. The lack of evidence for real world patients in some areas led to several of the included guidelines being based upon expert consensus with their associated limitations [399].

Real-world trial evidence may help to provide much needed data about what primary care providers can do to improve the delivery of judicious prescribing [400]. This evidence gap is particularly important to address given the author's work reporting increasing rates of psychoactive drug prescribing for older patients, particularly in deprived areas [16]. This patient group is likely to have mental-physical health multimorbidity with associated prescribing and chronic disease management challenges [40,401].

Efforts to use computer software to enhance prescribing and reduce adverse drug reactions for hospitalised older patients were disappointing in recent trial data [402]. The trial under-recruited its target by almost 300 patients and it is likely that human factors (e.g. busy clinical environments, limited knowledge that junior doctors have over specific patients they are completing paperwork for, perception of the relevance and importance of the adverse drug reactions etc) played a significant role in the intervention reporting no reduction in adverse drug reactions [402]. Future trials will be needed that do recruit to target and incorporate emergent developments in artificial intelligence and new drugs.

Further work combining clinical decision support decision tools with a clinician-led intervention is underway [403] which may reduce the risk of alert fatigue associated with computer systems and improve clinician engagement [404]. Primary care trials using clinical decision support systems targeting multimorbidity and polypharmacy remain limited, with recent qualitative work identifying important factors associated with the implementation, engagement and sustainability of such systems in general practice providing useful data for future research [405].

Shared decision making with patients remains important with prescribing decisions, with the role that GPs play in this especially valued by patients [406]. Deprescribing can be effectively implemented by GPs, using the Ariadne principles to frame discussions in a patient-centred manner. A multicentre mixed-methods study, performed as part of the European OPERAM trial, reported that although patients generally displayed positive attitudes towards medication reviews, they lacked information and communication about their medication changes after a period of hospitalisation [406]. Furthermore, there was a disconnect between how shared the decisions were felt to be from doctors (who felt the decisions were more shared) and patients (who felt the decisions were less shared) [406]. The OPERAM trial did not involve GPs directly in medication reviews, which was a limitation especially given how patients seemed to value GP input into this process [406].

Understanding the prescribing decision-making process of GPs remains important as interventions to improve prescribing in primary care are developed. GP recognition of the limitations of the evidence base for patients with multimorbidity, alongside making compromises or relaxing guideline-based targets depending on patient-led factors has been reported [407]. A further important finding was that in patients with stable chronic disease, GPs preferred the ‘status quo’ of continuing presently prescribed treatments [407]. Maintaining the status quo may be an easier path to take in a busy clinical context, but continuing certain medications such as antipsychotics for older people with dementia may be associated with significant potential future harm [19]. In the nursing home environment, prescribing reviews may be more effective if delivered proactively rather than reactively, mitigating the risk of iatrogenic harm and targeting important symptoms that affect quality of life [13,408,409].

Prescribing was an important component of the multi-component 3D trial which included a community pharmacist as part of the trial to simplify drug regimens and improve patient safety and support patient concordance [97]. Although the 3D trial did not report significant differences between the control and intervention group, in relation to prescribing [97], a systematic review and meta-analysis looking at pharmacist-led polypharmacy reviews reported a significant association with reduced emergency department visits [410]. Other research has reported that pharmacist-led reviews for polypharmacy are associated with reductions in medication discrepancies [411], potentially inappropriate medication prescriptions [412] and improved quality of prescribing [413,414].

There are now numerous different interventions proposed for polypharmacy in older adults, with a scoping review reporting both implicit and explicit criteria for medication review [415]. Given the broad range of potentially inappropriate medications, a focused polypharmacy review using explicit criteria (such as the Medication Appropriateness Index) with a drug sub-group focus may be a way to increase the effectiveness of medication reviews [415-417]. Challenges associated with interventions aiming to reduce the number of potentially inappropriate medications, include reluctance to interfere in medications started by a colleague or specialist, increased specialisation of care leading to disease-focused recommendations, poor coordination of prescribing practice and fragmentation of care [415-418]. These data extend themes identified in the author's work looking at disease rather than person-focused clinical guidelines [12,13], and the study presented in Paper 5 which demonstrated increasing psychoactive drug prescribing alongside considering the drivers of this change [16].

Judicious prescribing is particularly important in nursing homes. This group of patients are commonly dependent, cognitively impaired, and experience frequent behavioural and psychological symptoms, multimorbidity, and polypharmacy alongside being frequent users of NHS resources [419]. The author's work on centrally active drug prescribing in nursing homes [14], amongst other papers [419-422], reported high levels of potentially inappropriate medications, particularly psychoactive drug prescribing. This has been part of the focus of the implementation of the *Care Home Charter for Medications* [423], and the recent publication of the British Geriatrics Society *Ambitions for Change: Improving Healthcare In Care Homes* which seeks to address some of the challenges facing home nursing home residents [258].

As reported by the author in the study presented in Paper 3 [14], it is not a case that less prescribing is always better for care home residents with under-prescription associated with patient harm [424-426]. Patient-centred discussions with patients (or with caregivers/family in event of incapacity), use of polypharmacy tools, and communication of the risk and benefits of continued treatment may be a way to improve judicious prescribing. Research from Switzerland suggested that most older patients with polypharmacy are willing to deprescribe [427]. A 2021 systematic review and meta-analysis reported that almost 9 out of 10 patients were willing to stop some of their medications, with almost three-quarters of caregivers willing to stop medications of those in their care [428]. The heterogeneity of the included studies meant that the authors could not report whether patient or care-giver willingness to deprescribe varies by drug-class or by clinician type but has provided the first systematic review into this important component of deprescribing [428].

Research reporting GPs deprescribing decisions from 31 countries using a case vignette reported that GPs themselves were engaged in improving the appropriateness of prescribing, with deprescribing reported more often in cases of extreme age and increasing dependency [429]. Interestingly, the paper commented that GPs were more reluctant to adjust prescriptions in patients with higher rates of cardiovascular disease, possibly as the risk of cessation was deemed higher [429]. Understanding barriers to addressing judicious prescribing is important, as this may provide some useful approaches for targeted work that is feasible for busy practices to undertake or even for GP Cluster-based work.

There remain areas within polypharmacy and multimorbidity that require further research. From a clinical perspective, enabling user-friendly information regarding risks, benefits and drug interactions provided to GPs would be helpful. This may aid decision-making in areas such as medication cessation, adding new agents to patients on multiple medications and complex polypharmacy. Work in this area is in its infancy but hopefully may become part of mainstream primary care in the coming years. In a similar vein to the challenges of making multimorbidity a clinically useful term, there remains a similar need to make polypharmacy a clinically useful term. Simply being on five medications does not necessarily make it challenging to deliver care to a patient. Identification of types of polypharmacy most associated with harm remains crucial, with a RCT in 2016 reporting that feedback on prescribing safety data to GPs was associated with a reduction in particularly high-risk prescribing [430].

6.4 Financial Incentives & Prescribing

Following the author's published work [15] that investigated changes in hypnotic and anxiolytic drug prescribing over time, there has been work suggesting that the evidence base for pay-for-performance (P4P) schemes are limited with an association with unintended consequences such as reduced access to non-incentivised treatments [431,432]. Furthermore, financial incentivisation may influence prescribing in negative [433] and positive ways [434]. For example, a recent analysis from Austria reported higher antibiotic prescribing rate for practices with on-site pharmacy (dispensing pharmacies), with the authors suggesting that the difference may be explained by prescriber behaviour, which have the potential to significantly impact GP income [433]. However, the study was unable to make comment on the appropriateness of the antibiotic prescriptions and could not fully exclude a dispensing effect (where patients do not take their prescription to a pharmacy so they remain unfulfilled).

A Cochrane analysis of P4P schemes for hospitals reported that it is unclear whether these programmes improve outcomes for patients' quality of care, safety or equity [435]. This resonates with the finding from the author's study reported in Paper 4 that, alongside the pharmaceuticalisation [436] and medicalisation [437] of insomnia, financial incentives focusing upon certain targeted outcomes may not lead to the improvement in clinical practice that they aim for. However, in contrast to this there has been recent work identifying that the QOF scheme for primary care in Scotland may have had a role in recorded quality of care [438]. The 2023 controlled interrupted time series analysis that compared Scotland (which removed the QOF in 2016) to England (where QOF still is part of primary care), identified reductions in recorded mental health care planning, diabetic foot screening, blood pressure control in Scotland in comparison to England [438]. Aspects of this care are likely to be delivered but is not recorded in the same way (and thus would not have been picked up by the researchers). Nonetheless all three of these areas have the potential for significant patient harm especially when preventative healthcare and mental-physical multimorbidity management are key for improvements in multimorbidity outcomes.

The most recent Cochrane review on the effectiveness of financial incentivisation to improve prescribing practice reported that despite the importance and weight given to the policy across high-income countries, limited evidence of their effectiveness was found [439]. Financial incentivisation strategies to reward GPs for primary care provision have increased significantly, but the evidence base remains patchy with methodological limitations [440]. The sustainability of P4P programs is an additional concern. There have been assumptions that care standards will continue after removal of P4P incentives, having been embedded into routine clinical practice. These assumptions have been tested by Scottish [438] and English research [441]. Indeed, data from 2,819 English primary care practices reported an immediate decline in performance in line with performance quality measures following the removal of P4P payment to practices [441]. Such work extends the importance of behavioural change in a more general sense if policymakers are to use P4P to change long-term practice without having to continue payment programmes indefinitely. Careful consideration around how P4P and financial incentivisation programmes are designed and implemented more broadly is becoming increasingly recognised [438-442].

Developing financial incentive schemes and P4P may be more difficult when dealing with patients with multimorbidity [263,443] or promoting health and social care integration [444,445] due to the inherent complexity and heterogeneity of the patient group and interventions. The challenge presently is to generate robust evidence on what type of P4P or financial incentive may work, under what circumstances, for whom and what the intended and unintended consequences are [446]. However, it is likely that patient-centred approaches, such as the Ariadne principles, will remain important to identify what is important to the patient to help shape and agree treatment and interventions.

6.5 Mental Health, Deprivation & Multimorbidity

The relationship between physical and mental health multimorbidity and the broader interplay with social deprivation is an area of increasing focus since the study reported in Paper 5 was published [16]. As discussed in Chapter 4, there are several negative consequences associated with the combination of mental and physical health [447-452], and indeed between multimorbidity and social deprivation [172,350]. Data has also reported the interplay between all three of these factors, with research reporting an increased risk of hospital admission when patients with physical-mental health multimorbidity experience social deprivation [450].

Both polypharmacy [236] and physical and mental health multimorbidity [190, 264,451] are closely related to the social determinants of health with the current funding of primary care not reflective of the current morbidity burden on patients and providers [452]. Interrogation of the relationship between physical and mental health has developed recently, with research reporting that certain patterns of physical multimorbidity are associated with poor prognosis alongside depression and anxiety syndromes [453]. Such work will hopefully enable targeted integrated interventions for care providers, which may complement other work looking at temporal disease clustering [203,211]. It further builds on work using UK Biobank data reporting different clusters of physical health diseases to develop our understanding of the interplay between different conditions [group 1: myocardial infarction and angina;

group 2: 26 conditions centring on diabetes; group 3: large number of associations centring around asthma, depression and cancer] [454].

Prescribing in a variety of mental health medications occurs with greater frequency in more deprived areas, including antidepressant [455], hypnotic and anxiolytic [456] and antipsychotic drugs [457]. Recent NHS England data reported that between 2015/16 and 2019/20 all five psychoactive medication groups assessed were prescribed more commonly in deprived communities [458]. The relationship between social deprivation and psychiatric diagnoses is complex [218,459] and varies considerably by psychiatric diagnosis [460,461]. Broader aspects of community health are important as well, with local crime rates being associated with higher rates of antidepressant and antipsychotic drug prescribing based on a Scottish longitudinal data-linkage study [462]. There are several caveats to the work, such as the fact that the outcome measure was derived from the use of local services with access and funding differing between areas studied alongside differences in prescriber behaviour.

Extending the work around disease clustering discussed in Chapter 3, there has been research reporting multimorbidity-polypharmacy patterns (respiratory, mental health, cardiometabolic, endocrinological, osteometabolic, and mechanical pain) [463] which may be pertinent given physical-mental health morbidity is associated with particularly poor outcomes [448-450]. The author's work on regional prescribing [16] provided an original contribution to the literature by reporting that older patients are being prescribed psychoactive medications more often than previously thought and that the impact of this change is not proportionately felt across the socioeconomic gradient. Subsequent work has extended the broader challenges associated with understanding and addressing the challenges of multimorbidity, given its complexity and interacting components [40]. Overall, alongside broad policy change to reduce healthcare inequalities, patient centred GP consultations using frameworks such as the Ariadne principles that focus upon patient goals and preferences remains fundamental to support patients on an individual basis. Macro and micro level changes will be required throughout the healthcare system to improve care for patients with multimorbidity.

6.6 Readmission & Multimorbidity

Work reported in Paper 6 regarding causes and correlates associated with hospital readmission rates after in-patient rehabilitation has two core clinical implications [17]. Firstly, readmission rates remain significant even after a period of in-patient rehabilitation, with the mitigation of readmission rates remaining challenging [17]. Risk stratification tools to identify patients at the highest risk of readmission continues to be limited, and work in this area remains a priority. Such work will support efforts to deliver targeted interventions, likely integrated health and social care responses, to the right people and make use of limited resources. Secondly, readmission to hospital is often associated with a reason unrelated to the first admission [17]. This highlights the interplay between multimorbidity and frailty states, alongside interactions between prescribed medications, and different underlying health conditions. Thus, interventions will require to be multi-factorial in nature rather than disease or symptom focused alone.

Alongside the importance of hospital readmission to individual patients, readmission to hospital after a period of acute illness remains an important marker of judging success within health systems [464]. As such, interventions to reduce readmissions have been a significant focus of health policymakers. For example, in the US the Hospital Readmissions Reduction Program was introduced in 2010 to reduce preventable hospital readmissions by imposing financial penalties upon hospitals with higher than expected 30-day readmission rates initially focusing on pneumonia, heart failure and acute myocardial infarction [465]. Recent data have reported significant reductions in readmission rates [466,467] and that the programme has been associated with reduced costs, and improved patient experience [468]. Specialities such as cardiology and orthopaedics have reported other more nuanced findings in relation to index conditions of their interest [469,470]. The US health care system is clearly very different from Scotland or the UK. However, the extent to which similar approaches may be generalised to this side of the Atlantic raise policy questions.

My own work reporting that hospital readmission for older patients after a period of rehabilitation is more commonly related to conditions unrelated to the reason for the initial admission is pertinent in this context [17]. Patients with multimorbidity are more likely to be readmitted to hospital [51], which may reflect an increased risk of decompensation in different body systems, increased risk of drug interactions due to polypharmacy, and other related syndromes such as frailty. The complexity of this means that single disease-focused interventions or programmes may not prove overly successful in readmission reduction, a similar theme when compared to guideline-based care delivery [12,13]. The originality of examining readmission following in-patient rehabilitation in the UK was important as it provided evidence that readmission rates are high even when a patient has undergone a focused rehabilitation programme. The research extended US data reporting simply mitigating debility does not reduce readmission rates or indeed lead to long-term sustained improvements in function [470]. A lack of a control group when looking at readmissions was an important limitation, although the importance of a control group increases when developing and testing interventions to reduce readmissions. A 2022 Cochrane review looking at discharge planning (33 included studies), reported a small reduction in initial hospital length of stay and hospital readmission risk with a structured discharge plan [464]. However, the vast majority of studies within this systematic review focused on discharge from acute hospitals to the community rather than in-patient rehabilitation ward settings, which was the setting of my published work [17].

There are broader challenges associated with using readmission rates as a metric of quality in healthcare systems [471], with many hospital readmissions being deemed unavoidable [471], no globally agreed method to adjust for confounders [472] and globally high readmission rates [473]. Furthermore, a simple metric may overlook more complex healthcare or social factors [473]. For example, Norwegian research looking at readmission for older patients (≥75 years old) with multimorbidity reported surprising results that lower age and higher cognitive function were associated with higher readmission [474]. The authors were concerned that these results may reflect ageism within the healthcare system, leading to reduced access to hospitals for older cognitively impaired patients who may benefit from admission [474]. It may be that focusing on discharge planning which actively considers important syndromes of frailty, polypharmacy and multimorbidity [475] alongside investment in primary care [258] may be more effective in enhancing patient transitions from secondary to primary care systems. Such transitions are particularly important for patients with multimorbidity and may be one way that integrated health and social care may be able to target to improve outcomes for certain patient groups. Patient centred discharge planning, such as through the identification of patient treatment goals, may support early identification of ceilings of care, whether hospitalisation is wished in future and patient priorities in relation to their treatments.

Future work is required to further interrogate the relationship between readmission and multimorbidity. This may arise through disease cluster-based analyses to see whether there are particular aspects of multimorbidity associated with readmission (polypharmacy; social deprivation; mental-physical health multimorbidity) in order to shape multi-dimensional interventions. Qualitative work looking at PCC and identification of treatment goals after in-patient rehabilitation and how this may influence readmission in mixed-methods work would also provide useful insights.

6.7 Limitations of Papers forming this PhD by Published Works

In general, the methods used in the studies which form this PhD by Published Works are widely accepted and robust. The specific strengths and limitations of each paper have been outlined in the publications themselves [12-17] and in Chapter 2. However, there are general limitations to the publications when considered as a body of work which should be considered. This is key to considering future research.

Firstly, in relation to the complex group of patients with multimorbidity who formed the focus of this PhD, there are some challenges in relation to generalising findings from my research. Indeed, when defined by a simple disease count patients with multimorbidity are extremely diverse and as such will have varying clinical and healthcare needs. Therefore, attempting to extrapolate results from my studies can be challenging. This is mitigated slightly by the variety of different methodologies used, and some work has focused on certain patient groups such as patients recently admitted to geriatric rehabilitation [17] and residing in nursing homes [14]. Indeed, some of the conclusions of these studies are more focused on sub-groups of patients with multimorbidity. Further work is required to develop more generalisable results, possibly through analyses of certain clusters of conditions or sub-groups of patients with multimorbidity. Linked health and social care datasets may provide an avenue to interrogate further relationships and assist in the stratification of patient groups [476], which was something I was unable to achieve in the presented work.

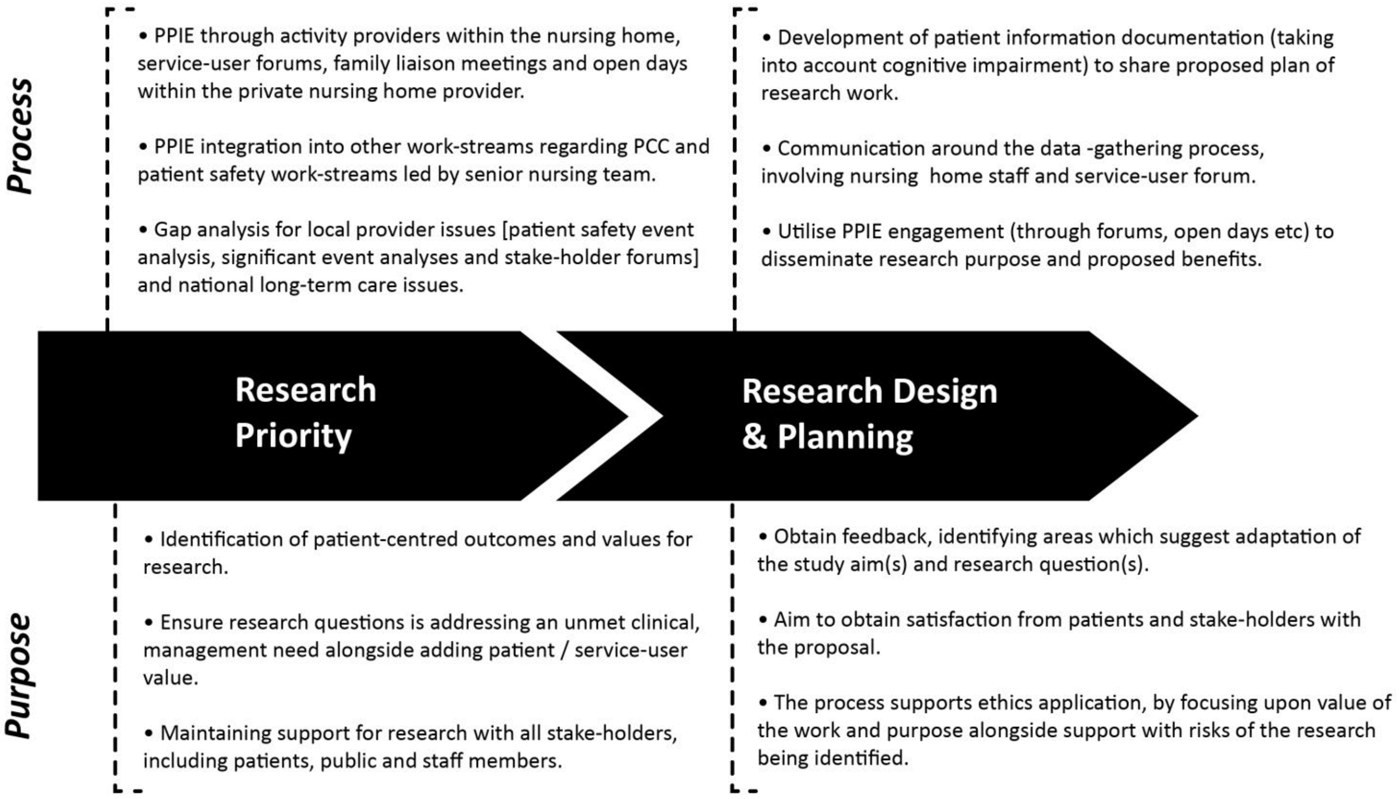
Secondly, the studies that have been published primarily describe and investigate some of the challenges associated with multimorbidity and helped inform the current understanding of the issues. None of the research studies involved developing and testing interventions for multimorbidity. The only exception to this was work on readmission [17], where we attempted to use data to form a set of predictors to help discriminate between those who were or were not readmitted for both the 30-day and 180-readmission cohorts. However, the discriminatory ability of identified readmission risk factors to predict readmission was modest and unlikely to be useful clinically, despite including a measure of functional ability (Barthel score). As the thesis eludes to, the development of multi-faceted interventions and indeed therapeutic approaches for multimorbidity, and their associated performance clinically has become an increasing area of focus for researchers. More broadly, research to improve the utility of the current clinical guidelines [212] and identify groups of patients most likely to gain from such interventions [203,209-211,449] are areas which have significantly expanded since my initial publications.

Thirdly, none of the research and associated six publications which form the basis of this thesis specifically explore and interrogate the health policy changes. This has become an increasing area of focus in relation to the mitigation of the negative sequelae associated with multimorbidity. Indeed, the major structural healthcare change within Scotland through the Public Bodies (Joint Working) (Scotland) Act 2014 was only fully implemented by 2016 [477], and many countries have incorporated multimorbidity into their healthcare strategies and strengthened efforts to develop health and social care integration [478]. The role of health and social care integration, and wider structural change upon important health outcomes relating to multimorbidity is ripe for future studies.

Finally, PPIE is key to all health service research, and this was lacking in the work that forms the basis of the PhD. There are a variety of reasons for this, including using pre-existing datasets and limitations of time, but certainly as discussed in Chapter 2.2 in future research, I will develop targeted PPIE to enhance the relevance and impact of clinical programmes of work.

Indeed, since the publication of my initial work the research culture and context has driven PPIE into centre stage. Figure 4 demonstrates how I may have approached designing, performing, and disseminating the clinical research reported in Paper 3 [14] in the current PPIE climate. This process would use aspects of the MRC framework [147], European work on PPIE [European Patients' Academy on Therapeutic Innovation] [479,480] and publications reporting a greater ability to engage nursing home residents in clinical research [149,150]. Greater PPIE and stakeholder engagement may develop research that improves understanding of the perspectives of patients with multimorbidity and healthcare professionals managing these patients, which has not been explored in the research which forms the basis of this thesis.

Figure 4: Integrating PPIE in developing 'Centrally Active Prescribing for Nursing Home Residents - how are we doing? [14]



Process – Research Priority

- PPIE through activity providers within the nursing home, service-user forums, family liaison meetings and open days within the private nursing home provider.
- PPIE integration into other work-streams regarding PCC and patient safety work-streams led by senior nursing team.
- Gap analysis for local provider issues [patient safety event analysis, significant event analyses and stake-holder forums] and national long-term care issues.

Process – Research Design & Planning

- Development of patient information documentation (taking into account cognitive impairment) to share proposed plan of research work.
- Communication around the data -gathering process, involving nursing home staff and service-user forum.
- Utilise PPIE engagement (through forums, open days etc) to disseminate research purpose and proposed benefits.

Purpose – Research Priority

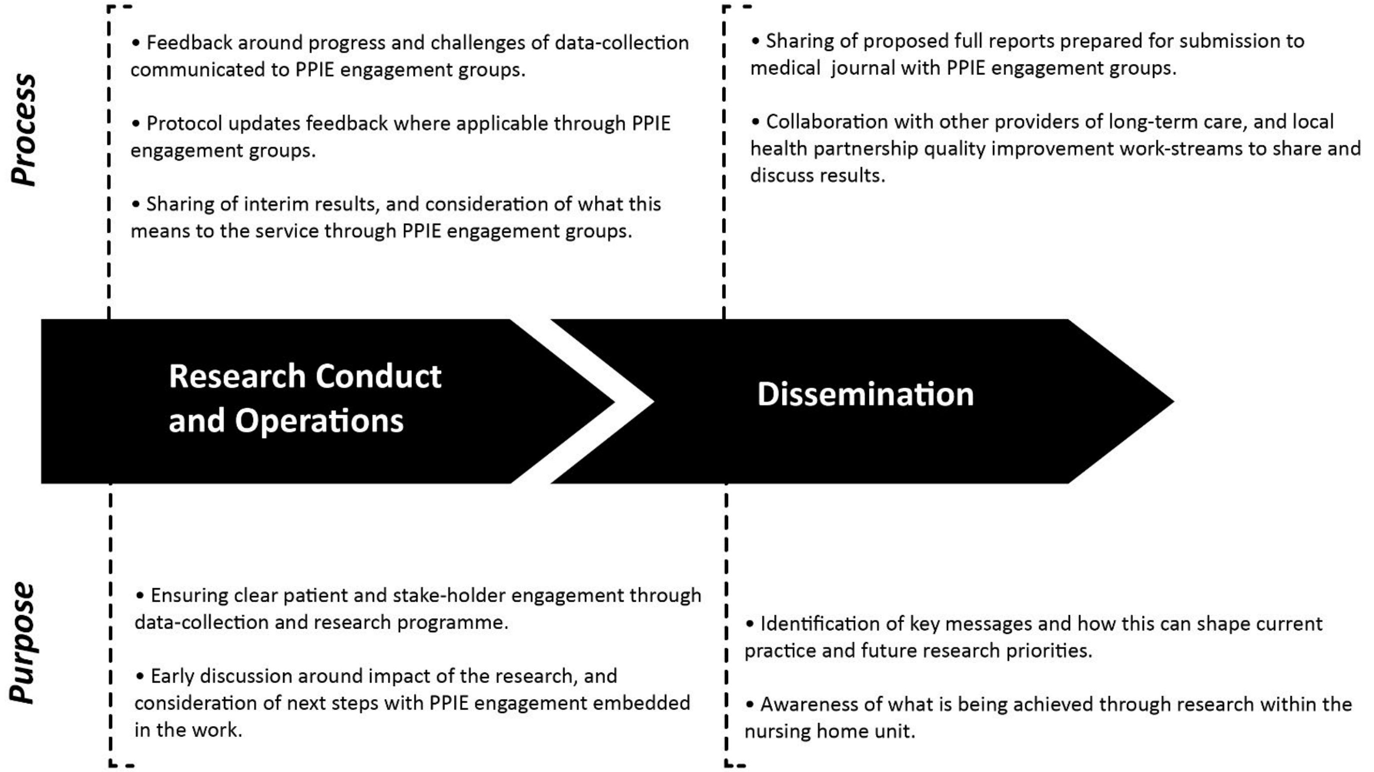
- Identification of patient-centred outcomes and values for research.
- Ensure research questions is addressing an unmet clinical, management need alongside adding patient / service-user value.
- Maintaining support for research with all stake-holders, including patients, public and staff members.

Purpose – Research Design & Planning

- Obtain feedback, identifying areas which suggest adaptation of the study aim(s) and research question(s).
- Aim to obtain satisfaction from patients and stake-holders with the proposal.
- The process supports ethics application, by focusing upon value of the work and purpose alongside support with risks of the research being identified.

Reference
Geissler, J., Ryll, B., di Priolo, S.L. et al. 2017. Improving Patient Involvement in Medicines Research and Development: A Practical Roadmap. Ther Innov Regul Sci. (51): 612–619.

Figure 4: Integrating PPIE in developing 'Centrally Active Prescribing for Nursing Home Residents - how are we doing? [14]



Process

- Feedback around progress and challenges of data-collection communicated to PPIE engagement groups.
- Protocol updates feedback where applicable through PPIE engagement groups.
- Sharing of interim results, and consideration of what this means to the service through PPIE engagement groups.

- Sharing of proposed full reports prepared for submission to medical journal with PPIE engagement groups.
- Collaboration with other providers of long-term care, and local health partnership quality improvement work-streams to share and discuss results.

Research Conduct and Operations

Dissemination

Purpose

- Ensuring clear patient and stake-holder engagement through data-collection and research programme.
- Early discussion around impact of the research, and consideration of next steps with PPIE engagement embedded in the work.

- Identification of key messages and how this can shape current practice and future research priorities.
- Awareness of what is being achieved through research within the nursing home unit.

Reference
Geissler, J., Ryll, B., di Priolo, S.L. et al. 2017. Improving Patient Involvement in Medicines Research and Development: A Practical Roadmap. Ther Innov Regul Sci. (51): 612–619.

6.8 Future Research Directions

In many regards, the field of multimorbidity, of which my work forms a part, is still in its early stages, with the recent development of a standardised approach to defining multimorbidity [51,481]. This has implications for my work both as a clinician and as a researcher moving forward. The Academy of Medical Sciences report on multimorbidity [51] has identified six research area priorities, with associated increases for research funding. Within the last six years there have been several RCTs testing interventions for patients with multimorbidity in areas of care coordination, support for self-management [87,482-484], and medicines management [485]. However, systematic reviews to date have not been able to report strongly evidenced intervention recommendations for clinical practice [191,206,398,399]. In this context there are several areas where further research is required.

Firstly, current approaches in measuring and clustering multimorbidity are helping to inform researchers, but further work is required to make this clinical useful.

Research aims to answer important pending questions such as:

(i) How does the treatment of single diseases impact morbidity and mortality for patients with certain clusters of multimorbidity?

(ii) How do different diseases interact with each other to impact clinically relevant outcomes?

(iii) How does guideline adherence impact survival for patients with different clusters of diseases?

Identification of common clusters is a crucial starting point, and this process is well underway [203,209-211,454].

Secondly, further research is needed in relation to mental-physical health multimorbidity. This includes whether primary care interventions targeting multimorbidity, particularly for patients in the most socioeconomically deprived areas, can improve quality of life, reduce hospital use and help address widening health inequalities. Furthermore, developing an understanding of the interplay between mental and physical health multimorbidity is another crucial area, with the hope that this will enable interventions to be developed and tested in clinical trials.

Thirdly, integrated care requires investment and collaboration to agree on a measurement of health and social care integration, alongside improving data collection within social and community services. This will enable the standardisation of comparisons between regions and areas, alongside improving the ability of datasets to answer important research and policy questions. Further research will ideally enable clarity of whether integration works, and in what form.

Fourthly, further research on shared decision making and personalised strategies to care for patients with multimorbidity is important. These interventions may provide individual GPs an opportunity to influence patient outcomes at an individual consultation level. Furthermore, research outlining how shared decision making influences patient experience, clinically relevant outcomes and healthcare costs is required. If this research demonstrates effectiveness then the practice will need to be integrated into clinical care. The Ariadne principles, which by definition encourage shared decision making, may be a good fit for clinical consultations for patients with multimorbidity and the basis of further research. It may be useful to explore the perspectives of healthcare professionals and patients on the framework.

Finally, there is a need to provide and communicate practical advice for clinicians in relation to managing patients with multimorbidity. There is evidence that relational continuity [486] and interventions targeting PCC [97,193] may be helpful but clear guidance, possibly in the manner of clinical case vignettes or worked examples are lacking at an operational level.

6.9 Learning through Research

Over the course of several years, I have been working within the field of multimorbidity, developing my understanding of different research methodologies to answer relevant research questions. This process has been associated with extensive learning and development on a personal and professional level.

Firstly, I have developed a wide array of research skills throughout the period of clinical research the result of which can be seen within the papers themselves and narrative thesis. I have been able to handle increasingly complex datasets over time and have developed my knowledge of commonly used statistical methods. I have continued to be actively involved in clinical research publishing several papers since the commencement of this PhD by Published Works [94, 122, 123, 352]. Recently I completed the Scottish Improvement Leader Programme, transferring my knowledge and understanding of research concepts into quality improvement work-streams.

Secondly, the transferability of my research and clinical understanding of issues surrounding multimorbidity has influenced my own practice, local policies and guidelines, alongside teaching and training. Table 6 summarises the clinical implications of my published work, in relation to clinical practice, policy and medical education.

Table 6: Clinical Implications of Published Work on Personal Practice

	Reference for the Paper	**Clinical Implications**
Paper 1	Hughes LD. ***Utilizing Clinical Practice Guidelines in Multimorbid Older Patients – A Challenging Clinical Dilemma***. Journal American Academy of Geriatrics 2012**.** 60:2180-1 [12]	*Medical Education* * This paper forms the basis of regular teaching I deliver to undergraduate MBChB students, trainee nurse practitioners, and Foundation Year doctors.
Paper 2	Hughes LD, McMurdo MET, Guthrie B. ***Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to older people with multiple co-morbidities.*** Age Ageing 2013; 42:62-69 [13]	*Clinical Practice* * Tayview Medical Practice has been developing a 'complex care clinic' where longer appointments are made available for patients with multiple long-term health conditions and frequent practice attendance. This will be the basis for a formal service development review and patient outcomes monitoring in summer 2024. *Policy* * There are discussions around a GP Cluster Complexity Clinic, potentially involving secondary care clinicians for focused virtual discussions with GPs about complex patients. My work has supported this process by identifying the challenges of guideline-based case for generalists. *Medical Education* * This paper forms the basis of regular teaching I deliver to undergraduate MBChB students, trainee nurse practitioners, and Foundation Years Doctors.
Paper 3	Hughes LD, Hanslip J & Witham MD. ***Centrally Active Prescribing for Nursing Home Residents-how are we doing?*** European Geriatric Medicine 2012 3 (5) p. 304–307 [14]	*Clinical Practice* * This research was used as a driver for implementing a nursing home prescribing programme in my previous practice (where I worked as nursing home clinical lead) with support from pharmacy team. Identification of under-treatment of pain was targeted alongside other prescribing indicators. *Medical Education* * This paper has led to a role where I deliver annual regional teaching for GPs in Angus on nursing home prescribing and pain assessment for patients with advanced dementia.

Table 6 (continued): Clinical Implications of Published Work on Personal Practice

	Reference for the Paper	**Clinical Implications**
Paper 4	Hughes LD, Raitt N, Riaz MA, Baldwin SJ, Erskine K, Graham G. ***Primary Care Hypnotic and Anxiolytic Prescription – Reviewing Prescribing Practice Over Eight Years.*** Journal of Family Medicine and Primary Care. 2016 5(3): p.652-657 [15]	*Policy* * This work has provided the background and justification to GP Cluster locality work within my previous practice in Arbroath. This work-stream justified and developed a pilot programme to improve mental health access to social prescribers, psychology / counselling services and mental health nurse provision within a small number of practices. *Medical Education* * The paper forms the basis of educational sessions delivered to junior doctors around quality improvement and potential for unexpected change in the context of incentivising certain outcomes.
Paper 5	Hughes LD, Cochrane L, McMurdo MET & Guthrie B. ***Psychoactive Prescribing for Older People – What difference does 15 years make?*** International Journal of Geriatric Psychiatry. 2016;31(1):49-57 [16]	*Policy* * This work has provided the background and justification to GP Cluster locality work within my previous practice in Arbroath. This work-stream justified and developed a pilot programme to improve mental health access to social prescribers, psychology / counselling services and mental health nurse provision within a small number of practices.
Paper 6	Hughes LD & Witham MD. ***Causes and correlates of 30 day and 180-day readmission following discharge from a Medicine for the Elderly Rehabilitation unit.*** BMC Geriatrics 2018. 18:197 [17]	*Clinical Practice* * Has supported development of a ’30-day hospital readmission virtual clinic’ within my previous practice in Arbroath and current practice at Tayview. This GP-led review identifies whether there are any particular areas where targeted input may support patients after discharge.

Within my current practice and the broader multi-disciplinary team, we have been developing a 'complex care clinic' where more time is made available for patients with multimorbidity with multiple (3 or more) recent attendances (within 3 months) to the practice or hospital. The practice is also actively reviewing patients readmitted within 30 days and 180 days in a proactive manner, which includes practice pharmacist time for polypharmacy reviews and deprescribing. Work published in the form of Paper 1 [12] and Paper 2 [13] are commonly used to stimulate discussions for undergraduate students on placement at our practice about the challenges associated with the management of long-term conditions on patients with multimorbidity. Extending this, I frequently deliver teaching on multimorbidity and frailty to junior doctors and trainee advanced nurse practitioners within daytime and out of hours general practice. The aim of such teaching is to increase awareness of the challenges but being positive about potential approaches which can support patients receive appropriate PCC and treatment. Expanding this into GP cluster, regional, and national change will require a continued variety of approaches (integrating research, teaching and engagement programmes) to promote and influence policy and clinical change.

Local policy work to improve anxiolytic and hypnotic drug prescribing in Angus (a rural area in the north-east of Scotland) used work published in Paper 4 [15] and Paper 5 [16] to adjust the overall approaches towards prescribing of these medications and increased awareness towards potential overuse of these medications. This included a broader range of resources and to support GPs make better prescribing choices through investment in community mental health nurses and social prescribers alongside a small number of rapid access psychology / counselling services (albeit on pilot basis). Clearly, I cannot fully attribute this change my work, but the process of placing research into context, and influencing policy was really exciting and is certainly something I wish to continue moving forwards. Scaling up this process to larger programmes of work will require further supported development.

The process of completing the PhD by Published Works has provided an opportunity to reflect on my previous work, and place it in a current context. Over my period of registration, focused consideration of research methodologies has been helpful in developing me as a researcher and planning my next steps towards academic development. I have become increasingly interested in qualitative methods, as I feel this would be a useful approach for exploring GP and patient experience of multimorbidity. Furthermore, as outlined in the section above (6.9), supporting shared decision making and exploring its impact for patients with multimorbidity is another area of clinical interest. The lens of the Ariadne principles may be a good place to develop research questions as this develops.

With hindsight if my research journey was commencing again, there are several areas I would consider:

Firstly, PPIE in clinical research was not actively considered throughout the programme of work which forms the basis of this thesis. There were a variety of reasons for this (e.g. focus upon ethical approval and logistics), but PPIE has undoubtedly developed into a crucial aspect of clinical research over the course of my studies. PPIE within nursing home research published in Paper 3 [14] may have influenced aspects of the data collection or different research focus secondary to expertise based on experience. It is clearly important given the imperative of inclusiveness and the potential to better understand both effective study design and findings. PPIE is clearly of importance to work moving forward.

Secondly, greater collaboration and networking would be beneficial as research is a team and collegiate endeavour, and all six publications [12-17] are testament to this, but at times I found research isolating especially as other non-research commitments increased. Upon reflection, developing more relationships with junior researchers and medical student research groups may have supported this process. Certainly, I feel that I have addressed this now and have working relationships with researchers at different stages and levels of seniority. It would also enable me to develop my own and others research capacity in this important area of investigation. Those networks would also strengthen the research through drawing on diverse methodological and research expertise.

Thirdly, throughout my undergraduate MBChB I regularly took on additional audit work, projects, and research programmes which led to a significant workload. It was a discussion with Professor Miles Witham who advised considering more focused endeavour on higher yield projects, as the volume of work I was doing was simply not sustainable. For example, completing several clinical audits in one locality may have been at the expense of spending time developing skills in systematic reviews. It was his conversation about all my work being robust and of high-quality, but perhaps not of high-value that actually drove some of my interest in value in healthcare alongside personal reflection. These are ongoing reflections as to how to prioritise work, ascertain best value projects and enable goals to be achieved effectively alongside considering opportunity costs.

Finally, there are some specific areas within a couple of studies which with hindsight I would have enhanced. I could have made more of an opportunity in both single-centre studies [14,15] to have expanded the datasets to include more nursing homes and GP practices which may have increased the external validity of the work. Similarly, I had an opportunity to revisit the nursing home for further data collection 1 year after the initial work but I was unable to deliver this to other work commitments at that time. A larger research team may have been able to have provide support for more longitudinal data collection.

6.10 Chapter Conclusion

Given that five years have elapsed since the publication of the most recent work which forms the body of the thesis, there have clearly been developments in the literature in the areas surrounding multimorbidity. There are several examples outlined within the chapter. Firstly, shared decision making and interventions to support prescribing and mitigate the challenges of polypharmacy are starting to enter the clinic although the process is at an early stage. Secondly, there is increasing evidence regarding the limitations of P4P programmes, alongside how their design implementation can maximise their benefits. Thirdly, the aim of PCC has continued to be a core focus of health policy, especially as a way to support the management of patients with multimorbidity.

There remain significant gaps in the literature, such as around how the identification of common multimorbidity clusters can be used to influence clinical care decisions and commissioning or how integrated care can improve healthcare outcomes for patients with multimorbidity. The case for preventative healthcare and social investment to reduce the impact of multimorbidity on communities, particularly those with higher rates of deprivation, remains strong but evidence for specific interventions continues to be limited. The Ariadne principles, which has shared decision making at its centre, remains a framework for patients with multimorbidity which would benefit from further research around how it can be operationalised.

There is no doubt that wide system changes are needed to improve healthcare outcomes for patients with multimorbidity, but change is also needed at the individual consultation level in order to realise these improvements.

Chapter 7

Thesis Conclusions

7. Thesis Conclusions

This thesis has brought together research reported in six papers published between 2012 and 2018 that explore important themes in relation to multimorbidity with an associated narrative. The connecting narrative has provided an opportunity to reflect on the body of work and discuss the challenges of the management of people with multimorbidity.

Many health services, models of care and clinical practice guidelines are not designed for patients with multimorbidity. Reorientation of the health system towards patient centred frameworks, such as the Ariadne principles [11], may be an approach to support this. The thesis has considered how my published work relates to the Ariadne principles and has discussed important themes closely associated with multimorbidity including deprescribing, treatment burden and PCC.

The studies reported in six publications which form the basis of this connecting narrative, provide evidence that I have published original and significant work contributing to the broader literature in relation to multimorbidity. These papers have been well cited (see Table 3), with the study presented in Paper 2 particularly well cited [13]. Furthermore, they have provided the basis for local and regional programmes to address some of the isolated difficulties such as prescribing practice, polypharmacy and readmission rates alongside medical education teaching programmes. Whilst the research associated with these papers have been the result of independent endeavour from the original ideas and design of the research to first author publication, I have been supported throughout this time by academics who have been inspirational and invaluable from both an academic and clinical perspective. Developing these research connections is a crucial part of my broader academic journey.

Multimorbidity provides both clinical and research challenges, with no panacea or unifying intervention to improve clinical outcomes for patients with multimorbidity.

The future will likely involve nuance, pragmatism and strong primary care systems to coordinate and deliver care to an ageing society.

There are several areas of future work within multimorbidity which are important. This includes understanding the clinical characteristics through disease clustering and developing and evaluating new models of care for different groups of people with multimorbidity. Integrated care continues to be an area with promise, but challenges remain across the UK and within Scotland it will be particularly closely watched with upcoming change in policies. It will be important from a clinical and research perspective to assess how the implementation of the National Care Service and next stage of the GP contract impact and influence the care and services provided by the health service for people with multimorbidity.

From my own perspective, I will be starting work through the University of St Andrews, looking at the GP cluster model of care with areas such as care continuity, how progress towards care integration is viewed by GPs, what GPs see as the ideal approach for multimorbidity care and what outcomes should be targeted. Qualitative work around shared decision making and PCC is an area I wish to research, using the Ariadne principles as a basis for future work.

Our ageing population ensures that delivering high-quality sustainable healthcare for patients with multimorbidity will remain a primary concern and area of research importance for many years to come. This will require significant time, expertise and investment from clinicians, academics, policymakers and politicians alike. On an individual level, this is an area that I relish the opportunity to continue working within.

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Appendix A: Six full-text papers which for the basis for PhD by Published Works

Paper 1: Hughes LD. Utilizing Clinical Practice Guidelines in Multimorbid Older Patients – A Challenging Clinical Dilemma. Journal American Academy of Geriatrics. 2012. 60:2180-1

in hospice or inpatient palliative care settings. A number of psychotherapies have been developed to address end-of-life concerns in terminally ill individuals, but their efficacy and applicability in a range of palliative care settings have yet to be established (see review[9]). Determining the prevalence of specific dignity-related concerns may help identify common core themes to target in developing psychotherapeutic interventions for palliative care. Furthermore, given that the controversial use of palliative sedation in managing existential distress is, in part, due to a poorly defined construct,[10] objective measures of psychological suffering such as the PDI may help establish clearer guidelines for the use of palliative sedation for psychological symptoms in terminally ill individuals.

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CASE REPORT

USING CLINICAL PRACTICE GUIDELINES IN MULTIMORBID OLDER ADULTS—A CHALLENGING CLINICAL DILEMMA

To the Editor: Clinical guidelines systematically bring together evidence regarding a single condition or group of related conditions and provide recommendations for management based on the evidence where it exists and consensus where it does not.[1] The implementation of clinical guideline recommendations reduces practice variation and is associated with fewer deaths and hospitalizations.[2] However, a recent study noted that U.S. clinical guidelines rarely address comorbidity, and adherence to guideline recommendations in caring for an older person with multimorbidity would often lead to a complex and sometimes contradictory drug regimen.[3] Similar findings have been noted in the United Kingdom and Canada, where national authorities develop guidelines in a more coordinated manner.[1,4] This case report reinforces the point that clinicians must use caution when applying clinical guideline recommendations to older adults.

Table 1. John Smith Clinical Guideline Recommendations[5–7]

Recommendations	Patient Care Plan Before Review (National Institute of Clinical Excellence Clinical Guideline Recommendations)	Patient Care Plan After Review
Pharmaceutical	Fluoxetine	Sertraline
	Ranitidine	Ranitidine
	Donepezil hydrochloride	Donepezil hydrochloride
	Paracetamol as needed	Paracetamol (twice daily)
	Topical ibuprofen	Topical ibuprofen
Follow-up	Active monitoring[a]	GP liaised with the patient and arranged several of these appointments to be combined at the practice
	Self-guided CBT[b]	
	Appointment to assess cognition	
	Structured group cognitive stimulation program	
	Memory Clinic Appointments	
	6-month review of acetylcholinesterase inhibitor therapy	

[a] General practitioner review 2 weeks after first appointment and then every 2–4 weeks for 3 months. Monthly follow-up depending upon patient symptoms and risk of relapse.

[b] Self-guided cognitive behavioral therapy (CBT) consists of a 9- to 12-week program of 6 to 8 sessions. Aspects of this could be repeated depending upon patient preference, engagement, and treatment response.

CASE REPORT

John Smith was a 74-year-old man with a confirmed diagnosis of unipolar depression (diagnosed 2 years previously), Alzheimer's disease (diagnosed 1 year previously), and long-standing symptomatic osteoarthritis. He was in otherwise excellent health and remained as active as possible with his wife, who was also well. His general practitioner (GP), who explicitly followed the National Institute of Clinical Excellence (NICE) guidelines for his three conditions, managed John in primary care.[5–7]

Six months after being diagnosed with Alzheimer's disease, John voiced concerns to his GP (Dr. A) after feeling like he "was never out of a doctor's reach for more than 5 days" and that "the doctors just tell me what is best according to the guidebook." Dr. A explained that he was following guidelines for each of his conditions because these recommendations were based upon the best available evidence for his conditions, but he agreed to review John's care recommendations with him at a subsequent appointment to take his concerns on board. This review process led to several changes in his care plan, in terms of prescribed medications and follow-up care. Table 1 summarizes his care plan before and after this GP-led review. Medications were changed after clinical assessment found that John required more-regular pain relief for his osteoarthritis and a selective serotonin reuptake inhibitor which caused less indigestion. John noted that making changes to his appointments (arranged explicitly following NICE guidelines), meaning that many appointments could be combined and reducing traveling to and from the GP practice had been a major improvement for him. GP-led review of medications and care plan reviews have been shown to be beneficial in reducing drug prescriptions, reducing costs, and improving patient–doctor relationships.[8,9]

Dr. A indicated that following guideline recommendations to meet practice targets meant he may have made some decisions without fully considering the effect upon John. He also stressed that linking guideline recommendations to financial incentives can make it hard to achieve patient-centered care while at the same time meeting healthcare center standards, which are reviewed regularly by the local health board. This latter point has been noted in the literature,[3] and there have recently been calls for incentive schemes to be more carefully designed before implementation.[10]

CONCLUSION

Current clinical practice guidelines provide clinicians with an accessible and reliable evidence-based resource to make clinical decisions for patients and are widely used as performance indicators in primary care.[1,3,4,10] This case study illustrates, there remain practical challenges in applying guideline recommendations to a multimorbid older adult for the clinician, and explicitly following guideline recommendations may lead to patient frustration with his or her health care. Concerted action is required to develop guidelines that are more aligned with the complicated clinical, social, and psychological needs of multimorbid older adults.[1,3,4]

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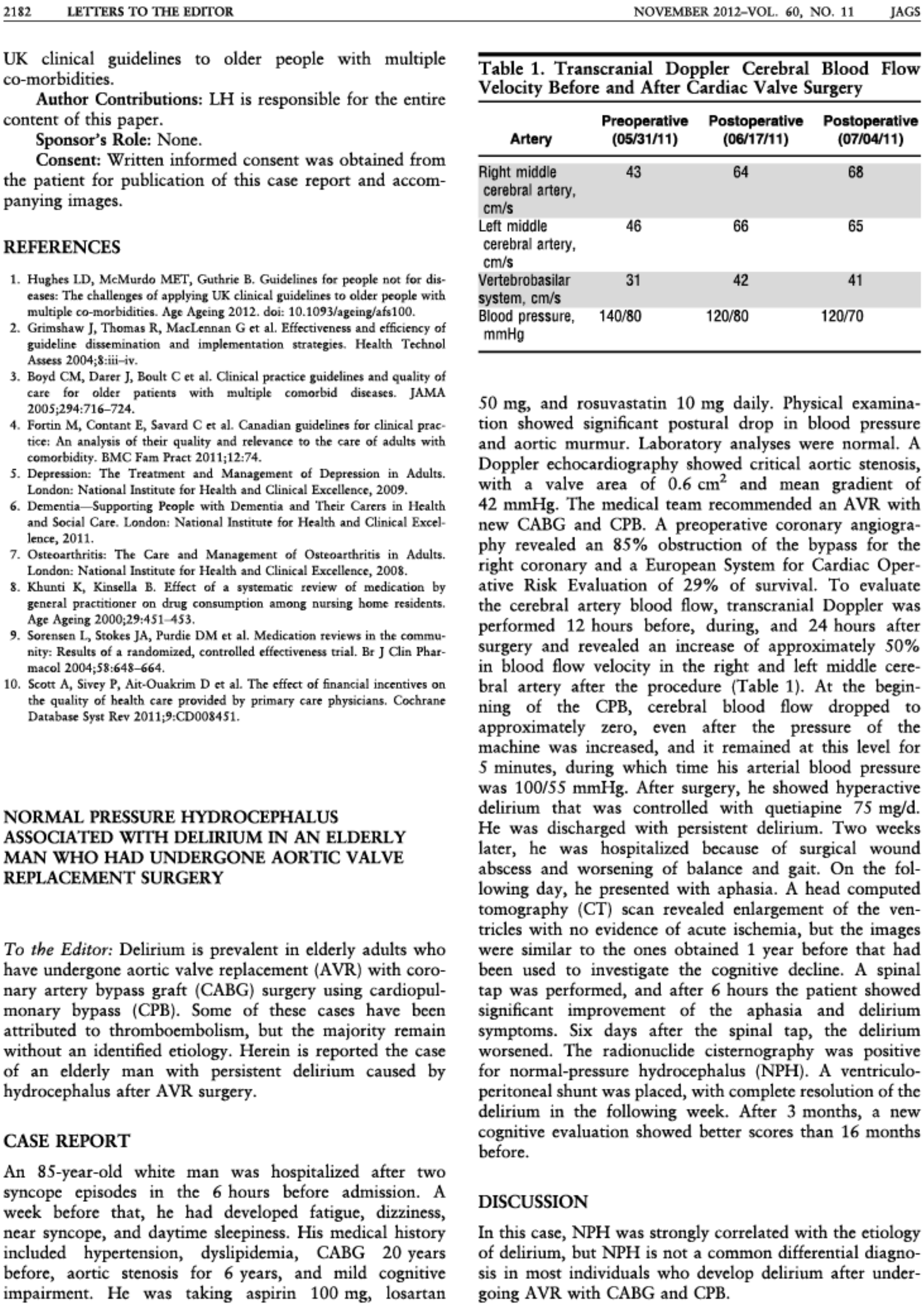

UK clinical guidelines to older people with multiple co-morbidities.

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Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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NORMAL PRESSURE HYDROCEPHALUS ASSOCIATED WITH DELIRIUM IN AN ELDERLY MAN WHO HAD UNDERGONE AORTIC VALVE REPLACEMENT SURGERY

To the Editor: Delirium is prevalent in elderly adults who have undergone aortic valve replacement (AVR) with coronary artery bypass graft (CABG) surgery using cardiopulmonary bypass (CPB). Some of these cases have been attributed to thromboembolism, but the majority remain without an identified etiology. Herein is reported the case of an elderly man with persistent delirium caused by hydrocephalus after AVR surgery.

CASE REPORT

An 85-year-old white man was hospitalized after two syncope episodes in the 6 hours before admission. A week before that, he had developed fatigue, dizziness, near syncope, and daytime sleepiness. His medical history included hypertension, dyslipidemia, CABG 20 years before, aortic stenosis for 6 years, and mild cognitive impairment. He was taking aspirin 100 mg, losartan 50 mg, and rosuvastatin 10 mg daily. Physical examination showed significant postural drop in blood pressure and aortic murmur. Laboratory analyses were normal. A Doppler echocardiography showed critical aortic stenosis, with a valve area of 0.6 cm^2 and mean gradient of 42 mmHg. The medical team recommended an AVR with new CABG and CPB. A preoperative coronary angiography revealed an 85% obstruction of the bypass for the right coronary and a European System for Cardiac Operative Risk Evaluation of 29% of survival. To evaluate the cerebral artery blood flow, transcranial Doppler was performed 12 hours before, during, and 24 hours after surgery and revealed an increase of approximately 50% in blood flow velocity in the right and left middle cerebral artery after the procedure (Table 1). At the beginning of the CPB, cerebral blood flow dropped to approximately zero, even after the pressure of the machine was increased, and it remained at this level for 5 minutes, during which time his arterial blood pressure was 100/55 mmHg. After surgery, he showed hyperactive delirium that was controlled with quetiapine 75 mg/d. He was discharged with persistent delirium. Two weeks later, he was hospitalized because of surgical wound abscess and worsening of balance and gait. On the following day, he presented with aphasia. A head computed tomography (CT) scan revealed enlargement of the ventricles with no evidence of acute ischemia, but the images were similar to the ones obtained 1 year before that had been used to investigate the cognitive decline. A spinal tap was performed, and after 6 hours the patient showed significant improvement of the aphasia and delirium symptoms. Six days after the spinal tap, the delirium worsened. The radionuclide cisternography was positive for normal-pressure hydrocephalus (NPH). A ventriculoperitoneal shunt was placed, with complete resolution of the delirium in the following week. After 3 months, a new cognitive evaluation showed better scores than 16 months before.

Table 1. Transcranial Doppler Cerebral Blood Flow Velocity Before and After Cardiac Valve Surgery

Artery	Preoperative (05/31/11)	Postoperative (06/17/11)	Postoperative (07/04/11)
Right middle cerebral artery, cm/s	43	64	68
Left middle cerebral artery, cm/s	46	66	65
Vertebrobasilar system, cm/s	31	42	41
Blood pressure, mmHg	140/80	120/80	120/70

DISCUSSION

In this case, NPH was strongly correlated with the etiology of delirium, but NPH is not a common differential diagnosis in most individuals who develop delirium after undergoing AVR with CABG and CPB.

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Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity

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Abstract

Background: currently one of the major challenges facing clinical guidelines is multimorbidity. Current guidelines are not designed to consider the cumulative impact of treatment recommendations on people with several conditions, nor to allow comparison of relative benefits or risks. This is despite the fact that multimorbidity is a common phenomenon.
Objective: to examine the extent to which National Institute of Health and Clinical Excellence (NICE) guidelines address patient comorbidity, patient centred care and patient compliance to treatment recommendations.
Methods: five NICE clinical guidelines were selected for review (type-2 diabetes mellitus, secondary prevention for people with myocardial infarction, osteoarthritis, chronic obstructive pulmonary disease and depression) as these conditions are common causes of comorbidity and the guidelines had all been produced since 2007. Two authors extracted information from each full guideline and noted the extent to which the guidelines accounted for patient comorbidity, patient centred care and patient compliance. The cumulative recommended treatment, follow-up and self-care regime for two hypothetical patients were then created to illustrate the potential cumulative impact of applying single disease recommendations to people with multimorbidity.
Results: comorbidity and patient adherence were inconsistently accounted for in the guidelines, ranging from extensive discussion to none at all. Patient centred care was discussed in generic terms across the guidelines with limited disease-specific recommendations for clinicians. Explicitly following guideline recommendations for our two hypothetical patients would lead to a considerable treatment burden, even when recommendations were followed for mild to moderate conditions. In addition, the follow-up and self-care regime was complex potentially presenting problems for patient compliance.

Conclusion: clinical guidelines have played an important role in improving healthcare for people with long-term conditions. However, in people with multimorbidity current guideline recommendations rapidly cumulate to drive polypharmacy, without providing guidance on how best to prioritise recommendations for individuals in whom treatment burden will sometimes be overwhelming.

Keywords: *multimorbidity, elderly, family practice, clinical guidelines*

Introduction

Clinical guidelines systematically bring together evidence regarding a single condition or group of related conditions, and provide recommendations for patient management based on the evidence where it exists and consensus where it does not. The implementation of clinical guideline recommendations reduces practice variation, and is associated with reduced deaths and hospitalisations [1]. These improvements have been achieved by linking guideline recommendations with financial incentives, such as the quality outcomes framework. Importantly, existing clinical guidelines largely focus on single diseases, and are usually based on evidence from highly selected populations who may not be typical of the actual population with the condition.

Currently one of the major challenges facing clinical guidelines is multimorbidity. Multimorbidity has been defined as 'the co-occurrence of multiple chronic or acute diseases and medical conditions within one person' [2]. Current guidelines are not designed to consider the cumulative impact of treatment recommendations on people with several conditions, nor to allow the comparison of relative benefits or risks. This is despite the fact that multimorbidity is a common phenomenon, and in older people is the norm [3–5]. Indeed, Uijen *et al.* [3] noted that 55% of Dutch people aged 75 and over have four or more chronic conditions.

This paper examines the application of National Institute of Health and Clinical Excellence (NICE) guidelines to people with multimorbidity and the implications for the creation of evidence and future guideline development.

Limitations of existing clinical guidelines

Existing guidelines are usually based on evidence from clinical trials carried out in relatively narrow subsets of the population. Older people have historically been systematically excluded from clinical trials, even though older people usually have the highest prevalence of chronic disease and are therefore the most likely targets of guideline recommendations [6, 7]. Trials also often exclude people with significant comorbidity, further narrowing the population studied [6, 7]. Key clinical trials in heart failure would only have included 13–25% of people with diagnosed heart failure in the community [8], with the corresponding figure for chronic obstructive pulmonary disease (COPD) being 10% [9]. Overall, 81% of randomised controlled trials published in high-impact journals excluded patients with medical comorbidities [6]. Ensuring the internal validity of trials is critical, but the external validity or generalisability of much current evidence is often relatively weak [10].

Driven by the nature of evidence and reflecting current health-care organisation, guidelines usually focus on a single condition, although most people with chronic disease have multiple conditions, and the majority of older people are multimorbid [3–5, 11, 12]. In 2005 Boyd *et al.* [13] examined the applicability of US clinical guidelines to older individuals with several comorbid diseases. The study reviewed clinical guidelines for nine chronic conditions to determine whether they adequately addressed the care needs of older patients with multiple comorbid diseases. The authors found that clinical guidelines rarely addressed comorbidity, and adherence to guideline recommendations in caring for an older person with multimorbidity would often lead to complex and sometimes contradictory drug and self-care regimes [13]. However, it is unclear whether the same applies in countries where guideline development is more co-ordinated, and the US study only examined guidelines for physical conditions despite physical–mental health comorbidity being common [3].

Methods

Applying NICE guidelines to people with multimorbidity

We examined the extent to which recent UK clinical guideline recommendations for five common conditions addressed care for older people, comorbidity and patient-centred care. The guidelines selected were for type 2 diabetes mellitus, secondary prevention in people with previous myocardial infarction (MI), osteoarthritis, chronic COPD and depression (two guidelines including one for managing depression in people with chronic physical problems) [14–19]. These conditions were chosen because they are common causes of morbidity and a NICE clinical guideline had been published in the past 5 years for each. The majority of people with these conditions will have significant comorbidity (71% of people with diabetes are multimorbid, 92% with coronary heart disease, 82% with osteoarthritis, 83% with COPD and 64% with depression) [2].

L.H. and B.G. extracted information from each full guideline and quick reference guide when available, which summarise the recommendations and are the documents most likely to be used by clinicians. We examined whether and how recommendations gave specific advice about care for older people or those with comorbidities, advice on providing patient-centred care by accounting for patient choice and preferences, and advice on promoting adherence to treatment recommendations. These criteria were selected as guidelines have been noted in previous studies to be limited in relation to age-specific and multimorbid-specific clinical recommendations, and in providing information about how patient-centred care can be achieved while following guidelines [13, 20]. In addition, despite patient adherence being recognised as a major problem, particularly in multimorbid patients, there has been limited reference on how this can be promoted in guideline recommendations [5, 13]. The authors wished to assess if UK-based guidelines had similar limitations or provided more comprehensive guidance for clinicians.

The authors noted the extent to which guidelines discussed these criteria and categorised this as *none*, *minimal* (criteria specifically noted on ≤2 occasions), *moderate* (criteria specifically noted on 3–5 occasions) or *extensive* (criteria specifically noted ≥5 occasions).

For each guideline, recommendations for chronic management were summarised for drug treatment, self-care and health service follow-up. The cumulative recommended treatment, follow-up and self-care regime for two hypothetical patients was then created to illustrate the potential cumulative impact of applying single disease recommendations to people with multimorbidity. These patients were Mrs A, a 78-year-old woman with all five conditions at mild-to-moderate severity, and Mr B, a 75-year-old man with two conditions (type 2 diabetes mellitus and COPD) at mild-to-moderate severity.

Results

Do the guidelines explicitly address age, comorbidity and patient-centred care?

All of the guidelines consider older patients to varying degrees, although usually via general statements suggesting that clinicians should consider individual drug characteristics and prescribe age-adjusted doses of relevant medications. More specific advice ranged from minimal mention of antidepressant choice in older people in the depression guideline to moderate discussion of particular recommendations in other guidelines, such as that age should not influence the offer of cardiac rehabilitation after MI. No guideline explicitly commented on the quality of the evidence in older people, or on the generalisability of trial evidence (Table 1).

Comorbidity was inconsistently accounted for in the guidelines, usually without detailed discussion. Comorbidity was most extensively addressed in the depression guidelines, which provided comprehensive advice on management in the presence of a physical condition with functional limitation and on important interactions of antidepressant drugs. Two of the physical disease guidelines provided extensive discussion for a few topics (holistic assessment in osteoarthritis and the promotion of uptake of cardiac rehabilitation in people with other conditions), but otherwise only relatively minimal comment in relation to particular treatments. Apart from the MI guideline, cross-referencing to other guidelines for important comorbidities was uncommon, and no information was provided on the relative risks and benefits of the different treatments recommended.

All the guidelines examined had a generic introduction emphasising the importance of tailoring treatment to patients' needs and preferences. However, this generic advice was very similar across guidelines, and provided limited disease-specific recommendations for achieving patient-centred care. In addition to the generic introduction, the depression guideline extensively discussed accounting for individual preference, whereas the physical disease guidelines varied from some discussion of patient preference in relation to particular drugs (oral hypoglycaemics in the diabetes guideline) through general advice on clearly communicating risks and benefits of treatment (osteoarthritis) to no explicit discussion (MI and COPD).

In terms of adherence to treatment recommendations, the depression guideline had a moderate amount of explicit discussion of ensuring adherence to antidepressant drugs by involving patients in the decision to initiate medication, and assessing adherence in non-responders. The physical disease guidelines ranged from moderate discussion in relation to particular topics (cardiac and pulmonary rehabilitation, inhaler technique, exercise) to no explicit discussion (diabetes), although research into the relationship between treatment regime complexity and adherence was recommended by the guidelines for osteoarthritis, secondary prevention of MI and type 2 diabetes mellitus (Table 1).

Overall, there was limited accounting for age, comorbidity, patient centredness and adherence in the recommendations made by guidelines, with the depression guideline providing significantly more comprehensive guidance than the physical disease guidelines which typically only discussed these issues in relation to particular recommendations. It was unclear why these recommendations were prioritised since, for example, adherence to blood pressure lowering medication in type 2 diabetes seems as likely to be problematic as adherence to oral hypoglycaemics.

Applying the guidelines to hypothetical patients

We identified guideline recommendations applicable to two patients:

- Mrs A: A 78-year-old woman with previous MI, type 2 diabetes, osteoarthritis, COPD and depression.
- Mr B: A 75-year-old man with type 2 diabetes mellitus and COPD.

These were used to derive a treatment plan that included prescribed drugs, self-care tasks and recommended healthcare follow-up.

Mrs A: 78-year-old multimorbid woman

Our hypothetical patient with 5 mild-to-moderate diseases would be prescribed 11 medications as a minimum, with up to 10 other drugs routinely recommended, depending on the intermediate outcome control, symptoms and progression of disease. She would be advised to routinely engage in nine self-

Table 1. Comorbidity, patient-centred care and clinical guidelines

	Depression [14, 15]	Type 2 diabetes [16]	Previous MI [17]	COPD [18]	Osteoarthritis [19]
Does guideline address treatment in over 75s?	Minimal focused on antidepressant drug choice	Minimal focused on oral hypoglycaemic drug choice	Moderate but focused on cardiac rehabilitation	Moderate across multiple areas including smoking cessation, inhaler use, use of theophyllines, referral for surgery	Moderate across several areas including exercise (a core treatment for all ages), avoiding NSAIDs in older people, referral for surgery
Does guideline address comorbidity? (either in terms of comorbid disease or drug treatment recommended for comorbid conditions)	Extensive consideration of detection and management of depression in people with physical conditions with functional limitation	Moderate discussion of oral hypoglycaemic choice in relation to physical comorbidity, and considering the psychological impact of painful neuropathy	Extensive discussion of making cardiac rehabilitation accessible to people with physical and mental health comorbidities. Moderate discussion of considering statin therapy in the context of comorbidities and life expectancy	Moderate discussion of theophylline use in relation to comorbidity and interacting antibiotics, and comorbidity contra-indications to pulmonary rehabilitation	Extensive discussion as part of holistic assessment (fitness for surgery, drug choice, falls, comorbidities compounding osteoarthritis) and role of exercise irrespective of comorbidity
	Extensive discussion of antidepressant choice in relation to physical comorbidity and other drug treatment Cross-referenced to anxiety guidelines	Cross-referenced to depression guideline	Cross-referenced to depression, anxiety, dyspepsia, hypertension and heart failure guidelines	Cross-referenced to depression guideline	Recommendation to screen for depression
Does guideline explicitly discuss patient choice and preferences?	Generic introduction with later extensive discussion of patient and carer involvement in the decision-making	Generic introduction emphasising self-care, with some later discussion about patient preference with regard to hypoglycaemic agents	Generic introduction only	Generic introduction only	Generic introduction, with some later discussion of clearly communicating risks and benefits of treatment to patients
Does guideline explicitly discuss potential challenges to patient adherence to recommended treatments?	Moderate discussion of involving patients in decision to use antidepressants, and checking/ addressing adherence if no response	None	Moderate discussion focused on actively promoting attendance at cardiac rehabilitation and tailoring components to individual needs	Moderate discussion focused on regular assessment of inhaler technique, and actively promoting attendance at pulmonary rehabilitation and tailoring components to individual needs	Minimal discussion focused on clinicians taking individual circumstances into account to promote exercise

Table 2. Recommended management plan for hypothetical patient, Mrs A

Morbidities and risk factors	MI diagnosed 2 years previously with no angina or heart failure
	Asymptomatic type 2 diabetes diagnosed at the time of her MI with hyperglycaemia uncontrolled on diet alone, but with no microvascular complications
	Osteoarthritis of the knee for 5 years with regular pain and some functional impairment
	COPD diagnosed 7 years previously currently with moderate airflow obstruction (FEV1/FVC < 0.7, FEV1 = 60%) and grade 3 Medical Research Council dyspnoea scale (walks slower than contemporaries on level ground due to shortness of breath and has to stop for breath)
	Depression of moderate severity diagnosed 2 months before managed solely in primary care with psychosocial support and antidepressant medication with reasonable response
	Smokes 10 cigarettes per day, would like to stop; *body mass index* of 29 kg/m^2
Minimal drug treatment recommendations[a]	Citalopram
	Omeprazole
	Metformin
	Inhaled salbutamol
	Inhaled salmeterol
	Aspirin
	Lisinopril
	Simvastatin
	Bisoprolol
	Paracetamol or topical ibuprofen gel
	Smoking cessation medication (nicotine replacement, varenicline or buproprion)
Self-care recommendations	Improve sleep hygiene
	20–30 min daily of aerobic exercise
	Local muscle strengthening exercise
	Mediterranean diet/healthy diet and eat 2–4 portions of oily fish
	Alcohol consumption within recommended limits
	Weight loss
	Self-monitoring of plasma glucose integrated with the educational programme
	Smoking cessation
	Appropriate footwear for diabetes and osteoarthritis
Follow-up recommendations	Active monitoring of mood by general practitioner[b]
	Low-intensity psychosocial intervention[c]
	Annual clinical review for diabetes (includes most recommended care post-MI)[d]
	Annual clinical review for COPD[d]
	Annual clinical review for osteoarthritis[d]
	Annual retinal screening by quality assured digital retinal photography programme
	3–6 monthly monitoring of HbA1c and 4–6 monthly monitoring of blood pressure
	One-off pneumococcal and annual influenza immunisation
	Offer referral to smoking intensive support service
	Offer referral for pulmonary rehabilitation

[a] Additional drugs routinely recommended for more severe disease, notably if poor control of blood pressure (up to three additional drugs), HbA1c control (up to three additional drugs) and/or lipids (up to one additional drug); poor pain control in osteoarthritis on simple analgesia (potentially multiple drug classes); persistent depression despite initial treatment (switching of antidepressant medication rather than addition); progressive symptoms or reduced lung function in COPD (up to two additional inhaled drugs).

[b] GP review 2 weeks after diagnosis, then every 2–4 weeks for 3 months, then monthly if stable.

[c] Individual guided self-help programme or computerised cognitive behavioural therapy (CBT), supported physical activity or group CBT.

[d] Multiple elements requiring a stand-alone and often extended appointment and/or consultation with more than one professional.

care/lifestyle alterations, with others recommended under some circumstances. As well as any unplanned appointments, she would be expected to attend 8–10 routine primary care appointments for her physical conditions, 4–6 GP appointments and 8–30 psychosocial intervention appointments for her depression, and multiple appointments for smoking cessation support and pulmonary rehabilitation if she chose to accept a referral. The guideline recommendations are summarised in Table 2.

Mr B: 75-year-old man with two conditions

NICE guidelines recommend Mr B be prescribed five medications as a minimum, with up to eight other drugs routinely recommended depending on the intermediate outcome control, symptoms and progression of disease. He would be advised to routinely engage in six self-care/lifestyle alterations, with others recommended under some circumstances (e.g. complications associated with diabetes). As well as any unplanned appointments, he would be expected to attend five to eight routine primary care appointments for his physical conditions, three to five GP appointments and multiple appointments for smoking cessation support and pulmonary rehabilitation if he chose to accept a referral. The guideline recommendations are summarised in Table 3.

Table 3. Recommended management plan for hypothetical patient, Mr B

Morbidities and risk factors	*Asymptomatic type 2 diabetes* with hyperglycaemia uncontrolled on diet alone, but with no microvascular complications COPD diagnosed 7 years previously currently with moderate airflow obstruction (FEV1/FVC < 0.7, FEV1 = 60%) and grade 3 Medical Research Council dyspnoea scale (walks slower than contemporaries on level ground due to shortness of breath and has to stop for breath) *Smokes* 10 cigarettes per day, would like to stop; *body mass index* of 29 kg/m^2
Minimal drug treatment recommendations[a]	Metformin Inhaled salbutamol Inhaled salmeterol Lisinopril Simvastatin Smoking cessation medication (nicotine replacement, varenicline or buproprion)
Self-care recommendations	20–30 min daily of aerobic exercise Local muscle strengthening exercise Alcohol consumption within recommended limits Weight loss Self-monitoring of plasma glucose integrated with educational programme Smoking cessation Appropriate footwear for diabetes
Follow-up recommendations	Annual clinical review for COPD[b] Annual retinal screening by quality-assured digital retinal photography programme 3–6 monthly monitoring of HbA1c and 4–6 monthly monitoring of blood pressure One-off pneumococcal and annual influenza immunisation Offer referral to smoking intensive support service Offer referral for pulmonary rehabilitation

[a] Additional drugs routinely recommended for more severe disease, notably if poor control of blood pressure (up to three additional drugs), HbA1c control (up to three additional drugs) and/or lipids (up to one additional drug); persistent depression despite initial treatment (initially change of drug rather than addition); progressive symptoms or reduced lung function in COPD (up to two additional inhaled drugs).

[b] Multiple elements requiring a stand-alone and often extended appointment and/or consultation with more than one professional.

Discussion

Cumulative impact of applying NICE guidelines

Despite examining guidelines produced by a single national organisation (NICE), our findings are consistent with a previous study examining US guidelines for physical disease [13], and are likely to apply in other countries. The cumulative impact of applying all five guidelines for Mrs A and two guidelines for Mr B was considerable, even when only recommendations for mild-to-moderate disease were considered. The treatment, self-care and follow-up regime recommended was highly complex, and would be challenging to adhere to because of the high treatment burden implied [21]. The guidelines studied did not explicitly address the treatment burden or adherence, nor provide any guidance on the relative risks and benefits of the many treatments recommended. Although NICE full evidence summaries do provide information on the risks and benefits of treatment, few clinicians will have the time or expertise to read and interpret these documents, and the information is not consistently presented to facilitate comparison. High treatment burden including polypharmacy is not intrinsically inappropriate, but particularly in people with physical frailty or limited life expectancy, better guidance on the relative risks and benefits of different treatments, and the likely time to benefit would assist clinical decision-making. Similarly, where patients have strong preferences about limiting treatment burden, particularly when treatments are primarily preventive rather than for symptoms, then such guidance would help prioritise decision-making.

Implications for the creation of evidence and future guideline development

Multimorbidity is already common, and will become more so as the population ages and survival from acute disease improves [4, 12]. Multimorbidity is strongly associated with higher mortality, poorer quality of life and functional status, and higher rates of health service use including emergency hospital admission [22, 23]. Better management of people with multimorbidity is therefore a key challenge for health-care systems internationally. Clinical guidelines have an important role to play in meeting this challenge, but are constrained by the evidence on which recommendations are based and by their current design [1, 13, 24]. Ultimately, it will always remain the clinician's role to assimilate and review the bodies of evidence relevant to the patient in front of them and then exert their clinical judgement. Concerns have been voiced about linking guideline recommendations with targets/financial incentives and whether this might result in prescriptions being made which materially benefit the prescriber but may not be in the best interests of particular patients [25]. Clearly, clinicians do not wish to be in a situation where they have to defend every deviation from guideline recommendations in order to achieve financial targets. Nor do they wish to be the subject of complaints based around their failure to follow guideline recommendation to the letter [26, 27].

Although there never will be perfect evidence for all situations, the generalisability of single disease research could be improved by targeted examination of the efficacy of very commonly prescribed treatments in more representative

multimorbid and older populations [7, 13, 24], and by significantly extending the scope and volume of existing research that focuses on the care for people with commonly comorbid conditions, such as studies of the collaborative management of depression, coronary heart disease and diabetes [28].

Guidelines could be made more useful in supporting the care for people with multimorbidity in a number of ways (Table 4) [13, 20, 24]. Firstly, existing guidelines should explicitly cross-reference each other when recommendations are synergistic or contradictory, and identify high-risk interactions between recommended treatments and other commonly prescribed drugs. The depression guideline provides a potential model in its provision of a table of drug and disease interactions for commonly used antidepressants. Secondly, clinical guidelines should include a small number of specific patient vignettes for common combinations of comorbidity seen in clinical practice. This may help avoid some of the issues associated with 'adding-up' clinical recommendations from different guidelines. Furthermore, these patient examples may also provide an opportunity for the guideline to list specific advice for practitioners to consider as the patient ages relating, for example, to drug dose or class. Thirdly, action to increase the participation of older people in clinical trials would make it more likely that the distillation of research evidence that forms guidelines had relevance to people with multimorbidity [28].

Current guidelines are largely paper based, and focus on individual diseases in isolation. In caring for people with multimorbidity, what would be more helpful would be a guideline that summarised and cross-referenced recommendations relevant to a particular patient from all single-disease guidelines, identifying when recommendations are synergistic, potentially risky or contradictory. Additionally, providing summarised and comparable information about the relative benefits and risks of different recommended treatments would help inform prioritisation, although in the face of such complexity, clinical judgement and careful accounting for patient choice preferences will always be critical. Internet-based platforms make delivering such guidelines for people feasible, although there are considerable challenges to their production. Although there will often be limited evidence to underpin explicit comparison of different treatments, existing NICE guideline methodology already uses modelling and expert consensus to address evidence gaps, and these could be applied to this problem. Research is needed to identify the best way to create such guidelines for people from existing guidelines for diseases and to evaluate their usability and usefulness to clinicians and patients [13, 23].

Table 4. Recommendations for improving clinical guidelines

- Providing summarised and comparable information about the relative benefits and risks of different recommended treatments would help inform prioritisation in multimorbid patients
- Existing guidelines should explicitly cross-reference each other when recommendations are synergistic or contradictory, and identify high-risk interactions between recommended treatments and other commonly prescribed drugs. *This may be done in an internet-based format*
- Clinical guidelines should include a small number of specific patient case examples for common combinations of comorbidity seen in clinical practice
- Guidelines should note some specific advice for practitioners when treating older patients (e.g. drug doses or class)
- Concerted action is needed to increase the participation of older people in clinical trials

Conclusion

Clinical guidelines have played an important role in improving health care for people with long-term conditions. However, in people with multimorbidity current guideline recommendations rapidly cumulate to drive polypharmacy, without providing guidance on how best to prioritise recommendations for individuals in whom the treatment burden will sometimes be overwhelming. Such prioritisation will always require the exercise of clinical judgement and meaningful engagement with patient preferences. Developing guidelines for people rather than guidelines for diseases will better ensure that treatment is in the individual's best interests.

Key points

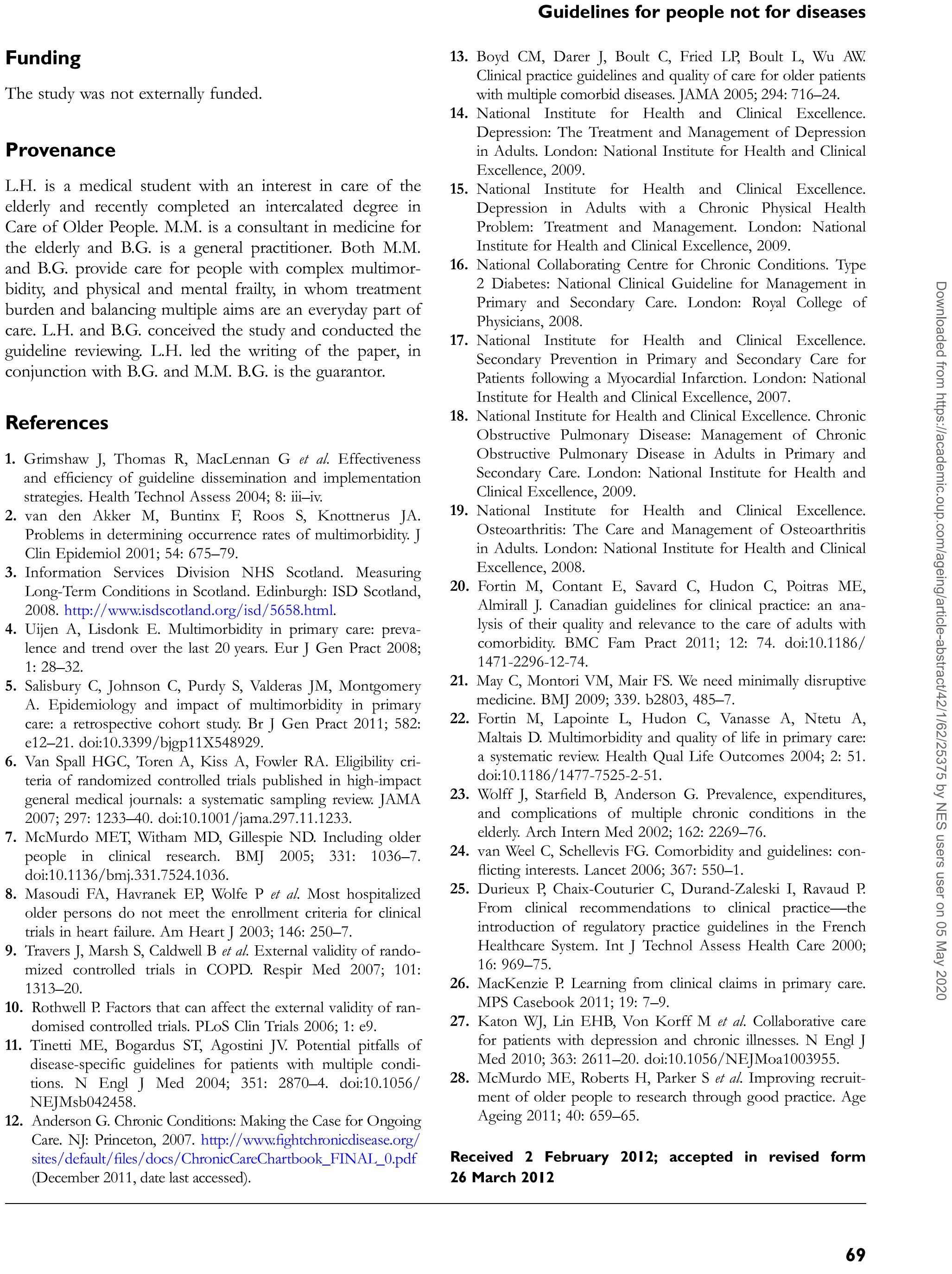
- The use of clinical guidelines in health-care services has helped to reduce practice variation, deaths and hospitalisations
- Clinical guidelines are known to be limited in their focus on single diseases and the evidence which these guidelines are based upon apply only to subsets of the population
- This study showed that explicitly following clinical guidelines for two hypothetical patients with physical and mental health comorbidities produced complex treatment regimes with a significant risk of adverse drug reactions.
- To make clinical guidelines more applicable to patients with comorbidity, future clinical guidelines should provide practical examples of how patient-centred care can be achieved for a disease process. Attempts should be made to integrate guidelines for similar disease processes.

Conflict of interest

All the authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that the study received no external funding and the authors have no financial conflicts of interest to report.

Ethical approval

This study did not require NHS Research Ethics approval.



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Provenance

L.H. is a medical student with an interest in care of the elderly and recently completed an intercalated degree in Care of Older People. M.M. is a consultant in medicine for the elderly and B.G. is a general practitioner. Both M.M. and B.G. provide care for people with complex multimorbidity, and physical and mental frailty, in whom treatment burden and balancing multiple aims are an everyday part of care. L.H. and B.G. conceived the study and conducted the guideline reviewing. L.H. led the writing of the paper, in conjunction with B.G. and M.M. B.G. is the guarantor.

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Research paper

Centrally active prescribing for nursing home residents - how are we doing?

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ABSTRACT

Introduction: Older patients in nursing homes are more likely to be prescribed multiple drugs than other age groups as multimorbidity is the norm. This clinical study reviewed all prescribed centrally active medications for residents in a nursing home in Dundee. Subsequent analysis was carried out to examine whether particular patient criteria are associated with an exposure to centrally acting drugs and to examine the adequacy of analgesia for care home residents.
Methods: The study was carried out in a Dundee nursing home with two different units with varying admission criteria. The research team reviewed patient records establishing background patient characteristics and medical diagnoses where psychoactive prescribing may be appropriate. In addition, information on specific prescribed medications, patient pain scores (PAINAD system), quantified cognition (6CIT score) was gathered. The non-parametric Mann Whitney U test ($P < 0.05$) was used to compare exposure to CNS active medications between nursing home floors.
Results: Patients with dementia in nursing homes are particularly likely to have bodily pain, insomnia and unipolar depression. Patients with more severe dementia were statistically more likely to be exposed to CNS active medications (P-value = 0.01). Importantly, despite being exposed to significant levels of psychoactive prescribing this patient group may be undertreated for chronic pain.
Conclusion: Centrally active prescribing in the community for geriatric patients remains high and may be associated with patient risk. Furthermore, despite this patients may be undertreated for pain syndromes.

1. Research in context

Older patients are more likely to be prescribed multiple drugs than other age groups as multimorbidity is the norm [1,2]. In addition, older patients are at a greater risk of adverse drug reactions (ADRs) in line with age-related reductions in hepatic metabolism and renal function and can often be more sensitive to the effects of medications than other age groups [3,4].

Older people are commonly prescribed medications with psychoactive properties [2]. Indeed, Guthrie et al. showed that patients with dementia in Tayside (Scotland) have a 17% chance of being prescribed one or more centrally active medications (including antipsychotics, antidepressants and hypnotic/anxiolytics) [5]. It is important to stress that the high levels of centrally active drug prescription are despite the well-documented health risks associated with these drugs, including an increased risk of worsening cardiovascular and cerebrovascular disease as well as cognitive decline [6,7]. Indeed, a Government funded review by Prof. Sube Banerjee indicated that there could be up to 1800 avoidable patient deaths annually associated with such medications [8].

This clinical study reviewed all prescribed centrally active medications for residents in a nursing home in Dundee. Subsequent analysis was carried out to examine whether particular patient criteria are associated with an exposure to centrally acting drugs and to examine the adequacy of analgesia for care home residents.

2. Methods

2.1. Study location and patient background

The study was undertaken in a purpose-built Dundee nursing home, in June 2010. The unit is specialized for patients with dementia, admitting patients with a confirmed diagnosis of dementia alongside appropriate social work assessment. Importantly, there are two floors (ground floor [GF] and first floor [FF]) with each floor having different admission criteria and run by a separate nursing and care team. An average patient on GF would have severe cognitive impairment, have the majority or all

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Table 1
Characteristics of patient cohort.

	All residents ($n=50$)	G F residents ($n=26$)	FF residents ($n=24$)
Age (years)	69–92 (mean 76)	72–92 (mean 77)	69–84 (mean 73)
Gender (♀ or ♂)	27 ♀:23 ♂	13 ♀:13 ♂	14 ♀: 10 ♂
Dementia Diagnosis			
Alzheimer's disease	35	18	17
Multi-infarct dementia	11	7	4
Dementia with Lewy bodies	3	1	2
Other	1	0	1
Cognition [6CIT]			
Normal (0–7)	NA	NA	NA
Mild (8–14)	6	0	6
Moderate (15–21)	29	15	20
Severe (22–28)	15	11	4
Indications for CNS Drugs			
Insomnia	19	5	14
Anxiety	5	1	4
Unipolar depression	21	9	12
Bodily pain*			
None/minimal (0–3)	10	1	9
Mild (4–7)	13	9	4
Moderate/severe (>7)	27	16	11

GF: ground floor; FF: first floor; 6CIT: 6-item cognitive impairment test; CNS: central nervous system.

* Scored using Pain Assessment in Advanced Dementia (PAINAD) Key.

personal and social care needs met by nursing staff and have very limited mobility. An average patient on FF would have good mobility (able to walk without staff assistance with or without the use of a walking aid), require limited support from nursing staff and display one or more signs of behavioural and psychological symptoms of dementia (BPSD). This provided a unique opportunity to draw comparisons between centrally active prescribing between the two groups of nursing home patients. Information regarding the characteristics of the patient cohort can be found in Table 1.

Resident care plans on both floors were reviewed by L.H. Medical indications for centrally acting medications were recorded including diagnosed dementia syndrome (most likely diagnosis listed in notes by general practitioner), sleep problems/insomnia, anxiety, and unipolar depression. All patients were examined by the research team for the presence of pain using the validated pain assessment tool, Pain Assessment in Advanced Dementia (PAINAD) [9,10]. The PAINAD assesses and ranks pain in five patient domains including breathing independent of vocalization, negative vocalization, facial expression, body language, consolability [9,10]. Patients are scored between 0 (no pain) –10 (maximal pain) [9,10].

Patient cognition was quantified using the Six Item Cognitive Impairment Test, validated for use in a nursing home setting (6CIT) [11]. Patients were graded using their mean 6CIT score into normal cognition (0–7 points on 6CIT), mild cognitive impairment (8–14 points on 6CIT), moderate cognitive impairment (15–21 points on 6CIT) and severe cognitive impairment (22–28 points on 6CIT).

L.H. anonymously collected drug information from the residents Medication Administration Record (MAR) sheets. Information about all centrally active medications including drug class, drug dose, and drug forms were recorded. Centrally active medications were defined according to the recently developed central nervous system drug model, which includes benzodiazepine receptor agonists, antidepressants (all classes), antipsychotics (first and second generation) and opioid analgesia [3]. Ninety-five percent confidence intervals of a proportion were calculated for each CNS drug class prevalence comparing FF to GF using the non-parametric Wilson statistical method. The non-parametric Mann Whitney U test ($P \leq 0.05$) was used to compare exposure to CNS active medications between nursing home floors.

3. Results

At the time of the study there were 26 residents on the GF and 24 residents on the FF. There were four different groups of dementia syndromes in the patient group with 35/50 (70%) of the patients being diagnosed with Alzheimer's dementia, 11/50 (22%) being diagnosed with multi-infarct (vascular) dementia and 4/50 (8%) being diagnosed with Lewy body dementia or other. Twenty-nine out of 50 (58%) patients had moderate cognitive impairment compared to 15/50 (30%) having severe cognitive impairment and 6/50 (12%) having mild cognitive impairment. There were several medical indications for centrally acting medications. The most common conditions included moderate/severe bodily pain (27/50), depression (21/50), and insomnia (19/50). Table 2 provides information on the prevalence of individual classes and overall CNS medication. The most commonly prescribed medicine classes were opioid analgesia (16/50) and antidepressants (13/50). At the time of the study, 58% of residents were exposed to one or more centrally acting medication.

When the residents between nursing homes units were compared, a number of important observations were made. Firstly, 25/26 of patients in the higher dependency unit had a recorded PAINAD bodily pain score of 4 or greater compared to 15/24 in the lower dependency unit. However, despite the high levels of pain experienced by residents' only 16 patients in the nursing home were prescribed opioid analgesia. Secondly, patients living on the FF had on average a higher baseline cognition level, but this was accompanied with significantly higher levels of insomnia and anxiety and unipolar depression. Table 3 provides information on the cumulative burden of psychoactive medications after CNS model calculation between patient groups. Of the 29 patients prescribed centrally active drugs, four were on the highest dose (> 3 standardized daily dose [SDD]), 13 on the moderate dose (1–3 SDD), and 12 were on the lowest dose use (< 1.0 SDD). GF floor residents were statistically more likely to be exposed to CNS active medications (*P*-value = 0.001).

Table 2
Prevalence of individual classes and overall CNS medication.

CNS medication	*All residents* ($n=50$)	*GF residents* ($n=26$) [95% confidence intervals]	*FF residents* ($n=24$) [95% confidence intervals]
Antipsychotics (combined)	4	1 [0.007–0.189]	3 [0.043–0.31]
First generation	1	1	0
Second generation	3	0	3
Benzodiazepine receptor agonist	4	1 [0.007–0.189]	3 [0.043–0.31]
Antidepressants (combined)	13	9 [0.194–0.538]	4 [0.067–0.359]
SSRIs	8	6	2
TCAs	0	0	0
SNRIs	5	3	2
Opioid analgesic use	16	14 [0.355–0.713]	2 [0.023–0.258]
Total number of patients on CNS drugs	29	17 [0.462–0.806]	12 [0.314–0.686]

GF: ground floor; FF: first floor; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressant; SNRI: serotonin-norepinephrine reuptake inhibitor.

Table 3
Comparison of cumulative burden between patient groups.

Cumulative CNS Burden Score	All residents ($n = 50$)	GF residents ($n = 26$)	FF residents ($n = 24$)
No exposure	21	9	12
Lowest dose use (< 1.0 SDD)	12	8	4
Moderate dose use (1–3 SDD)	13	8	5
Highest dose use (> 3 SDD)	4	1	3

GF: ground floor; FF: first floor; SDD: standardized daily.

4. Discussion

4.1. Patient characteristics

This study has noted the high prevalence of pain in this nursing home with 80% of the 50 residents having a recorded PAINAD bodily pain score of 4 or greater. It is known that chronic pain is a frequent health problem in the elderly [12]. Indeed, chronic pain is associated with a reduced quality of life, with prevalence levels ranging between 45% and 80% in line with age-related increases in patient comorbidity [12,13]. Importantly, a 2011 BMJ study by Rosenberg et al. noted that a systematic pain management protocol was associated with improvements in BPSD [14]. Rates of unipolar depression and insomnia/sleeping disturbances were both significant (42% and 38% of nursing home residents respectively) but in line with rates for this patient group noted in current literature [15,16].

4.2. Drug prescribing

In this nursing home the most commonly prescribed medicine classes were opioid analgesic receptor agonists and antidepressants. At the time of the study, an overall 58% was exposed to one or more centrally acting medication. Interestingly, each nursing home unit had significant variation in the nature of drugs prescribed. Residents on the GF were prescribed the vast majority of opioid analgesia with antidepressants being the second most commonly prescribed. Drugs with more potent sedative potential (antipsychotics and benzodiazepines) were limited to one resident on the GF. In contrast, three quarters of antipsychotics were prescribed on the on FF, where patients have higher levels of mobility and BPSD. However, just under 10% of these patients received opioid receptor analgesia despite only having slightly reduced levels of pain compared to residents on GF.

This review notes that secondary care and community prescribers clearly have tailored prescribing to the patient needs with the notable exception of pain relief. It appears that patients on the FF who have higher levels of BPSD, anxiety, and insomnia appear to be undertreated for pain. Other papers have documented the under treatment of chronic pain in elderly patients, particularly those with comorbid psychiatric disturbance [17,18].

4.3. Limitations

There are numerous limitations for this research project. Firstly, the study is limited by the single centre nature of the study and subsequent small sample size. In addition, the population in this nursing home is relatively homogeneous, with the vast majority of residents being White Scottish/British. Another important limitation was the study used only a direct observational pain assessment tool (PAINAD). The PAINAD was selected in line with the significant communication deficits of the nursing home residents on both floors [19,20] and staff were already familiar with the scale. However, there is work that suggests that self-reporting scales, the gold standard measure of pain assessment, may be similarly efficacious in this patient population [12,21]. Therefore, in future work we would use a combination of observational scales and a self-report scale. However, despite these limitations the authors feel that this small centre projects is able to reflect some of the real life challenges of prescribing medication for nursing home residents.

5. Conclusion

This community project reinforces previous work that centrally active prescribing in the community for geriatric patients remains high [5]. The authors have noted that patients with dementia in nursing homes are particularly likely to have bodily pain, insomnia and unipolar depression. In addition, the authors note that patients with more severe dementia were statistically more likely to be exposed to CNS active medications (P-value = 0.001). Importantly, despite being exposed to significant levels of psychoactive prescribing this patient group there may be undertreated for chronic pain. It is hoped that this study will stimulate further research into this important area of community geriatrics in Scotland.

Keypoints

- Older patients are more likely to be prescribed multiple drugs than other age groups as multimorbidity is the norm.
- Psychoactive prescribing in the community for nursing home patients remains high despite the documented risks associated with these drugs.
- Importantly, despite being exposed to significant levels of psychoactive prescribing this patient group there may be undertreated for chronic pain.

Disclosure of interest

LDH was a member of staff at the care home where the study took place for the duration of the study. MDW and JH have no conflict of interest to declare.

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Paper 4: Hughes LD, Raitt N, Riaz MA, Baldwin SJ, Erskine K, Graham G. Primary Care Hypnotic and Anxiolytic Prescription — Reviewing Prescribing Practice Over Eight Years. *Journal of Family Medicine and Primary Care*. **2016**; 5(3):652-657

Original Article

Primary care hypnotic and anxiolytic prescription: Reviewing prescribing practice over 8 years

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AbstrAct

Introduction: Over the last few years, hypnotic and anxiolytic medications have had their clinical efficacy questioned in the context of concerns regarding dependence, tolerance alongside other adverse effects. It remains unclear how these concerns have impacted clinical prescribing practice. **Materials and Methods:** This is a study reviewing community-dispensed prescribing data for patients on the East Practice Medical Center list in Arbroath, Scotland, in 2007, 2011 and 2015. Anxiolytic and hypnotic medications were defined in accordance with the British National Formulary chapter 4.1.1 and chapter 4.1.2. All patients receiving a drug within this class in any of the study years were collated and anonymized using primary care prescribing data. The patients' age, gender, name of the prescribed drug(s), and total number of prescriptions in this class over the year were extracted. **Results:** The proportion of patients prescribed a benzodiazepine medication decreased between 2007 and 2015: 83.8% ($n = 109$) in 2007, 70.5% ($n = 122$) in 2011, and 51.7% ($n = 138$) in 2015 ($P = 0.006$). The proportion of these patients prescribed a nonbenzodiazepine drug increased between 2007 and 2015: 30% ($n = 39$) in 2007, 46.2% ($n = 80$) in 2011, and 52.4% ($n = 140$) in 2015 ($P = 0.001$). There was a significant increase in the number of patients prescribed melatonin ($P = 0.020$). **Discussion:** This study reports a reduction in benzodiazepine prescriptions in primary care alongside increases in nonbenzodiazepine and melatonin prescribing, with an increase in prescribing rates of this drug class overall. **Conclusion:** Changes in this prescribing practice may reflect the medicalization of insomnia, local changes in prescribing practice and alongside national recommendations.

Keywords: Anxiolytic, benzodiazepines, hypnotic, nonbenzodiazepines, prescribing, primary care

Introduction

Insomnia, agitation, and anxiety are common presentations to primary care clinicians, with these frequently being treated with anxiolytic and hypnotic medications (defined by the British National Formulary [BNF] chapters 4.1.1 and 4.1.2).[1] These medications may also be used as part of a program of alcohol withdrawal, treatment for epilepsy or muscle spasms although this represents a minority of prescriptions in clinical practice.[1,2]

It is recognized that the long-term use of these medications in general practice is generally not appropriate and should be limited to short-term prescriptions and kept off repeat prescription.[2] The combination of perceived effectiveness by patients and risks associated with long-term use such as dependence and tolerance make this medication group challenging to manage in primary care. Indeed, there are ongoing concerns about the rates of prescribing of this medication group in clinical practice,[1,2] with particular concerns voiced for patients over 65 including falls and cognitive impairment.[3,4] Over the last few years, these medications have had their clinical efficacy questioned in the context of increasing concerns regarding dependence, tolerance, and alongside other adverse effects.

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A 2012 meta-analysis and systematic review of the US Food and Drug Administration data reported that after reviewing 13 studies containing 65 Z-drug-placebo comparisons, Z-drugs produce only slight improvements in subjective polysomnographic sleep latency, regardless of the type of drug used.[5] The authors noted that although the drug effect and placebo response were small and of uncertain clinical significance, the two together produced reasonable clinical response.[5] Furthermore, a retrospective cohort study published in 2014 of 34,727 aged 16 years old and older attending the UK primary care reported that anxiolytic and hypnotic drugs were associated with significantly increased risk of mortality over a 7-year period, after adjusting for a range of potential confounders.[6] There has been recent work noting that there is a clear evidence that the use of hypnotic and anxiolytic medications are associated with an increased risk falls and hip fractures in older people.[7] Furthermore, these medications may lead to cognitive problems in older patients, with a meta-analysis reporting increased rates of memory problems, confusion, and disorientation more common in patients receiving benzodiazepines and Z-drugs.[8] There have even been reports that benzodiazepine use increases the risk of developing Alzheimer's disease, with this association increasing with prolonged exposure.[9]

It remains unclear how these concerns have impacted clinical prescribing practice on the coalface of primary care clinical practice. This is particularly relevant as they have been changes in guidelines in 2014, which have promoted an active approach to reducing the prescription of these medications.[1] This was adopted locally by a Clinic B monitoring program where patients on repeat doses of these medications were actively reviewed and either had doses reduced or switched to less harmful agents.

This study aimed to assess changes in prescribing practice of hypnotic and anxiolytic medications between 2007 and 2015 which would encompass local and national changes in clinical practice using routinely collected prescribing data in a single primary care practice in Arbroath (Scotland).

Materials and Methods

The analysis used community-dispensed prescribing data for patients from the East Practice, Springfield Medical Centre in Arbroath in Scotland held by NHS Tayside and community prescribing bodies in 2007, 2011, and 2015. Data were held by the medical practice as a matter of normal clinical care.

Service characteristics

The East Practice Springfield Medical Centre is one of four practices providing primary care services to the population of Arbroath and is staffed with three-partner general practitioners (GPs): one nurse practitioner, one practice nurse, and one health-care assistant alongside support staff. The practice serves approximately 4000 patients in a densely populated town with marked deprivation, based on the Scottish Index of Multiple Deprivation Quintile (SIMD). The SIMD is based on information from major population surveys in Scotland and allows comparison between the most deprived and the rest of the population in Scotland in numerous domains.[10] In 2007, there was a local process of coding patients being prescribed benzodiazepines (particularly those on repeat) to aid GP review of their prescriptions and facilitate reduction in benzodiazepine prescriptions. This process was extended in 2014 following the national guideline recommendations.

Data collected and analysis

For each individual, all community-dispensed prescriptions for anxiolytic and hypnotic medications were extracted between January 01 and December 31 for the study years of 2007, 2011, and 2015. The prescriptions were reviewed on a four yearly basis to assess for changes following the introduction of Clinic B monitoring in 2007 with subsequent update and review in 2011 and adjusted national guideline recommendations in late 2014/early 2015. There were also difficulties in obtaining other years as a result of local information technology challenges, so these year groups represented a pragmatic approach.

Anxiolytic and hypnotic medications were defined in accordance to BNF drug groupings, hypnotics (drugs defined in BNF chapter 4.1.1), and anxiolytics (BNF chapter 4.1.2).[11] Information regarding the patients' age, gender, medication name, and number of prescriptions in this drug class over the course of the year were extracted. Over the course of the year, all prescriptions were reviewed with the number of different drug classes documented with the maximal number being 5 (benzodiazepines, nonbenzodiazepine hypnotics, sedative antihistamines, azapirones, and melatonin).

These data were fully anonymized, and any patient identifiable information was removed before analysis. The analysis was carried out in SPSS v22.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY).[12] Baseline data were compared using one-way ANOVA for normally distributed continuous variables, Kruskal–Wallis test for nonnormally distributed variables, and Chi-squared test for categorical variables. P values reported note the significance of differences between the 3 years groups in each of the data comparisons. As a result of the small sample size, medications were compared between years as an overall drug class (e.g., benzodiazepines) rather than individual agents. This study was deemed not to require ethical approval as it entailed analysis of routinely collected clinical data.

Results

There were 4155 patients, 4239 patients, and 4255 patients registered at East practice in 2007, 2011, and 2015, respectively. Of this group, 3.1% (n = 130), 4.1% (n = 173), and 6.3% (n = 267) were prescribed a hypnotic or anxiolytic medication at least once over the course of 2007, 2011, and 2015, respectively (P = 0.375).

Table 1 summarizes baseline patient characteristics alongside individual drug group comparisons.

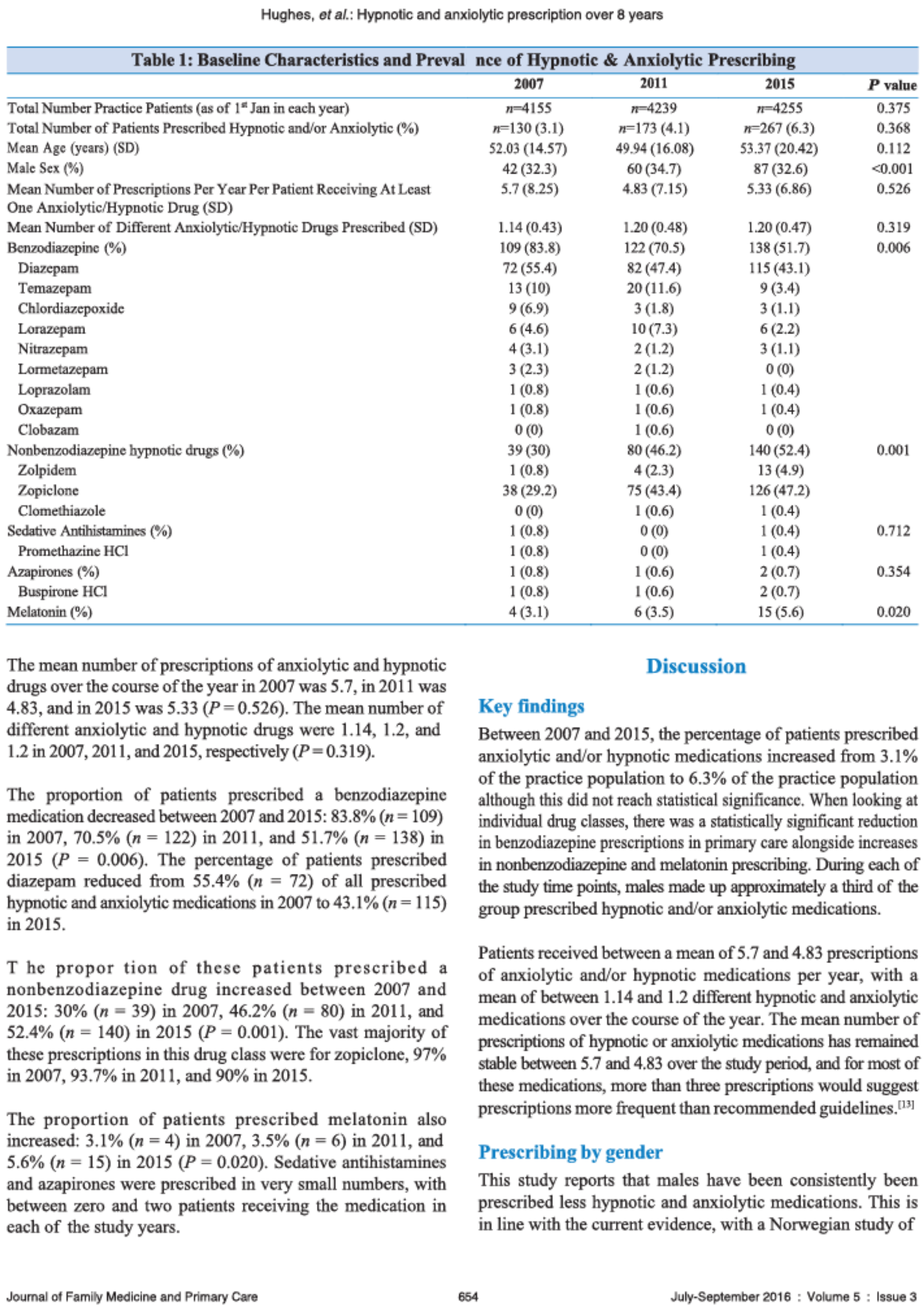

Table 1: Baseline Characteristics and Prevalence of Hypnotic & Anxiolytic Prescribing

	2007	2011	2015	*P* value
Total Number Practice Patients (as of 1st Jan in each year)	*n*=4155	*n*=4239	*n*=4255	0.375
Total Number of Patients Prescribed Hypnotic and/or Anxiolytic (%)	*n*=130 (3.1)	*n*=173 (4.1)	*n*=267 (6.3)	0.368
Mean Age (years) (SD)	52.03 (14.57)	49.94 (16.08)	53.37 (20.42)	0.112
Male Sex (%)	42 (32.3)	60 (34.7)	87 (32.6)	<0.001
Mean Number of Prescriptions Per Year Per Patient Receiving At Least One Anxiolytic/Hypnotic Drug (SD)	5.7 (8.25)	4.83 (7.15)	5.33 (6.86)	0.526
Mean Number of Different Anxiolytic/Hypnotic Drugs Prescribed (SD)	1.14 (0.43)	1.20 (0.48)	1.20 (0.47)	0.319
Benzodiazepine (%)	109 (83.8)	122 (70.5)	138 (51.7)	0.006
Diazepam	72 (55.4)	82 (47.4)	115 (43.1)	
Temazepam	13 (10)	20 (11.6)	9 (3.4)	
Chlordiazepoxide	9 (6.9)	3 (1.8)	3 (1.1)	
Lorazepam	6 (4.6)	10 (7.3)	6 (2.2)	
Nitrazepam	4 (3.1)	2 (1.2)	3 (1.1)	
Lormetazepam	3 (2.3)	2 (1.2)	0 (0)	
Loprazolam	1 (0.8)	1 (0.6)	1 (0.4)	
Oxazepam	1 (0.8)	1 (0.6)	1 (0.4)	
Clobazam	0 (0)	1 (0.6)	0 (0)	
Nonbenzodiazepine hypnotic drugs (%)	39 (30)	80 (46.2)	140 (52.4)	0.001
Zolpidem	1 (0.8)	4 (2.3)	13 (4.9)	
Zopiclone	38 (29.2)	75 (43.4)	126 (47.2)	
Clomethiazole	0 (0)	1 (0.6)	1 (0.4)	
Sedative Antihistamines (%)	1 (0.8)	0 (0)	1 (0.4)	0.712
Promethazine HCl	1 (0.8)	0 (0)	1 (0.4)	
Azapirones (%)	1 (0.8)	1 (0.6)	2 (0.7)	0.354
Buspirone HCl	1 (0.8)	1 (0.6)	2 (0.7)	
Melatonin (%)	4 (3.1)	6 (3.5)	15 (5.6)	0.020

The mean number of prescriptions of anxiolytic and hypnotic drugs over the course of the year in 2007 was 5.7, in 2011 was 4.83, and in 2015 was 5.33 ($P = 0.526$). The mean number of different anxiolytic and hypnotic drugs were 1.14, 1.2, and 1.2 in 2007, 2011, and 2015, respectively ($P = 0.319$).

The proportion of patients prescribed a benzodiazepine medication decreased between 2007 and 2015: 83.8% ($n = 109$) in 2007, 70.5% ($n = 122$) in 2011, and 51.7% ($n = 138$) in 2015 ($P = 0.006$). The percentage of patients prescribed diazepam reduced from 55.4% ($n = 72$) of all prescribed hypnotic and anxiolytic medications in 2007 to 43.1% ($n = 115$) in 2015.

The proportion of these patients prescribed a nonbenzodiazepine drug increased between 2007 and 2015: 30% ($n = 39$) in 2007, 46.2% ($n = 80$) in 2011, and 52.4% ($n = 140$) in 2015 ($P = 0.001$). The vast majority of these prescriptions in this drug class were for zopiclone, 97% in 2007, 93.7% in 2011, and 90% in 2015.

The proportion of patients prescribed melatonin also increased: 3.1% ($n = 4$) in 2007, 3.5% ($n = 6$) in 2011, and 5.6% ($n = 15$) in 2015 ($P = 0.020$). Sedative antihistamines and azapirones were prescribed in very small numbers, with between zero and two patients receiving the medication in each of the study years.

Discussion

Key findings

Between 2007 and 2015, the percentage of patients prescribed anxiolytic and/or hypnotic medications increased from 3.1% of the practice population to 6.3% of the practice population although this did not reach statistical significance. When looking at individual drug classes, there was a statistically significant reduction in benzodiazepine prescriptions in primary care alongside increases in nonbenzodiazepine and melatonin prescribing. During each of the study time points, males made up approximately a third of the group prescribed hypnotic and/or anxiolytic medications.

Patients received between a mean of 5.7 and 4.83 prescriptions of anxiolytic and/or hypnotic medications per year, with a mean of between 1.14 and 1.2 different hypnotic and anxiolytic medications over the course of the year. The mean number of prescriptions of hypnotic or anxiolytic medications has remained stable between 5.7 and 4.83 over the study period, and for most of these medications, more than three prescriptions would suggest prescriptions more frequent than recommended guidelines.[13]

Prescribing by gender

This study reports that males have been consistently been prescribed less hypnotic and anxiolytic medications. This is in line with the current evidence, with a Norwegian study of approximately 15,000 middle-aged adults with a mean 18-year follow-up reported that the proportion of anxiolytic or hypnotic drug users was 6.6% among men and 16.2% among women.[14] Furthermore, women are more likely to be treated for a mental health problem that men (29% vs. 17%)[15,16] and are more likely attend the primary care physician for management of their mental health diagnoses.[17] It is pertinent to note that there is a national strategy for women's mental health but no equivalent for men although there is a new drive to manage suicide risk in young men.[17,18] Finally, men are more likely to have mental health disorders such as alcohol and substance misuse where prescription of these medications is not as commonly utilized.[15]

Changes anxiolytic and hypnotic drug class as a whole

Over the course of the review, there was an increase in the percentage of patients prescribed hypnotic and/or anxiolytic medications to 6.3%, which is similar albeit lower when compared to a larger population-based studies in Scotland that have placed hypnotic/anxiolytic prescriptions at between 7.5%[3] and 8.1%.[15] Rates of hypnotic and anxiolytic prescriptions are lower when compared to other nations including Norway,[14] Australia,[19] and France.[20] East practice appears to have lower rates of hypnotic and anxiolytic prescribing although the rates are increasing closer to the published Scottish prevalence for these agents.

Changes in specific drug classes

The reduction in benzodiazepine prescribing is likely to have been combination of nationally driven targets for reducing benzodiazepine prescribing,[21] locally driven targeted intervention for patients on benzodiazepine through "Clinic B" monitoring and increasing recent research linking benzodiazepines to the development of Alzheimer's disease,[9] falls and fractures in older patients[7] and overall all-cause mortality[6,14] changing prescribing practice. There is a good body of evidence that some of the newer antidepressants can manage symptoms with anxiety,[22,23] with nondrug options for managing anxiety[24] and insomnia[13,21,25] having a strong evidence basis. However, it should be noted that a meta-analysis reviewing the use of antidepressant medications (selective serotonin reuptake inhibitors [SSRIs]) and benzodiazepines for anxiety disorder reported that the change in the prescribing pattern favoring newer SSRIs over benzodiazepines in the treatment of anxiety disorders has occurred without supporting evidence and direct comparison is recommended.[23]

The reported increase in nonbenzodiazepine may reflect patients being prescribed short-courses of these agents rather than short-acting benzodiazepines. There has been recent concern about the possible medicalization of sleep disorders which may explain increases in these prescriptions.[26] The expectation of uninterrupted sleep by patients with the availability of new medications has certainly impacted clinical practice. Indeed, an American study reported a large increase in patient complaints of sleeplessness with associated increases in the use of benzodiazepine and nonbenzodiazepine hypnotic medications between 1993 and 2007.[26] Indeed this US study suggested that life problems may be being treated with medical solutions, after reporting that there was a 21 fold increase in non-benzodiazepine medications between 1993 and 2007 in the context of only a 5 times increase in imsomnia diagnoses made by clinicians.[26]

The current National Institute for Clinical Excellence guidelines only recommended hypnotic drug therapy is used for the management of severe insomnia interfering with normal daily life only after due consideration of the use of nonpharmacological measures for short periods of time only.[13] As there is no evidence suggesting superiority of one hypnotic drug to another,[5,13] patients should be prescribed the medication with lowest purchase cost and patients experiencing side effects from one agent or experiencing lack of benefit from one agent should not be trailed on other hypnotic agents (excluding melatonin).[2,13] Crucially, hypnotics are not particularly effective with high number needed to treat to obtain benefit in the context of high rates of adverse effects. Glass *et al*. reported that for 13 people taking a hypnotic for 1 week, twelve people's sleep would either improve or not irrespective of whether they had taken a hypnotic or a placebo and one person would experience sleep improvement; two patients would experience an adverse event.[8] The increase in this drug group should be seen in context with a reduction in benzodiazepines, but it is a concern that this group of medication is consistently increasing. It is postulated that the medicalization of insomnia and patient expectations are leading to clinician pressure to prescribe hypnotic agents for patients. Efforts are going to be made locally to provide advice and information about nondrug approaches to managing sleep problems, which aims to reduce the use of these medications in the coming years.

There was a statistically significant increase in the number of patients being prescribed melatonin over the course of the 8 years. Melatonin is an endogenous hormone produced in the body in response to darkness that is important in regulating circadian rhythms.[2] Levels are known to be reduced in some middle-aged and elderly patients with insomnia, and studies to date have reported a benign side effect profile compared to other agents.[27]

A recent meta-analysis reported that melatonin decreases sleep onset latency, increases total sleep time, and improves overall sleep quality without any major side effect reported.[26] The benefits noted did not decrease with prolonged use unlike other hypnotic agents, and although the absolute benefits were small given the favorable side effect profile, this agent may have a role for middle-aged and elderly patients.[26] It appears that the increase in data regarding the safety and role of melatonin in primary sleep disorders, alongside the possible role in adolescent,[28,29] has led to a small increase in prescribing which is likely to increase in time as the cost of the medication decreases and further studies are published.

Limitations and further work

This research paper has several limitations. First, the paper reports patients prescribed an anxiolytic and/or hypnotic medications at three time points (2007, 2011, and 2015). Therefore, the data obtained does not allow us to fully ascertain the changes in prescribing practice over this time. However, such work does provide a useful platform for discussing general changes in prescribing and considering for these changes. Second, this was a single center study of a general practice with a small patient list in an urban-deprived area. These results are not necessarily generalizable to other areas of the United Kingdom or further afield. However, the proportion of patients prescribed anxiolytic and hypnotic medications were similar to published Scottish data.[3,15] Third, due to the small sample size, we were unable to break down each of the cohorts into high-risk patient groups such as patients with multi-morbidity or elderly patients. Finally, the study did not include larger number of different drug groups in the analyses due to the nature of the data set. It is possible that by focusing on only two classes of medications, we may have missed broader trends in psychoactive prescribing.

Despite the limitations of this research paper, this study has provided an opportunity to review and assess a single GP practices prescriptions of hypnotic and anxiolytic medications. Following work on the data used for analyses, it is planned to perform further work looking at prescribing rates of psychoactive medications more broadly involving more local GP practices to assess different patient subgroups. There has been published work noting large-scale variation in anxiolytic and hypnotic prescribing by GPs, with demographic factors more powerful determinants of this.[30] However, high prescribing practices were less well developed, in that their quality and outcomes framework scores were lower and they were less likely to be training practices.[30] It is hoped that further work will allow further data be obtained with regard to GP prescribing variation.

Conclusions

This study reports a reduction in benzodiazepine prescriptions in primary care alongside increases in nonbenzodiazepine and melatonin prescribing, with an increase in prescribing rates of this drug class overall. Changes in this prescribing practice may reflect the medicalization of insomnia, local changes in prescribing practice, and alongside national recommendations.

This clinical paper provides a useful platform for discussing community-based prescribing for this challenging group of medications and reports that locally available Scottish prescribing data can be utilized to look in more detail in primary care prescribing practice at a single practice level. This study will be the basis for future work in this area with an increase in the number of practices involved to allow targeted analysis at high-risk patients for the adverse side effects of psychoactive medications alongside other high-risk medications.

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Conflicts of interest

There are no conflicts of interest.

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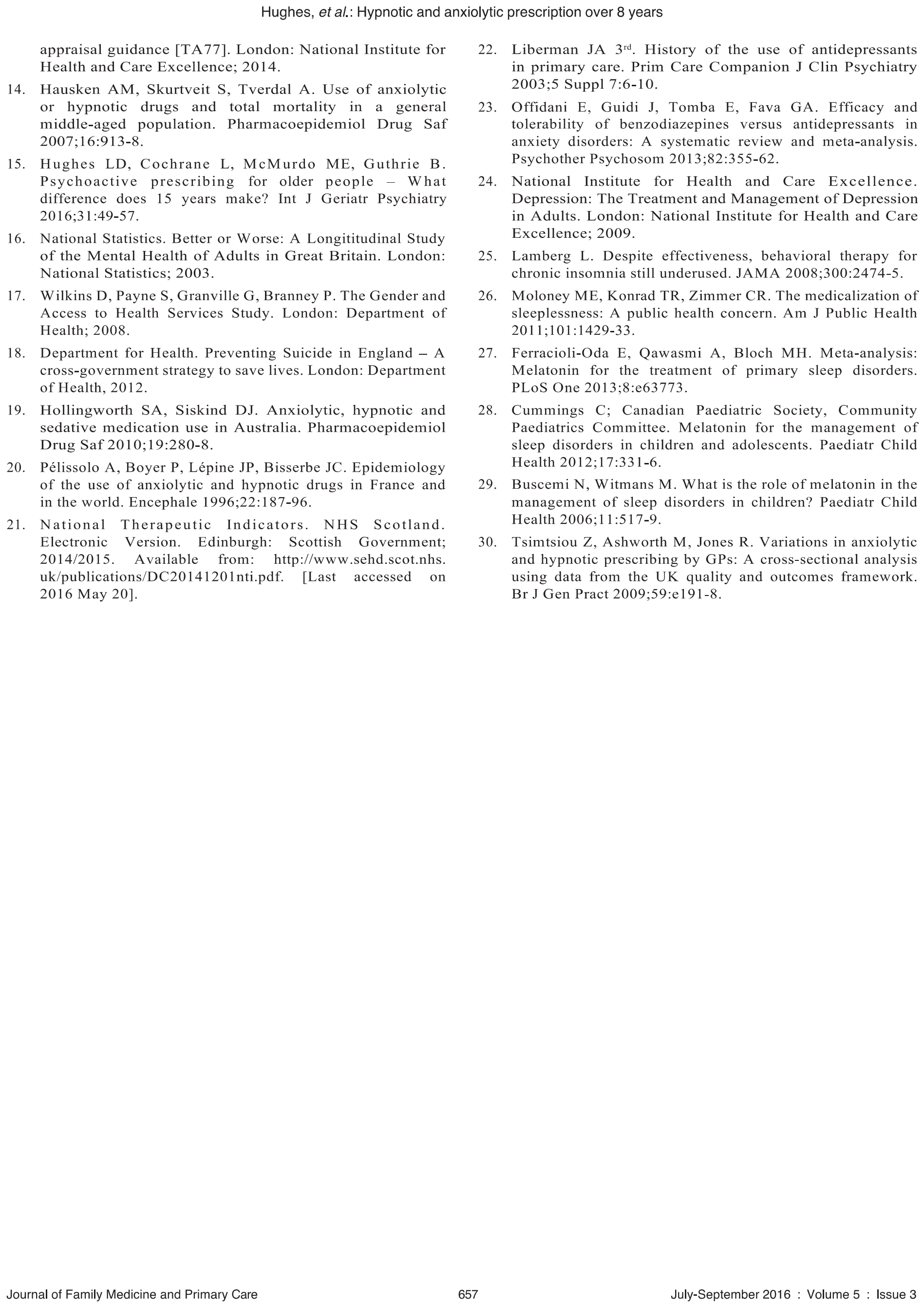

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Paper 5: Hughes LD, Cochrane L, McMurdo MET & Guthrie B. Psychoactive Prescribing for Older People – What difference does 15 years make?. *International Journal of Geriatric Psychiatry*. **2016**;31(1):49-57.

RESEARCH ARTICLE

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Psychoactive prescribing for older people—what difference does 15 years make?

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Objective: The objective of the study was to review prescribing of psychoactive medications for older residents of the Tayside region of Scotland.

Methods: The analysis used community prescribing data in 1995 and 2010 for all older residents in Tayside. For each psychoactive drug class, the name of the most recently prescribed drug and the date prescribed were extracted. The relative risk (RR) and 95% confidence intervals (CI) for patients receiving psychoactive medication in 2010 were compared with those for patients in 1995. Psychoactive prescribing was analyzed by year, age, gender, and deprivation classification. The chi-squared test was used to calculate statistical significance.

Results: Total psychoactive prescribing in people over the age of 65 years has increased comparing 1995 with 2010. Antidepressant [$RR = 2.5$ (95% CI 2.41–2.59) $p < 0.001$] and opioid analgesia [$RR = 1.21$ (1.19–1.24) $p < 0.001$] prescriptions increased between 1995 and 2010. Hypnotics/anxiolytic [$RR = 0.69$ (0.66–0.71) $p < 0.001$] and antipsychotic [$RR = 0.83$ (0.77–0.88) $p < 0.001$] prescriptions decreased between 1995 and 2010. An increase in psychoactive prescribing is particularly marked in lower socioeconomic groups. Patients in the least affluent fifth of the population had $RR = 1.25$ (1.20–1.29) [$p < 0.001$] of being prescribed one to two psychoactive medications and $RR = 1.81$ (1.56–2.10) [$p < 0.001$] of being prescribed three or more psychoactive medications in 2010 compared with those in 1995. The RRs for the most affluent fifth were $RR = 1.14$ (1.1–1.19) [$p < 0.001$] and $RR = 1.2$ (1.01–1.42) [$p < 0.001$] for one to two, and three or more medications, respectively.

Conclusion: Psychoactive medication prescribing has increased comparing 1995 with 2010, with increases disproportionately affecting patients in lower socioeconomic groups. The availability of new psychoactive drugs, safety concerns, and economic factors may explain these increases. Copyright © 2015 John Wiley & Sons, Ltd.

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Introduction

Older people (>65 years) have specific healthcare needs, are commonly prescribed multiple drugs, and are at greater risk of both adverse drug reactions (ADRs) and ADR-related hospital admissions (United Nations Report, 2009; Mizokami *et al.,* 2012; Ruiter *et al.,* 2012). Importantly, older people are often prescribed medications with psychoactive properties, agents that affect mood, perception, cognition, behavior, or consciousness as a result of changes in the functioning of the central nervous system (Thronson and Pagalilauan, 2014). These medications have a considerable side-effect profile in older patients (Guthrie *et al.,* 2010). Assessments of psychoactive drug prescribing in older patients showed that patients over 65 years are not uncommonly prescribed antidepressants (10.8%), hypnotic/anxiolytics

(7.5%), and antipsychotic medications (1%; Guthrie *et al.,* 2010). Furthermore, it is common for patients to be prescribed more than one agent with psychoactive properties (Guthrie *et al.,* 2010; Hughes *et al.,* 2012). However, there are few studies of temporal changes in psychoactive prescribing, and these have primarily focused on individual drug classes.

The assessment of trends in the prescribing of a single psychoactive drug is valuable. However, assessing changes in multiple psychoactive drug groups over a prolonged period indicates how these drugs as a whole are utilized by healthcare professionals, how broader changes in clinical practice may influence the prescription rates of certain agents, and how different groups of patients are affected. Furthermore, reviewing the prescribing of multiple psychoactive drugs will assist further research into the potential pharmacological burden that patients prescribed several psychoactive drugs may experience. Indeed, psychoactive drug burden is emerging as an important research issue in areas such as falls (Pratt *et al.,* 2014) and cognition (Narayan *et al.,* 2013).

This study reports a descriptive epidemiology study of dispensed psychoactive medications in a representative population of older people residing in the Tayside region of Scotland. The study reviewed prescribing trends of psychoactive medications for older patients in 1995 and 2010 providing information on patients taking single and multiple psychoactive agents. In addition to reviewing the overall changes in psychoactive prescribing, we compared how different demographic variables were associated with changes in prescribing between 1995 and 2010.

Methods

The analysis used community-dispensed prescribing data for all residents of the Tayside region of Scotland held by the University of Dundee Health Informatics Centre (HIC).

Data were fully anonymized by HIC, and analysis complied with HIC Standard Operating Procedures approved by the NHS East of Scotland Research Ethics Service and the NHS Tayside Caldicott Guardian. Ethical review of this project was therefore not required. Analysis was carried out in SPSS v18.0 (SPSS Inc, 2009). Data were extracted for people aged 65 years and over on two dates—31 March 1995 and 31 March 2010. After reviewing the datasets, 165 duplicate records were removed (i.e., identical patient records appearing twice in either the 1995 or 2010 dataset). Demographic data extracted included age, gender, postcode, and assigned deprivation score (quintiles of Scottish Index of Multiple Deprivation (SIMD)) and were linked to dispensed prescribing data. The SIMD is based upon information from the major population surveys in Scotland and allows comparison between the most deprived areas and the rest of the population in Scotland in numerous domains (Scottish Index of Multiple Deprivation. SIMD Results, 2012).

For each individual, community-dispensed prescriptions for psychoactive drugs were extracted. Psychoactive medications were defined after consulting the British National Formulary (BNF; BNF, 2012). Thus, drugs defined as psychoactive included hypnotics (defined as drugs in BNF chapter 4.1.1), anxiolytics (BNF chapter 4.1.2), drugs used in psychosis (BNF chapter 4.2), antidepressants (BNF chapter 4.3), and opioid analgesics (BNF chapter 4.7). All of these drug classes have been associated with clinically important side effects for older people as they affect the central nervous system (Moore and O'Keeffe, 1999; Fastbom and Schmidt, 2010; Milos *et al.,* 2014).

For each drug class, the name of the most recently prescribed drug and the date prescribed were extracted, and a drug was defined as "currently prescribed" if it had been dispensed in 84 days before 31 March 1995 or 31 March 2010. Therefore, only drugs dispensed in the last 84 days in both datasets were deemed a current prescription and used in the analysis. The proportion of people aged 65 years and over prescribed each drug class was calculated for patients in 1995 and in 2010. The 11 combinations of medications using antipsychotics, hypnotic/anxiolytics, antidepressants, and opioid analgesia were then analyzed. In addition, to establish baseline characteristics of total prescribing for each individual (i.e., not only psychoactive prescribing), community-dispensed prescription for all drugs was recorded as a total number (with no information about drug name and dose).

The relative risk (RR) and 95% confidence intervals (CI) for patients receiving psychoactive medication in 2010 were compared with those for patients in 1995. A psychoactive drug count was calculated by adding up prescribed medications in all of the psychoactive drug classes. Hypnotic and anxiolytic medications were distinguished in the analysis, giving a psychoactive drug count ranging from 0 to 5. Psychoactive prescribing trends were analyzed by year, age, gender, and deprivation classification. The chi-squared test was used to determine whether observed changes were significantly different from chance.

Results

Patient characteristics in 1995 and 2010

A total of 67,608 patients aged 65 years and over were registered with a Tayside practice in 1995 and 73,465 patients in 2010. Table 1 summarizes the patient characteristics in the 1995 and 2010 datasets.

There was a considerable increase in the net number of patients over the age of 65 years living in Tayside between 1995 and 2010, with the median age increasing by 1 year to 74 years. Additional differences in the gender ratios and deprivation quintiles were evident comparing 1995 with 2010. The proportion of patients over the age of 65 years who were women decreased by 3.4% [$p < 0.001$], and there was a decrease in the number of patients in the more deprived quintiles, leading to over 50% of the population being in the two lower deprivation quintiles in 2010 [$p < 0.001$]. There was a considerable increase in the number of total medications (i.e., all types of medications not just psychoactive medications) that patients were prescribed. Indeed, there was a 24.5% increase in the total number of patients being prescribed five or more drugs, with the number of patients prescribed 10 or more medications almost trebling between 1995 and 2010 [$p < 0.001$]. Importantly, there was almost a 50% reduction in the proportion of patients prescribed no medications [$p < 0.001$].

Prescribing trends by age band and gender

Table 2 presents the proportions of patients prescribed any psychoactive medications in 1995 and 2010 by age and gender. Patients in all age groups were relatively more likely to be prescribed one or more psychoactive agents in 2010 compared with those in 1995. At both time points, there was a steady increase in the proportion of patients prescribed a psychoactive medication as they aged, with the proportions for all five age groups being greater in 2010.

Women were prescribed more psychoactive medication than men in both 1995 and 2010, although the overall relative percentage increase in prescribing comparing 1995 with 2010 was higher in men. In 1995, the RR of a woman being prescribed any psychoactive medication compared with that of a man was 1.69 [95% CI 1.65–1.74 $p < 0.001$] with this decreasing to 1.49 [95% CI 1.49–1.52 $p < 0.001$] in 2010. In particular, women were more likely to be prescribed three or more psychoactive medications in both 1995 and 2010 compared with men, with an RR of 2.97 [95% CI 2.59–3.41 $p < 0.001$] in 1995 and RR of 2.15 [95% CI 1.95–2.36 $p < 0.001$] in 2010.

Prescribing trends by socioeconomic status

Overall, there has been an increase in psychoactive medication prescribing across all socioeconomic groups between 1995 and 2010. However, changes in

Table 1 Description of patient characteristics

1995 Tayside dataset [$n = 67,608$]	2010 dataset [$n = 73,465$]	Two-tailed p-value
Median age: 73 years [IQR: 69–80 years]	Median age: 74 years [IQR: 69–80 years]	<0.0001
60.1% female ($n = 40,632$)	56.7% female ($n = 41,655$)	<0.0001
39.9% male ($n = 26,976$)	43.3% male ($n = 31,810$)	<0.0001
Number of all drugs dispensed in the last 84 days		
Median number of dispensed drugs: 3 drugs [IQR: 0–5 drugs]	Median number of dispensed drugs: 5 drugs [IQR: 2–8 drugs]	
23.8% ($n = 16,091$) are taking 0 medications	12.1% ($n = 8889$) are taking 0 medications	<0.0001
46.7% ($n = 31,573$) are taking 1–4 medications	33.9% ($n = 24,904$) are taking 1–4 medications	<0.0001
29.5% ($n = 19,944$) are taking 5+ medications	54% ($n = 39,671$) are taking ≥5 medications	<0.0001
Scottish deprivation quintiles*		
Q1—17.7% ($n = 11,967$)	Q1—12.6% ($n = 9257$)	<0.0001
Q2—17.7% ($n = 11,967$)	Q2—14.5% ($n = 10,652$)	<0.0001
Q3—17.9% ($n = 12,101$)	Q3—17.5% ($n = 12,856$)	0.1021
Q4—29.9% ($n = 20,215$)	Q4—33.7% ($n = 24,758$)	<0.0001
Q5—16.8% ($n = 11,358$)	Q5—21.7% ($n = 15,942$)	<0.0001

IQR, interquartile range.
*Scottish Deprivation Quintiles socioeconomic deprivation based on the Scottish Index of Multiple Deprivation score for the patients' postcode of residence. Quintile 1 is most deprived, and Quintile 5 is most affluent.

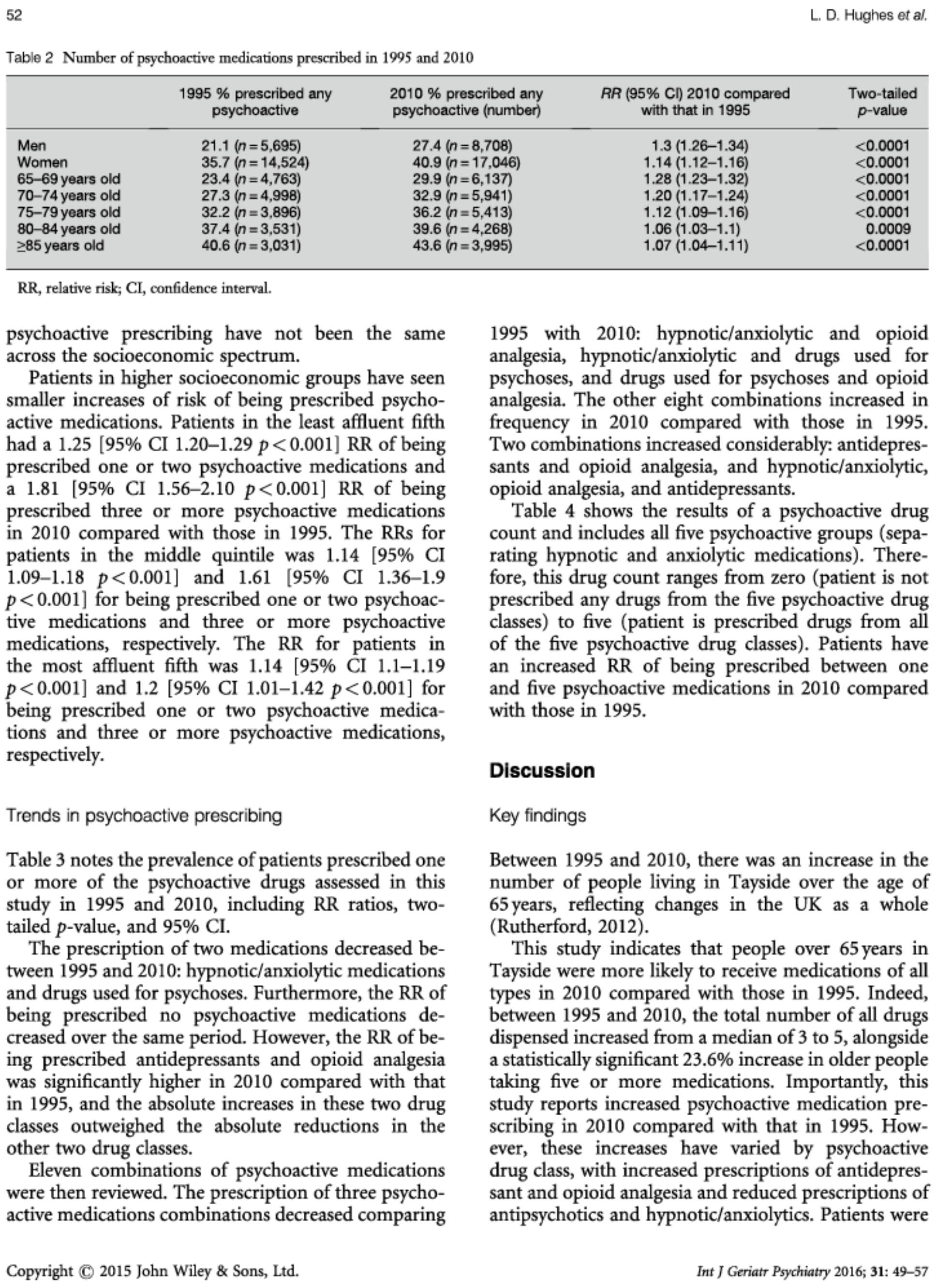


Table 2 Number of psychoactive medications prescribed in 1995 and 2010

	1995 % prescribed any psychoactive	2010 % prescribed any psychoactive (number)	*RR* (95% CI) 2010 compared with that in 1995	Two-tailed *p*-value
Men	21.1 ($n = 5{,}695$)	27.4 ($n = 8{,}708$)	1.3 (1.26–1.34)	<0.0001
Women	35.7 ($n = 14{,}524$)	40.9 ($n = 17{,}046$)	1.14 (1.12–1.16)	<0.0001
65–69 years old	23.4 ($n = 4{,}763$)	29.9 ($n = 6{,}137$)	1.28 (1.23–1.32)	<0.0001
70–74 years old	27.3 ($n = 4{,}998$)	32.9 ($n = 5{,}941$)	1.20 (1.17–1.24)	<0.0001
75–79 years old	32.2 ($n = 3{,}896$)	36.2 ($n = 5{,}413$)	1.12 (1.09–1.16)	<0.0001
80–84 years old	37.4 ($n = 3{,}531$)	39.6 ($n = 4{,}268$)	1.06 (1.03–1.1)	0.0009
≥85 years old	40.6 ($n = 3{,}031$)	43.6 ($n = 3{,}995$)	1.07 (1.04–1.11)	<0.0001

RR, relative risk; CI, confidence interval.

psychoactive prescribing have not been the same across the socioeconomic spectrum.

Patients in higher socioeconomic groups have seen smaller increases of risk of being prescribed psychoactive medications. Patients in the least affluent fifth had a 1.25 [95% CI 1.20–1.29 $p < 0.001$] RR of being prescribed one or two psychoactive medications and a 1.81 [95% CI 1.56–2.10 $p < 0.001$] RR of being prescribed three or more psychoactive medications in 2010 compared with those in 1995. The RRs for patients in the middle quintile was 1.14 [95% CI 1.09–1.18 $p < 0.001$] and 1.61 [95% CI 1.36–1.9 $p < 0.001$] for being prescribed one or two psychoactive medications and three or more psychoactive medications, respectively. The RR for patients in the most affluent fifth was 1.14 [95% CI 1.1–1.19 $p < 0.001$] and 1.2 [95% CI 1.01–1.42 $p < 0.001$] for being prescribed one or two psychoactive medications and three or more psychoactive medications, respectively.

Trends in psychoactive prescribing

Table 3 notes the prevalence of patients prescribed one or more of the psychoactive drugs assessed in this study in 1995 and 2010, including RR ratios, two-tailed *p*-value, and 95% CI.

The prescription of two medications decreased between 1995 and 2010: hypnotic/anxiolytic medications and drugs used for psychoses. Furthermore, the RR of being prescribed no psychoactive medications decreased over the same period. However, the RR of being prescribed antidepressants and opioid analgesia was significantly higher in 2010 compared with that in 1995, and the absolute increases in these two drug classes outweighed the absolute reductions in the other two drug classes.

Eleven combinations of psychoactive medications were then reviewed. The prescription of three psychoactive medications combinations decreased comparing 1995 with 2010: hypnotic/anxiolytic and opioid analgesia, hypnotic/anxiolytic and drugs used for psychoses, and drugs used for psychoses and opioid analgesia. The other eight combinations increased in frequency in 2010 compared with those in 1995. Two combinations increased considerably: antidepressants and opioid analgesia, and hypnotic/anxiolytic, opioid analgesia, and antidepressants.

Table 4 shows the results of a psychoactive drug count and includes all five psychoactive groups (separating hypnotic and anxiolytic medications). Therefore, this drug count ranges from zero (patient is not prescribed any drugs from the five psychoactive drug classes) to five (patient is prescribed drugs from all of the five psychoactive drug classes). Patients have an increased RR of being prescribed between one and five psychoactive medications in 2010 compared with those in 1995.

Discussion

Key findings

Between 1995 and 2010, there was an increase in the number of people living in Tayside over the age of 65 years, reflecting changes in the UK as a whole (Rutherford, 2012).

This study indicates that people over 65 years in Tayside were more likely to receive medications of all types in 2010 compared with those in 1995. Indeed, between 1995 and 2010, the total number of all drugs dispensed increased from a median of 3 to 5, alongside a statistically significant 23.6% increase in older people taking five or more medications. Importantly, this study reports increased psychoactive medication prescribing in 2010 compared with that in 1995. However, these increases have varied by psychoactive drug class, with increased prescriptions of antidepressant and opioid analgesia and reduced prescriptions of antipsychotics and hypnotic/anxiolytics. Patients were

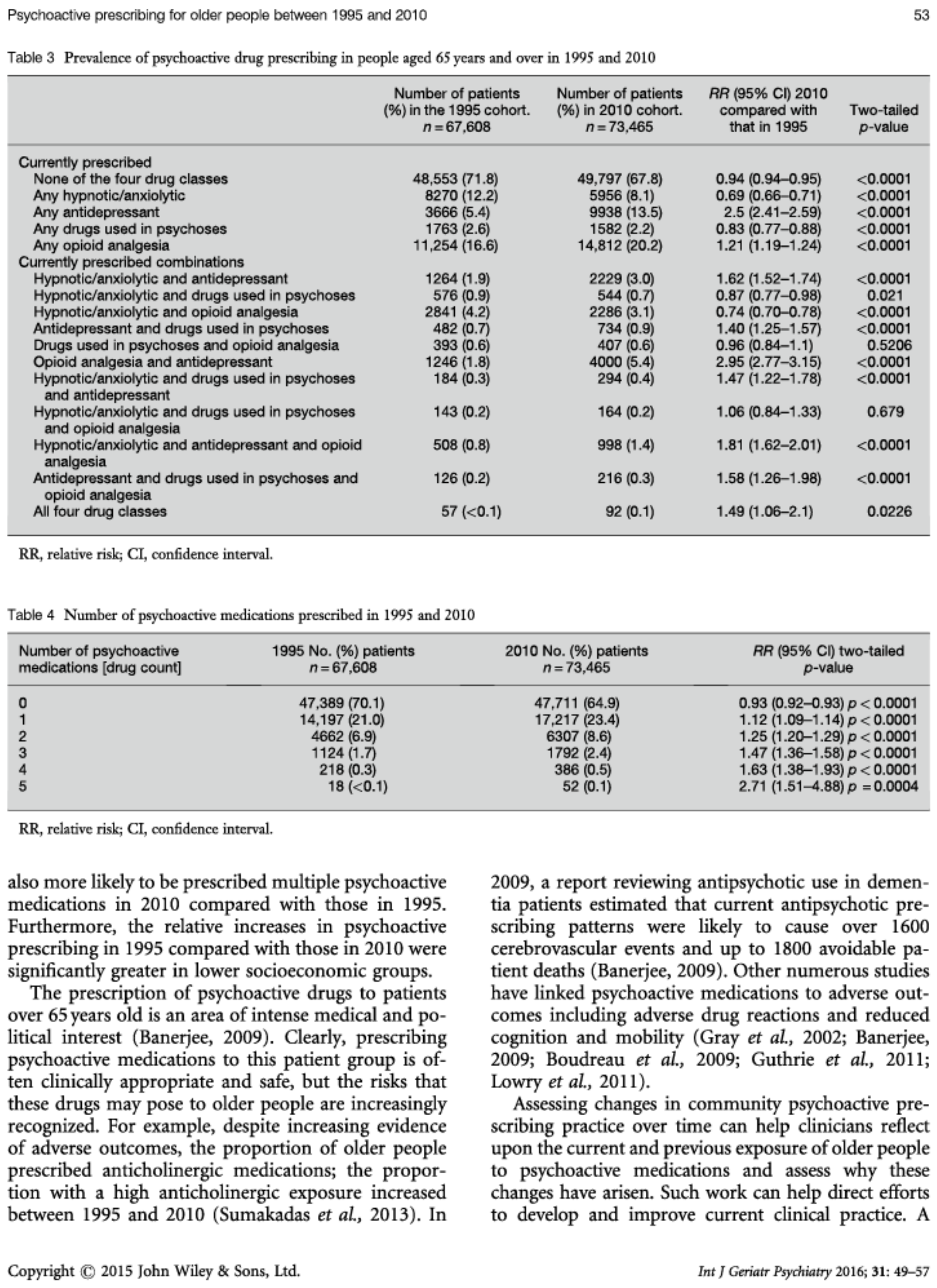


Table 3 Prevalence of psychoactive drug prescribing in people aged 65 years and over in 1995 and 2010

	Number of patients (%) in the 1995 cohort. $n = 67{,}608$	Number of patients (%) in 2010 cohort. $n = 73{,}465$	*RR* (95% CI) 2010 compared with that in 1995	Two-tailed *p*-value
Currently prescribed				
None of the four drug classes	48,553 (71.8)	49,797 (67.8)	0.94 (0.94–0.95)	<0.0001
Any hypnotic/anxiolytic	8270 (12.2)	5956 (8.1)	0.69 (0.66–0.71)	<0.0001
Any antidepressant	3666 (5.4)	9938 (13.5)	2.5 (2.41–2.59)	<0.0001
Any drugs used in psychoses	1763 (2.6)	1582 (2.2)	0.83 (0.77–0.88)	<0.0001
Any opioid analgesia	11,254 (16.6)	14,812 (20.2)	1.21 (1.19–1.24)	<0.0001
Currently prescribed combinations				
Hypnotic/anxiolytic and antidepressant	1264 (1.9)	2229 (3.0)	1.62 (1.52–1.74)	<0.0001
Hypnotic/anxiolytic and drugs used in psychoses	576 (0.9)	544 (0.7)	0.87 (0.77–0.98)	0.021
Hypnotic/anxiolytic and opioid analgesia	2841 (4.2)	2286 (3.1)	0.74 (0.70–0.78)	<0.0001
Antidepressant and drugs used in psychoses	482 (0.7)	734 (0.9)	1.40 (1.25–1.57)	<0.0001
Drugs used in psychoses and opioid analgesia	393 (0.6)	407 (0.6)	0.96 (0.84–1.1)	0.5206
Opioid analgesia and antidepressant	1246 (1.8)	4000 (5.4)	2.95 (2.77–3.15)	<0.0001
Hypnotic/anxiolytic and drugs used in psychoses and antidepressant	184 (0.3)	294 (0.4)	1.47 (1.22–1.78)	<0.0001
Hypnotic/anxiolytic and drugs used in psychoses and opioid analgesia	143 (0.2)	164 (0.2)	1.06 (0.84–1.33)	0.679
Hypnotic/anxiolytic and antidepressant and opioid analgesia	508 (0.8)	998 (1.4)	1.81 (1.62–2.01)	<0.0001
Antidepressant and drugs used in psychoses and opioid analgesia	126 (0.2)	216 (0.3)	1.58 (1.26–1.98)	<0.0001
All four drug classes	57 (<0.1)	92 (0.1)	1.49 (1.06–2.1)	0.0226

RR, relative risk; CI, confidence interval.

Table 4 Number of psychoactive medications prescribed in 1995 and 2010

Number of psychoactive medications [drug count]	1995 No. (%) patients $n = 67{,}608$	2010 No. (%) patients $n = 73{,}465$	*RR* (95% CI) two-tailed *p*-value
0	47,389 (70.1)	47,711 (64.9)	0.93 (0.92–0.93) $p < 0.0001$
1	14,197 (21.0)	17,217 (23.4)	1.12 (1.09–1.14) $p < 0.0001$
2	4662 (6.9)	6307 (8.6)	1.25 (1.20–1.29) $p < 0.0001$
3	1124 (1.7)	1792 (2.4)	1.47 (1.36–1.58) $p < 0.0001$
4	218 (0.3)	386 (0.5)	1.63 (1.38–1.93) $p < 0.0001$
5	18 (<0.1)	52 (0.1)	2.71 (1.51–4.88) $p = 0.0004$

RR, relative risk; CI, confidence interval.

also more likely to be prescribed multiple psychoactive medications in 2010 compared with those in 1995. Furthermore, the relative increases in psychoactive prescribing in 1995 compared with those in 2010 were significantly greater in lower socioeconomic groups.

The prescription of psychoactive drugs to patients over 65 years old is an area of intense medical and political interest (Banerjee, 2009). Clearly, prescribing psychoactive medications to this patient group is often clinically appropriate and safe, but the risks that these drugs may pose to older people are increasingly recognized. For example, despite increasing evidence of adverse outcomes, the proportion of older people prescribed anticholinergic medications; the proportion with a high anticholinergic exposure increased between 1995 and 2010 (Sumakadas *et al.*, 2013). In 2009, a report reviewing antipsychotic use in dementia patients estimated that current antipsychotic prescribing patterns were likely to cause over 1600 cerebrovascular events and up to 1800 avoidable patient deaths (Banerjee, 2009). Other numerous studies have linked psychoactive medications to adverse outcomes including adverse drug reactions and reduced cognition and mobility (Gray *et al.*, 2002; Banerjee, 2009; Boudreau *et al.*, 2009; Guthrie *et al.*, 2011; Lowry *et al.*, 2011).

Assessing changes in community psychoactive prescribing practice over time can help clinicians reflect upon the current and previous exposure of older people to psychoactive medications and assess why these changes have arisen. Such work can help direct efforts to develop and improve current clinical practice. A strength of this study is that it examined community-dispensed use for a representative sample of an entire geographical population (Sumakadas *et al.,* 2013).

Prescribing trends by age band and gender

This study reports that the total number of all drugs dispensed increased in 2010 compared with that in 1995. Regarding psychoactive medications, there was an increase in RR of receiving one or more psychoactive medications for all five age bands between 1995 and 2010.

As people age, they are more likely to be prescribed medications of all forms (Mizokami *et al.,* 2012; Ruiter *et al.,* 2012). A recent focus has promoted rational prescribing and reviewing medication because of the increase in polypharmacy (O'Mahony *et al.,* 2010; The Model of Care Polypharmacy Working Group, 2012; Wise, 2013). Initiatives to optimize prescribing for older people through service developments within primary care (The Model of Care Polypharmacy Working Group, 2012) are particularly important as it has been reported that physicians can feel that solutions to inappropriate prescribing, in particular, psychoactive prescribing, are beyond the scope of the individual physician (Damestoy *et al.,* 1999). Previous successful approaches to optimize prescribing for older people have usually been either educational or administrative, and a combined approach is recommended (Mort and Aparasu, 2002). For example, in America, the Omnibus Budget Reconciliation Act of 1987 served as an impetus for clinical review and changed practice style for prescribing in nursing homes (Lantz *et al.,* 1996) and was reduced antipsychotic prescribing by linking Medicare reimbursement to appropriate prescribing (Lantz *et al.,* 1996; Gurvich and Cunningham, 2000; Mort and Aparasu, 2002). In UK, linking prescribing reviews to the quality outcomes framework, which awards family doctors points based upon patient management, may be able to achieve similar results by allowing primary care physicians to be paid for reviewing older patients prescriptions and making appropriate adjustments. In the future, making exception reporting easier (e.g., allowing a doctor to remove patients from pay-for-performance measures if there are good reasons to do so) may allow family practitioners to provide rational prescribing to older people both in terms of psychoactive prescribing and more broadly.

Women were more likely to prescribed psychoactive medications compared with men in both 1995 and 2010. This may be because women are more likely to have been treated for a mental health problem than men (29% vs. 17%; National Statistics, 2003). Indeed, women report symptoms of the most common mental health disorders more readily to primary care physicians than men (Gurvich and Cunningham, 2000; National Institute for Health and Care Excellence, 2009). Furthermore, men are more likely to develop conditions where long-term psychoactive prescribing is not indicated, such as alcohol and substance misuse (National Statistics, 2003). Psychoactive prescribing increased for both genders between 1995 and 2010, which may relate to the management of depression and anxiety disorders with newer antidepressants not available in 1995, alongside the increased use of opioid prescribing for non-cancer chronic pain syndromes.

Prescribing trends by socioeconomic status

Older patients in lower economic quintiles were more likely to be prescribed psychoactive medications in both 1995 and 2010. In 2010, over 50% of the over 65-year-old population were placed in the two lower deprivation quintiles following complex social and economic changes to the population. Based upon analysis of previous economic experiences, a nation's economic health is inextricably linked with its mental and physical health (The Black Report, 1980; Cooper, 2011). Financial crises and associated rising unemployment and social inequality and insecurity have been linked with higher suicide rates and less clear relationships with increases in prevalence of psychiatric illnesses, alcohol-related disorders, and drug use (Cooper, 2011). Indeed, English data collected between 2008 and 2011, following the recession, reported a more than 40% increase in the number of people seeking treatment for mental health disorders and an 11.5% increase in the number of people diagnosed with depression (SSentif Online, 2013). Therefore, increased social deprivation in 2010 may partially explain the higher rates of psychoactive prescribing compared with that in 1995. This increase may also reflect higher rates of both mental and physical ill health in patients in the least affluent economic quintiles.

Trends in psychoactive prescribing

The prescription of hypnotic/anxiolytic medications and drugs used for psychoses decreased between 1995 and 2010. We postulate that the reduction in drugs used for psychoses mainly reflected the large-scale reduction in thioridazine prescribing, rather than a reduction of all agents in this drug group.

Thioridazine was an atypical antipsychotic used in the 1990s as an anxiolytic and sedative (at lower doses) and was withdrawn from the market worldwide in 2005 following concerns about cardiotoxicity and fatal dysrhythmias compared with other antipsychotics (Reilly *et al.,* 2000; Purhonen *et al.,* 2012). Indeed, in contrast to our documented reduction in antipsychotic prescribing, there have been concerns about the over-use of antipsychotic medications in older patients with dementia to manage behavioral and psychological symptoms of dementia, despite the literature being skeptical of their efficacy (Banerjee, 2009; Guthrie *et al.,* 2010; Declercq *et al.,* 2013; Gustafsson *et al.,* 2013). Furthermore, a study of prescribing patterns of psychoactive drugs in nursing home residents with dementia concluded that antipsychotics were the most commonly prescribed drug class of all psychoactive drugs (Wetzels *et al.,* 2011).

The significant reduction in the prescription of hypnotic and anxiolytic agents may reflect concerns about drug dependence, tolerance, and efficacy alongside the occurrence of significant side effects in older people. Indeed, there is clear evidence that benzodiazepines and other sedative–hypnotic medications significantly increase the risk of falls and hip fractures in older people (AGS Choosing Wisely Workgroup, 2013). Furthermore, these medications may lead to cognitive problems in people over the age of 65 years, with a meta-analysis of randomized controlled trials enrolling older adults reporting that memory problems, disorientation, and confusion are more common with benzodiazepines and newer non-benzodiazepine hypnotics than placebo (Glass *et al.,* 2005). Finally, evidence suggests that newer antidepressants might manage patients with anxiety more safely (Lieberman, 2003), while non-drug options for managing anxiety (National Institute for Health and Care Excellence, 2009) and insomnia (Lamberg, 2008) have a good evidence base.

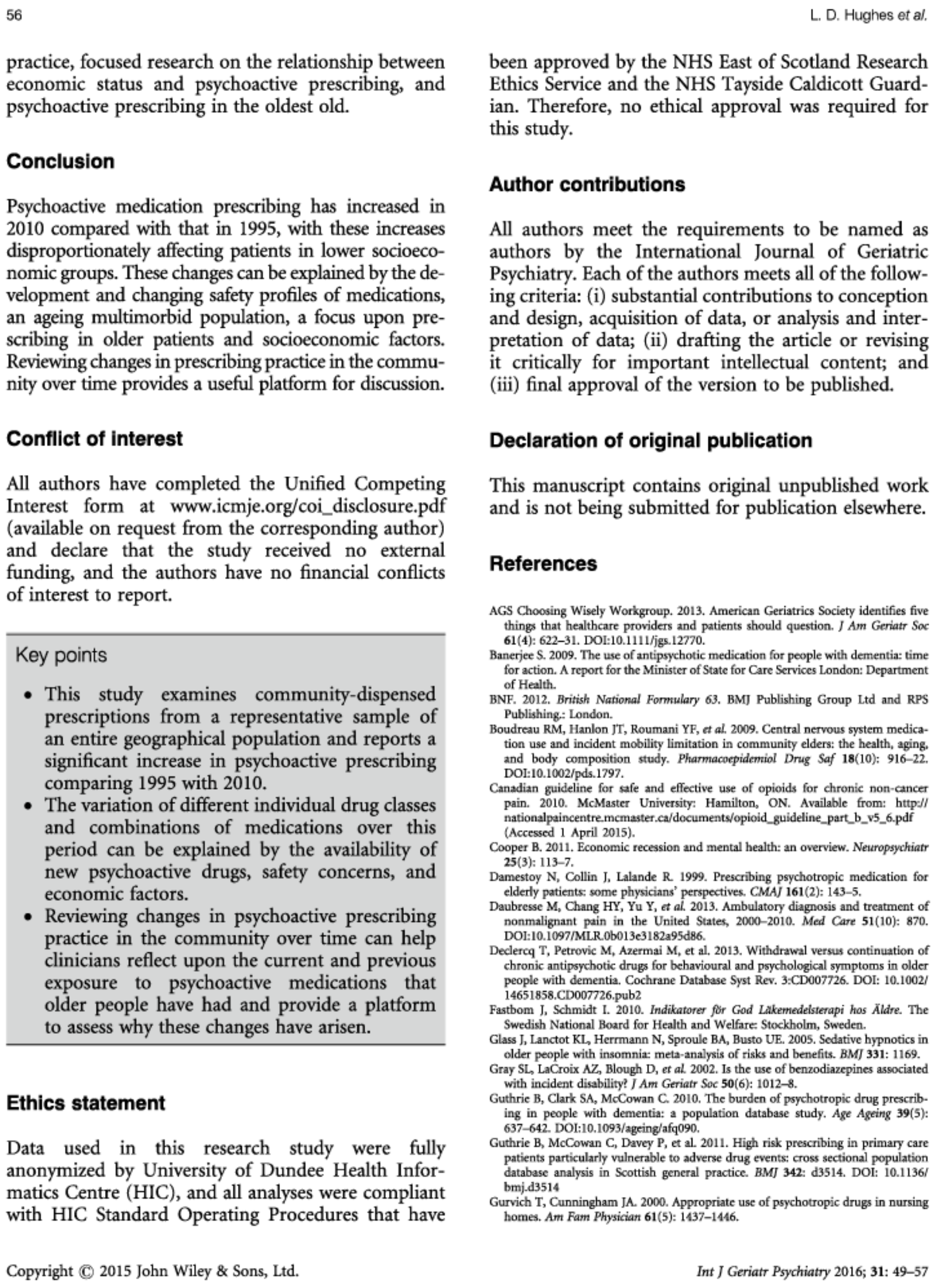
The prescription of antidepressants and opioid analgesia increased between 1995 and 2010. Antidepressant medications have evolved since 1995 with dual-acting (norepinephrine and serotonin) antidepressants such as venlafaxine, duloxetine, and mirtazapine now available (National Institute for Health and Care Excellence, 2009). In addition, over the last decade, research has explored how these agents could treat other conditions including anxiety and neuropathic pain (National Institute for Health and Care Excellence, 2009). Finally, compared with those in 1995, most patients with depression have their condition and prescriptions handled entirely in the community by primary care physicians (National Institute for Health and Care Excellence, 2009; van Weel *et al.,* 2009).

The increased opioid analgesia prescribing appears to relate primarily to efforts over the last decade to improve pain management in older patients, which has historically been under-treated (Hughes, 2012; National Institute for Health and Care Excellence, 2012; Schofield, 2014). National Institute for Health and Care Excellence reported that strong opioids are the principal treatments for pain related to advanced and progressive diseases, and their use has increased significantly in primary care in recent years (National Institute for Health and Care Excellence, 2012). Indeed, numerous guidelines that have reviewed the use of opioid analgesia in older people suggested that these medications are effective and safe in older people when prescribing cautions are implemented (Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain, 2010; National Institute for Health and Care Excellence, 2012). However, there remain concerns in the USA that the prescription of opioid analgesia in non-cancer patients may be excessive with other therapeutic options under-used (Daubresse *et al.,* 2013).

The changes in drug combinations between 1995 and 2010 appear to reflect changes in individual psychoactive medications during this period.

Limitations

This research paper has several limitations. Firstly, this paper reports a patient being prescribed a psychoactive medication based upon community prescription data at two specific time points, that is, 1995 and 2010. Therefore, the data obtained do not allow us to fully ascertain the changes in prescribing practice that have arisen over this period, merely to compare these two points in time. However, such work does provide a platform for discussing psychoactive drug prescribing. Secondly, because of the nature of the dataset, we were unable to analyze high-risk patient groups in relation to psychoactive prescribing, such as those residing in nursing homes, care homes, sheltered housing, or receiving significant community support. This will be the focus of future clinical research, as assessing psychoactive prescribing in these groups and comparing them with community-dwelling adults are important. Thirdly, no information on the dose of the drug or whether it was an acute, delayed, or repeat prescription was available. Finally, the data only reflect community prescribing practice, and changes in the same period in secondary care are out of the scope of this report. However, the paper highlights several potential areas for further work such as hospital prescribing



practice, focused research on the relationship between economic status and psychoactive prescribing, and psychoactive prescribing in the oldest old.

Conclusion

Psychoactive medication prescribing has increased in 2010 compared with that in 1995, with these increases disproportionately affecting patients in lower socioeconomic groups. These changes can be explained by the development and changing safety profiles of medications, an ageing multimorbid population, a focus upon prescribing in older patients and socioeconomic factors. Reviewing changes in prescribing practice in the community over time provides a useful platform for discussion.

Conflict of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that the study received no external funding, and the authors have no financial conflicts of interest to report.

Key points

- This study examines community-dispensed prescriptions from a representative sample of an entire geographical population and reports a significant increase in psychoactive prescribing comparing 1995 with 2010.
- The variation of different individual drug classes and combinations of medications over this period can be explained by the availability of new psychoactive drugs, safety concerns, and economic factors.
- Reviewing changes in psychoactive prescribing practice in the community over time can help clinicians reflect upon the current and previous exposure to psychoactive medications that older people have had and provide a platform to assess why these changes have arisen.

Ethics statement

Data used in this research study were fully anonymized by University of Dundee Health Informatics Centre (HIC), and all analyses were compliant with HIC Standard Operating Procedures that have been approved by the NHS East of Scotland Research Ethics Service and the NHS Tayside Caldicott Guardian. Therefore, no ethical approval was required for this study.

Author contributions

All authors meet the requirements to be named as authors by the International Journal of Geriatric Psychiatry. Each of the authors meets all of the following criteria: (i) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (ii) drafting the article or revising it critically for important intellectual content; and (iii) final approval of the version to be published.

Declaration of original publication

This manuscript contains original unpublished work and is not being submitted for publication elsewhere.

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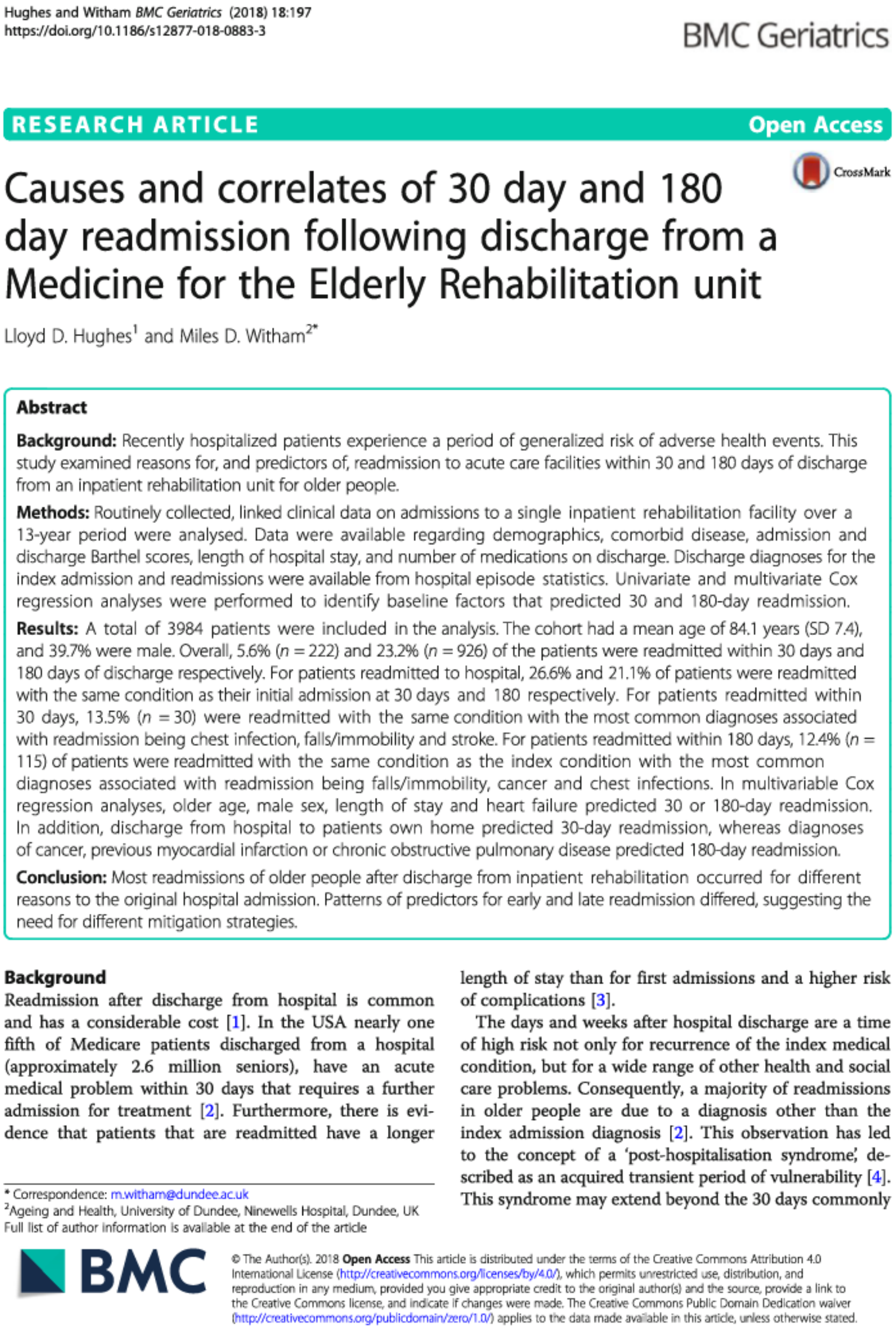

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Causes and correlates of 30 day and 180 day readmission following discharge from a Medicine for the Elderly Rehabilitation unit

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Abstract

Background: Recently hospitalized patients experience a period of generalized risk of adverse health events. This study examined reasons for, and predictors of, readmission to acute care facilities within 30 and 180 days of discharge from an inpatient rehabilitation unit for older people.

Methods: Routinely collected, linked clinical data on admissions to a single inpatient rehabilitation facility over a 13-year period were analysed. Data were available regarding demographics, comorbid disease, admission and discharge Barthel scores, length of hospital stay, and number of medications on discharge. Discharge diagnoses for the index admission and readmissions were available from hospital episode statistics. Univariate and multivariate Cox regression analyses were performed to identify baseline factors that predicted 30 and 180-day readmission.

Results: A total of 3984 patients were included in the analysis. The cohort had a mean age of 84.1 years (SD 7.4), and 39.7% were male. Overall, 5.6% ($n = 222$) and 23.2% ($n = 926$) of the patients were readmitted within 30 days and 180 days of discharge respectively. For patients readmitted to hospital, 26.6% and 21.1% of patients were readmitted with the same condition as their initial admission at 30 days and 180 respectively. For patients readmitted within 30 days, 13.5% ($n = 30$) were readmitted with the same condition with the most common diagnoses associated with readmission being chest infection, falls/immobility and stroke. For patients readmitted within 180 days, 12.4% ($n = 115$) of patients were readmitted with the same condition as the index condition with the most common diagnoses associated with readmission being falls/immobility, cancer and chest infections. In multivariable Cox regression analyses, older age, male sex, length of stay and heart failure predicted 30 or 180-day readmission. In addition, discharge from hospital to patients own home predicted 30-day readmission, whereas diagnoses of cancer, previous myocardial infarction or chronic obstructive pulmonary disease predicted 180-day readmission.

Conclusion: Most readmissions of older people after discharge from inpatient rehabilitation occurred for different reasons to the original hospital admission. Patterns of predictors for early and late readmission differed, suggesting the need for different mitigation strategies.

Background

Readmission after discharge from hospital is common and has a considerable cost [1]. In the USA nearly one fifth of Medicare patients discharged from a hospital (approximately 2.6 million seniors), have an acute medical problem within 30 days that requires a further admission for treatment [2]. Furthermore, there is evidence that patients that are readmitted have a longer length of stay than for first admissions and a higher risk of complications [3].

The days and weeks after hospital discharge are a time of high risk not only for recurrence of the index medical condition, but for a wide range of other health and social care problems. Consequently, a majority of readmissions in older people are due to a diagnosis other than the index admission diagnosis [2]. This observation has led to the concept of a 'post-hospitalisation syndrome', described as an acquired transient period of vulnerability [4]. This syndrome may extend beyond the 30 days commonly

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used as the benchmark for readmission rates, perhaps as long as 6 months after the index admission [5].

Because of the risks and costs associated with readmission, there is considerable interest in identifying which patients are at risk of readmission, with a view to intervening to reduce readmission rates. The use of readmission rates as a quality standard in healthcare gives further impetus to these efforts. There has been some work developing predictive models to assist in the reduction in readmission rates, with varying degrees of success [6–9]. The majority of studies in this area to date have however excluded patients discharged to nursing homes and have focused on patient discharges from acute receiving hospitals. Indeed, predictive algorithms for readmission [1, 5, 6] have not specifically studied older patients, who may have differing reasons for readmission compared to younger patients.

There are also limited data on readmission rates for patients who have experienced a period of in-patient rehabilitation after a period of prolonged illness, with evidence to date from American studies. These patients typically remain in hospital for a number of weeks, and thus subsequent readmissions may be less likely to be related to hasty or incomplete discharge planning, allowing the impact of post-hospitalisation syndrome rather than incomplete discharge planning and community support to be dissected out.

Ottenbacher et al. reviewed centrally held data from 1365 post-acute inpatient rehabilitation facilities (n = 736,536), reported 30-day readmission rates of between 5.8 and 18.8% for different sub-groups of patients [10]. 50% of readmissions were within 11 days. The same research group have published further work focusing upon patients with 'debility', and reported higher rates of hospital readmission of 19% at 30 days and 34% at 90 days [11]. There are considerable differences between the manner in which rehabilitation is provided in the USA and in Europe (in relation to providers of care, differing financial incentives, type of rehabilitation facilities where care is provided) meaning that these findings may not be directly comparable.

This study therefore aimed to use routinely collected healthcare data to establish a) the reasons for readmission to acute care facilities in a cohort of older people discharged from inpatient rehabilitation after an acute illness, b) whether the reasons for readmission varied by the reason for the index admission, and c) what the predictors for 30 and 180 day readmission were in this cohort.

Methods

Service characteristics

The Dundee Medicine for the Elderly rehabilitation service offers inpatient rehabilitation to patients located within Dundee (Scotland, United Kingdom) unitary authority (population 150,000). Patients over the age of 65 years, are accepted to the unit following an admission at acute receiving hospitals for acute medical or surgical illness from a variety of specialties including general medicine, general surgery, orthopedics, stroke medicine and neurosurgery. Patients are also accepted from sub-acute Medicine for the Elderly wards. Patients were selected following review by a consultant geriatrician; patients selected were those felt to have potential to achieve independence in domains of self-care who were medically stable after their acute admission. Patients who had limited to no expectation of functional improvement within a reasonable period of time or those felt unlikely to survive to discharge were not selected for transfer to the rehabilitation unit.

Inpatient rehabilitation is carried out on dedicated rehabilitation wards by a multidisciplinary team, including physiotherapists, occupational therapists, dieticians, social workers and speech and language therapists. This process is over-seen by a consultant geriatrician, with patient progress meetings at weekly intervals to discuss progress and any issues that may affect discharge success. The model of care on the rehabilitation unit remained unchanged throughout the analysis period.

Data sources

This analysis was conducted using linked, routinely collected clinical data in Tayside, Scotland. Anonymised data are held by the University of Dundee Health Informatics Centre (HIC) in an access-controlled Safe Haven environment. Analysis complied with HIC Standard Operating Procedures approved by the NHS East of Scotland Research Ethics Service and the NHS Tayside Caldicott Guardian. Separate ethics review for this project was therefore not required.

Data collected

Data used in this analysis were prospectively collected on all admissions to the Dundee Medicine for the Elderly rehabilitation unit between 1 January 1999 and 31 December 2011. Data were collected as part of routine clinical care and reviewed by the team caring for the patient during inpatient rehabilitation. The cohort was followed up until the end of May 2012. Mortality data were obtained using death certification information derived from Scottish Register Officer. This cohort has been described in detail previously [12–14].

Variables included age, sex, Scottish Index of Multiple Deprivation Quintile [15], discharge destination (home versus other options, which comprised long-stay hospital beds or care home), comorbid disease, admission and discharge 20-point Barthel scores, length of rehabilitation hospital stay, and number of medications on discharge.

Comorbid disease diagnoses were obtained in two different ways. A diagnosis of chronic kidney disease was coded based upon estimated glomerular filtration rate (eGFR) taken from linked clinical data using the MDRD equation [16]. Other diagnoses were obtained using International Classification of Diseases (ICD) 10 discharge diagnosis codes from hospital admissions prior to the index acute admission [17]. These included a diagnosis of previous myocardial infarction, stroke, congestive cardiac failure, and chronic obstructive pulmonary disease (COPD). The presence of diabetes mellitus was ascertained from the Scottish Care Information – Diabetes Collaborative (SCI-DC) database.

In addition, information on dynamic changes in C-reactive protein (CRP) was obtained as a measure of biological resilience [18], including maximum-recorded value during admission and time taken for elevated levels to halve in value.

Classification of admission and readmission diagnoses

The main diagnostic reason (recorded as ICD-10 codes) for admission to acute hospital prior to the rehabilitation referral for all patients was obtained from HIC datasets, alongside the main first readmission diagnosis to acute hospital for patients who were readmitted within 30 or 180 days. Only the first readmission was considered in this analysis.

These ICD codes were recorded, and collated into broader categories. For example, all cancer diagnoses were collated into 'Cancer Diagnoses' and different forms of dementia were collated into 'Dementia States'. In the 30-day and 180-day readmission groups, the 10 most common reasons for admission to hospital were established after reviewing collated diagnoses lists. The diagnoses for readmission were then charted by initial admission diagnosis for each of the two readmission groups in order to establish any relationships between initial admission and readmission diagnoses.

Data analysis

Statistical analyses were carried out in SPSS v22.0 (IBM, New York USA), and a two-sided p value of < 0.05 was taken as significant for all analyses. Individuals were excluded from the analysis if they died during their inpatient admission, or did not have a discharge Barthel score. The number of days between patients discharge from rehabilitation hospital discharge to next acute hospital admission was calculated, with readmission to acute hospital within 30 days and 180 days analysed separately. Cox regression analysis was used to examine the association between baseline factors and acute hospital readmission with dates censored at 30 days and 180 days after discharge (or at death if this was earlier). Analyses were adjusted for age, sex, and comorbid disease; variables with a p-value < 0.3 on univariate analysis were also entered into the adjusted model.

Results

Of the 4449 patients in the complete medicine for the elderly rehabilitation dataset, 409 died during admission and were excluded from analysis, with a further 65 excluded due to the absence of a discharge Barthel score. A total of 3984 patients were included in the analysis.

Baseline characteristics

The characteristics of the overall patients group, patients readmitted to acute hospital care within 30 days and 180 days of discharge from the rehabilitation hospital are given in Table 1. Twenty-nine patients died within 30 days of discharge without being readmitted, and 325 died within 180 days of discharge without being readmitted. Patients readmitted to acute hospital facilities within 30 or 180 days were more likely to have a diagnosis of cancer, chronic obstructive pulmonary disease, congestive cardiac failure, previous myocardial infarction, a higher number of general hospitalizations over the period of data-collection (1999–2012) and a higher admission Barthel score.

Readmission to acute hospital diagnoses

For patients readmitted within 30 days, 27% ($n = 59/222$) of patients were readmitted with the same condition as their initial admission. For patients readmitted within 180 days, 21% ($n = 196/926$) of patients were readmitted with the same condition as their initial admission. The most common reasons for readmission for patients readmitted within 30 days were chest infection ($n = 20$), stroke ($n = 14$) and falls/immobility ($n = 13$). The most common reasons for readmission for patients readmitted within 180 days were admission secondary to falls/immobility ($n = 99$), chest infection ($n = 55$) or secondary to cancer ($n = 51$).

Figures 1 and 2 show how both deaths and readmissions for the 30 and 180 day time periods varied over the study period. Figures 3 and 4 show the main readmission diagnoses at 30 days and 180 days respectively, broken down by the original admission diagnosis.

Multivariate analyses for acute hospital readmissions

Table 2 shows the results of univariate analysis for readmissions within 30 days and 180 days. Tables 3 and 4 show the results of multivariate regression analyses, conducted firstly using time to readmission as the dependent variable and censoring at death or end of the follow up period, and secondly using time to either death or readmission (whichever came first) as the dependent variable. Multivariate analysis showed that for patients readmitted within 30 days, older age, male sex,

Table 1 Characteristics of overall cohort, patients readmitted within 30 days and patients readmitted within 180 days

	Whole cohort *n* = 3984	Readmitted by 30 days *n* = 222	Not readmitted and alive at 30 days (*n* = 3733)	Readmitted by 180 days *N* = 926	Not readmitted and alive at 180 days (*n* = 2733)	Died before readmission and before 180 days (*n* = 325)
Mean age (years) (SD)	84.1 (7.4)	82.7(7.3)*	84.2 (7.4)	83.6 (7.3)**	84.4 (7.4)	82.8 (7.5)
Male sex (%)	1582 (39.7)	112 (50.5)*	1459 (39.1)	419 (45.2)**	1017 (37.2)	146 (44.9)
Discharged to own home (%)	2982 (74.8)	161 (72.5)	2810 (75.3)	757 (81.7)**	2072 (75.8)	153 (47.1)
SIMD Quintiles (%)						
1 (most deprived)	1167 (29.3)	65 (29.3)	1090 (29.2)	277 (30.0)	784 (28.7)	106 (32.6)
2	572 (14.4)	31 (14.0)	536 (14.4)	127 (13.7)	388 (14.2)	57 (17.5)
3	490 (12.3)	27 (12.2)	459 (12.3)	109 (11.8)	333 (12.2)	48 (14.8)
4	1073 (26.9)	66 (29.7)	1002 (26.8)	241 (26.0)	758 (27.7)	74 (22.8)
5 (least deprived)	596 (15)	28 (12.6)	565 (15.1)	147 (15.9)	412 (15.1)	37 (11.4)
Missing Value	86 (2.2)	5 (2.3)	81 (2.2)	25 (2.7)	58 (2.1)	3 (0.9)
Mean Admission Barthel Score (SD)	10.4 (3.8)	11.1 (3.8)*	10.4 (3.8)	10.4 (3.6)	10.5 (3.8)	9.4 (4.3)
Mean Discharge Barthel Score (SD)	14.4 (4.6)	14.7 (4.4)	14.4 (4.6)	14.5 (4.3)	14.7 (4.5)	10.6 (6.0)
Median Length of Stay (days) (IQR)	33 (18–62)	28 (16–52)*	34 (18–62)	33 (20 – 56)	34 (18–64)	29 (18–55)
Median Number of Medications on Discharge (IQR)	2 (0–5)	2 (0–5)	2 (0–5)	3 (0–6)	3 (0–5)	0 (0–3)
Previous Myocardial Infarction (%)	683 (17.1)	52 (23.4)*	628 (16.8)	188 (20.3)**	435 (15.9)	60 (18.5)
Previous Stroke (%)	286 (7.2)	16 (7.2)*	266 (7.1)	67 (7.2)	189 (6.9)	30 (9.2)
Congestive Heart Failure (%)	342 (8.6)	33 (14.9)*	304 (8.1)	109 (11.8)**	183 (6.7)	50 (15.4)
eGFR < 60 ml/min/1.73m^2 (%)	2019 (50.7)	109 (49.1)	1891 (50.7)	482 (52.1)	1373 (50.2)	164 (50.5)
eGFR 30–59	1090 (27.4)	57 (25.7)	1023 (27.4)	251 (27.1)	762 (27.9)	77 (23.7)
eGFR 15–29	709 (17.8)	40 (18.0)	664 (17.8)	170 (18.4)	473 (17.3)	66 (20.3)
eGFR < 15	220 (5.5)	12 (5.4)	204 (5.5)	61 (6.6)	138 (5.0)	21 (6.5)
COPD (%)	553 (13.9)	46 (20.7)*	502 (13.4)	157 (17.0)**	338 (12.4)	58 (17.8)
Previous Diagnosis of Cancer (%)	467 (11.7)	34 (15.3)	428 (11.5)	125 (13.5)**	262 (9.6)	80 (24.6)
Diabetes Mellitus (%)	709 (17.8)	50 (22.5)	654 (17.5)	168 (18.1)	501 (18.3)	40 (12.3)

SIMD Scottish Index Multiple Deprivation Quintiles, *SD* standard deviation, *IQR* inter-quartile range, *eGFR* estimated glomerular filtration rate, *COPD* Chronic obstructive pulmonary disease
*$p < 0.05$ vs group not readmitted at 30 days
**$p < 0.05$ vs group not readmitted at 180 days

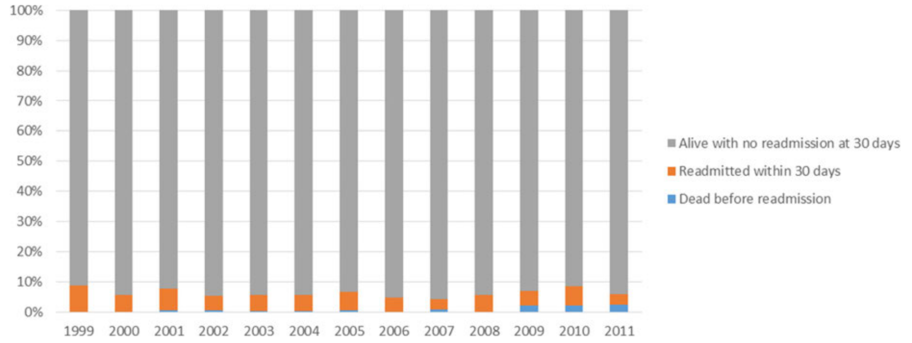

Fig. 1 Death of Readmission within 30 days by year of index admission

shorter length of hospital stay, discharge to own home and a previous diagnosis of chronic heart failure independent predictors of readmission within 30 days. For patients readmitted within 180 days, older age, male sex, shorter length of hospital stay and previous diagnosis of chronic heart failure were again independent predictors, but in addition previous myocardial infarction, previous diagnosis of cancer, and previous diagnosis of chronic obstructive pulmonary disease were additional independent predictors of readmission within 180 days. Results were very similar for readmission alone and for readmission or death as the outcome variable.

The ability of these sets of predictors to discriminate between those readmitted and those not readmitted was limited, with a c-statistic of 0.64 (95%CI 0.60 to 0.68) for readmission within 30 days, and 0.59 (95%CI 0.57 to 0.61) for readmission within 180 days.

Discussion

There are several key findings from this study. Readmissions to acute care in this cohort were due to a wide range of diagnoses, and were due to a different diagnosis to the index admission in over three-quarters of cases. Patterns differed between early and late readmission, and some index diagnoses (e.g. dementia, delirium, cardiovascular disease) were associated with a much higher chance of readmission with the same problem. The 30-day acute care readmission rate of 5.6% following a period of in-patient rehabilitation was lower than readmission rates reported in studies from the USA that ranged between 5.8–18.8% [10, 11, 19].

Risk factor patterns for early vs late readmission differed - for patients readmitted within 30 days a diagnosis of heart failure was the single factor increasing the likelihood of readmission, with discharge to the patients own home, and longer length of stay associated with reduced

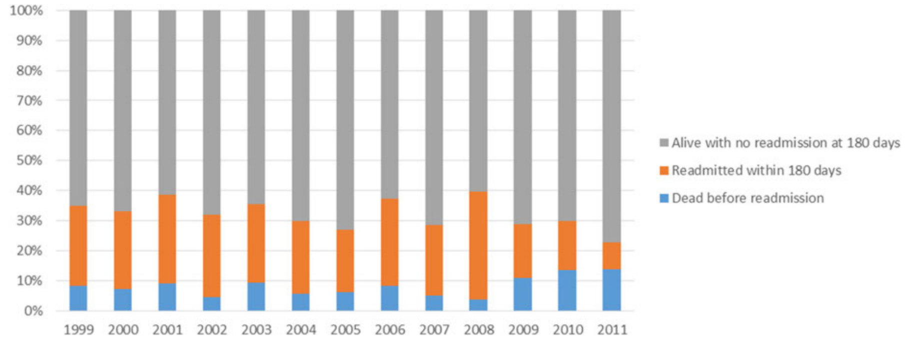

Fig. 2 Death of Readmission within 180 days by year of index admission

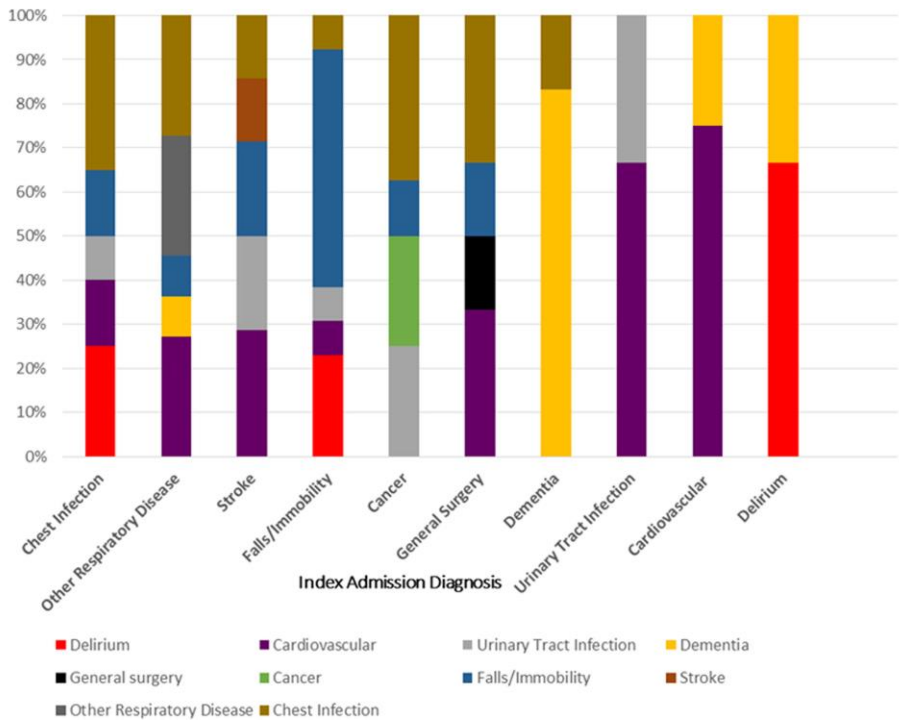

Fig. 3 Diagnoses leading to readmission compared to first admission diagnoses (30 day readmissions)

risk of readmission. In contrast, for patients readmitted within 180 days, the burden of comorbid disease as shown by a range of diagnoses and number of medications was associated with readmission. Although a longer length of stay was weakly associated with reduced risk of readmission to acute facilities, discharge to one's own home was not a protective factor. The discriminatory ability of a combination of the above factors for early or late readmission was only modest and is unlikely to be helpful in clinical practice, despite the inclusion of a measure of functional ability. Markers of inflammation and of biological resilience (maximum CRP and rate of CRP recovery) were not associated with the risk of readmission.

Our findings are consistent with previous work from the USA, where two-thirds of readmissions were for a different problem than the index admission [2]. The even higher rate of discrepant diagnoses seen in our analysis is likely to be due to the older age and increased comorbidity of our study population. A large number of comorbid diseases means more opportunity for a problem to arise in a different organ system. Furthermore, although we did not measure frailty in our study population, it is highly likely that frailty was prevalent as is the case in other groups of older inpatients. Analysis of trends in English hospitals reported that overall frailty burden, based on the coding of at least one frailty syndrome, has increased from 12 to 14% between 2005 and 2013 for older patients admitted electively or acutely [20]. Frailty denotes a loss of homeostatic reserve across multiple body systems. Thus a disturbance or illness in one system can easily precipitate failure of a different system, which would be consistent with our findings.

The risk factors for readmission that were significant in our cohort are similar to those seen in other studies. Cancer, COPD, ischaemic heart disease, heart failure and stroke have all been associated with high readmission rates [21–23], and our results are consistent with previous studies

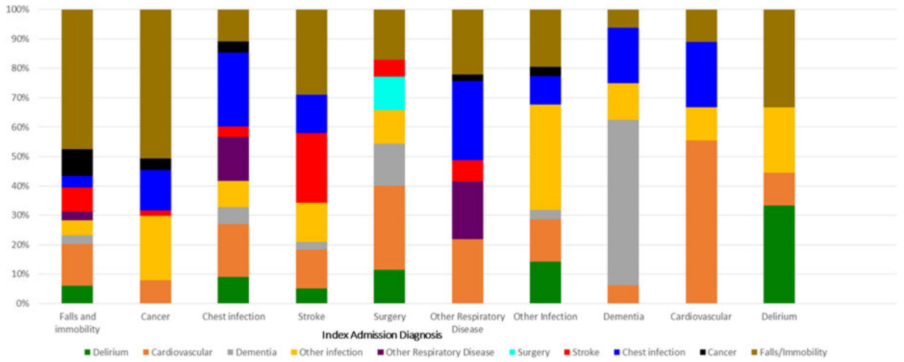

Fig. 4 Diagnoses leading to readmission compared to first admission diagnoses (180 day readmissions)

where multimorbidity and previous hospitalisations were risk factors for readmission [24–27]. A study from the USA looking at readmission following a period of in-patient rehabilitation reported that heart failure, infections, nutritional and metabolic disorders alongside digestive disorders were the most common reasons for readmission [10]. We did not find that these last two diagnoses were commonly associated with readmission to acute care in our cohort.

Previous work has also shown that men are more likely to be readmitted to hospital within 30 days of discharge, possibly due to reduced health-seeking behaviors [28]. Differences in health-seeking behaviors, the lower role placed by men on preventative care and overly optimistic self-perceived health status may explain the apparent contradiction between higher morbidity in females in older age but higher risk of readmission for men after discharge [29, 30].

In contrast to previous studies from acute hospitals [9, 26, 27, 31], older age was associated with a reduced risk of readmission in our analysis. This may reflect patient selection – very old, very frail patients may not be selected for rehabilitation but may be transferred directly to nursing care facilities rather than the rehabilitation unit, whereas similarly frail younger patients may be

Table 2 Univariate Cox regression analyses – time to readmission

Variable in Analysis	Censored at 30 days		Censored at 180 days	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Age (per year)	0.97 [0.96–0.99]	0.004	0.99 [0.98–0.99]	< 0.001
Female Sex	0.64 [0.49–0.83]	0.001	0.85 [0.80–0.90]	< 0.001
Admission Barthel score (per point)	1.05 [1.01–1.08]	0.01	1.01 [1.00–1.03]	0.13
Discharge Barthel score (per point)	1.01 [0.98–1.04]	0.34	1.01 [0.99–1.02]	0.39
Discharge Home	0.87 [0.65–1.16]	0.30	0.74 [0.64–0.85]	< 0.001
Length of Hospital stay (days)	0.997 [0.994–1.000]	0.04	0.998 [0.997–0.999]	< 0.001
Previous Myocardial Infarction	1.49 [1.09–2.03]	0.01	1.35 [1.17–1.56]	< 0.001
Previous Stroke	1.02 [0.61–1.69]	0.94	1.03 [0.82–1.29]	0.81
Congestive Cardiac Failure	1.90 [1.32–2.76]	0.001	1.68 [1.41–2.00]	< 0.001
Previous Diagnosis of Cancer	1.38 [0.96–1.99]	0.09	1.30 [1.10–1.53]	0.002
Diabetes Mellitus	1.11 [0.99–1.27]	0.09	1.04 [0.98–1.11]	0.19
Chronic Obstructive Pulmonary Disease	1.65 [1.19–2.28]	0.003	1.44 [1.24–1.68]	< 0.001
Medication Count on Discharge (per drug)	1.01 [0.98–1.05]	0.63	1.02 [1.00–1.03]	0.08
Maximum CRP Reading (per mg/L)	1.000 [0.998–1.001]	0.77	1.000 [0.999–1.001]	0.84
Time to half maximum CRP (per week)	0.997 [0.991–1.002]	0.23	1.000 [0.999–1.001]	0.87

Table 3 Multivariate Cox regression analysis – time to readmission censored at 30 days

Variable in Analysis	Risk of readmission (censored at 30 days or death)		Risk of readmission or death (censored at 30 days)	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Age (per year)	0.98 [0.96–1.00]	0.04	0.98 [0.96–1.00]	0.06
Female Sex	0.76 [0.57–1.00]	0.05	0.76 [0.57–1.00]	0.05
Admission Barthel score (per point)	1.04 [1.00–1.08]	0.07	1.03 [1.00–1.07]	0.08
Discharge Home	0.54 [0.38–0.77]	0.001	0.51 [0.36–0.72]	< 0.001
Length of Hospital Stay (per day)	0.994 [0.991–0.998]	0.003	0.994 [0.990–0.998]	0.001
Previous Myocardial Infarction	1.25 [0.88–1.77]	0.21	1.19 [0.84–1.68]	0.32
Congestive Cardiac Failure	1.54 [1.02–2.34]	0.04	1.65 [1.10–2.47]	0.02
Previous Diagnosis of Cancer	1.33 [0.91–1.95]	0.14	1.30 [0.89–1.90]	0.18
Diabetes Mellitus	1.24 [0.89–1.72]	0.21	1.24 [0.89–1.72]	0.20
COPD	1.34 [0.94–1.90]	0.11	1.34 [0.95–1.90]	0.10

COPD Chronic obstructive pulmonary disease

selected for rehabilitation. Another possible explanation is that the rehabilitation team might view very old patients as at higher risk than younger patients, and accordingly plan discharges in such a way to mitigate this risk.

An association between shorter length of stay and increased risk of readmission has previously been reported for older patients discharged from acute hospitals [32–34]. However, we found only a small effect of length of stay on readmission risk; perhaps because patients admitted for rehabilitation have a relatively long length of stay, allowing comprehensive discharge planning and recovery from acute illness. The incremental benefit from an even longer stay may thus be minimal.

The discriminant ability of the risk factors we measured to predict future readmission was poor – too poor to be of use in planning clinical services. A systematic review for risk prediction models for hospital readmission reported that most current readmission risk prediction models, whether designed for comparative or clinical purposes, perform poorly [8]. The review looked at 30 studies that assessed 26 unique models, and commented that few of these examined variables associated with overall health and function, illness severity, or social determinants of health. This lack may be particularly important for older patients where social determinants of health alongside broader markers of function are crucial in terms of planning both primary, secondary and social care services.

Reducing readmissions in this patient group will be challenging. A systematic review of both in-hospital (17 studies) and home-care (15 studies) interventions aimed at reducing readmissions for in older people (> 75 years old) found that most did not have any effect on readmission [34]. However, those interventions with home-care

Table 4 Multivariate Cox regression analysis – time to readmission, censored at 180 days

Variable in Analysis	Risk of readmission (censored at 180 days or death)		Risk of readmission or death (censored at 180 days)	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Age (per year)	0.99 [0.98–1.00]	0.03	0.99 [0.98–1.00]	0.01
Female Sex	0.80 [0.71–0.91]	0.001	0.77 [0.69–0.87]	< 0.001
Admission Barthel score (per point)	0.99 [0.98–1.01]	0.44	0.98 [0.79–0.92]	0.03
Discharge Home	1.02 [0.86–1.21]	0.85	0.79 [0.68–0.92]	0.003
Length of Hospital Stay (per day)	0.997 [0.995–0.998]	< 0.001	0.995 [0.994–0.997]	< 0.001
Previous Myocardial Infarction	1.21 [1.03–1.42]	0.02	1.25 [1.07–1.45]	0.004
Congestive Cardiac Failure	1.48 [1.22–1.79]	< 0.001	1.57 [1.31–1.88]	< 0.001
Previous Diagnosis of Cancer	1.30 [1.10–1.55]	0.003	1.48 [1.27–1.73]	< 0.001
Diabetes Mellitus	1.00 [0.94–1.07]	1.00	0.99 [0.86–1.15]	0.93
COPD	1.24 [1.06–1.46]	0.009	1.23 [1.05–1.43]	0.009
Medication Count on Discharge	1.01 [0.99–1.03]	0.28	0.99 [0.98–1.01]	0.41

COPD Chronic obstructive pulmonary disease components were more likely to be successful [34]. There is current work in the United Kingdom bringing together health and social care, in part to try and start addressing these concerns. However, the proportion of readmissions that are deemed avoidable after standardized and reliable review is not high; recent research reports less than 20% of readmissions are avoidable [27]. Furthermore, although readmission and hospitalization are important markers for disease severity, prognosis and quality of life there are clearly limits to any single metric as a surrogate for standard of care.

Our results reinforce the need to take a multisystem, holistic approach to reducing readmissions. Whilst some success has been noted with disease-specific interventions, e.g. for patients with heart failure [35], it is unlikely that interventions targeting a single disease (e.g. heart failure) will be successful in reducing readmissions due to other disease diagnoses after an index admission. Indeed, a focus on a single disease risks generating unintended knock-on consequences – rigorous control of heart failure may increase the risk of readmission with dehydration or acute kidney injury for example. Although a measure of biological resilience (CRP recovery rate) did not provide a useful way of predicting readmission in this analysis, similar measures of frailty or resilience may still provide both a way of predicting readmission and provide a target for intervention to reduce readmissions. Furthermore, other studies looking at readmission from rehabilitation units have suggested that information on functional status measures that are easily monitored by health care providers may improve plans for smooth transition of care delivery and aid the reduction of risk for hospital readmission [11].

Our analysis has a number of strengths. We used detailed health and functional outcomes data on a large set of patients undergoing rehabilitation in a medicine for the elderly unit. Studies to date have not assessed readmission following in-patient rehabilitation in a general older rehabilitation population, and there are differences between this group of patients compared to older adults discharged directly from acute hospitals [10, 11]. As this study analyzed routinely collected data, the data represents real-world clinical information that enables greater generalizability of the results.

There are several limitations that deserve comment. Our data were examined retrospectively and were not collected with this study in mind. Data quality is usually imperfect in datasets of routinely collected clinical data, and not all patients had Barthel scores available for analysis. Although the range of discharge diagnoses that we could classify from discharge coding data was wide, such data depends on both accurate diagnosis and accurate recording of the discharge diagnoses for coding, which is not always the case in routine clinical care. Use of this source of diagnoses prevented us from including poorly-coded diagnoses such as dementia, and alternative sources (e.g. primary care records) were not available for linkage at the time of our analysis. The large number of reasons for the index hospital admissions precluded easy use of these reasons as a variable in the analyses of risk factors for readmission, but future work using larger datasets may be able to address this issue.

Patients who have been admitted to a rehabilitation unit have the ideal opportunity for discharge planning in a clinical environment geared towards optimizing hospital discharges. The results of our analysis may not necessarily be generalizable to other patients groups with shorter length of stay and less comprehensive discharge planning. Out of hospital care services have developed considerably since 2012 (the end of study period). Changes have included early community intervention services, Hospital @ Home teams and use of step-up intermediate care beds rather than admission to acute units. These changes have taken place in our locality after the end of the period studied in this analysis.

Conclusion

Our results confirm and extend previous work that readmissions of older people after hospital admission are due to a wide range of causes, and are often not due to a recurrence of the index problem. Work is needed to develop intervention packages that address readmission risks common to a range of diseases and syndromes of ageing, with a focus both on optimizing physiology, but also supporting patients and carers. In parallel, further work is required to identify those at highest risk of readmission so that such intervention packages can be targeted appropriately.

Abbreviations

CCF: Congestive cardiac failure; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CRP: C – reactive protein; eGFR: estimated glomerular filtration rate; HIC: Health Informatics Centre; ICD: International Classification of Diseases; IQR: Inter-quartile range; MDRD: Modification of Diet in Renal Disease Study (MDRD) equation; NHS: National Health Service; NI: Not included; SCI-DC: Scottish Care Information Diabetes Collaborative; SD: Standard deviation; USA: United States of America

Funding

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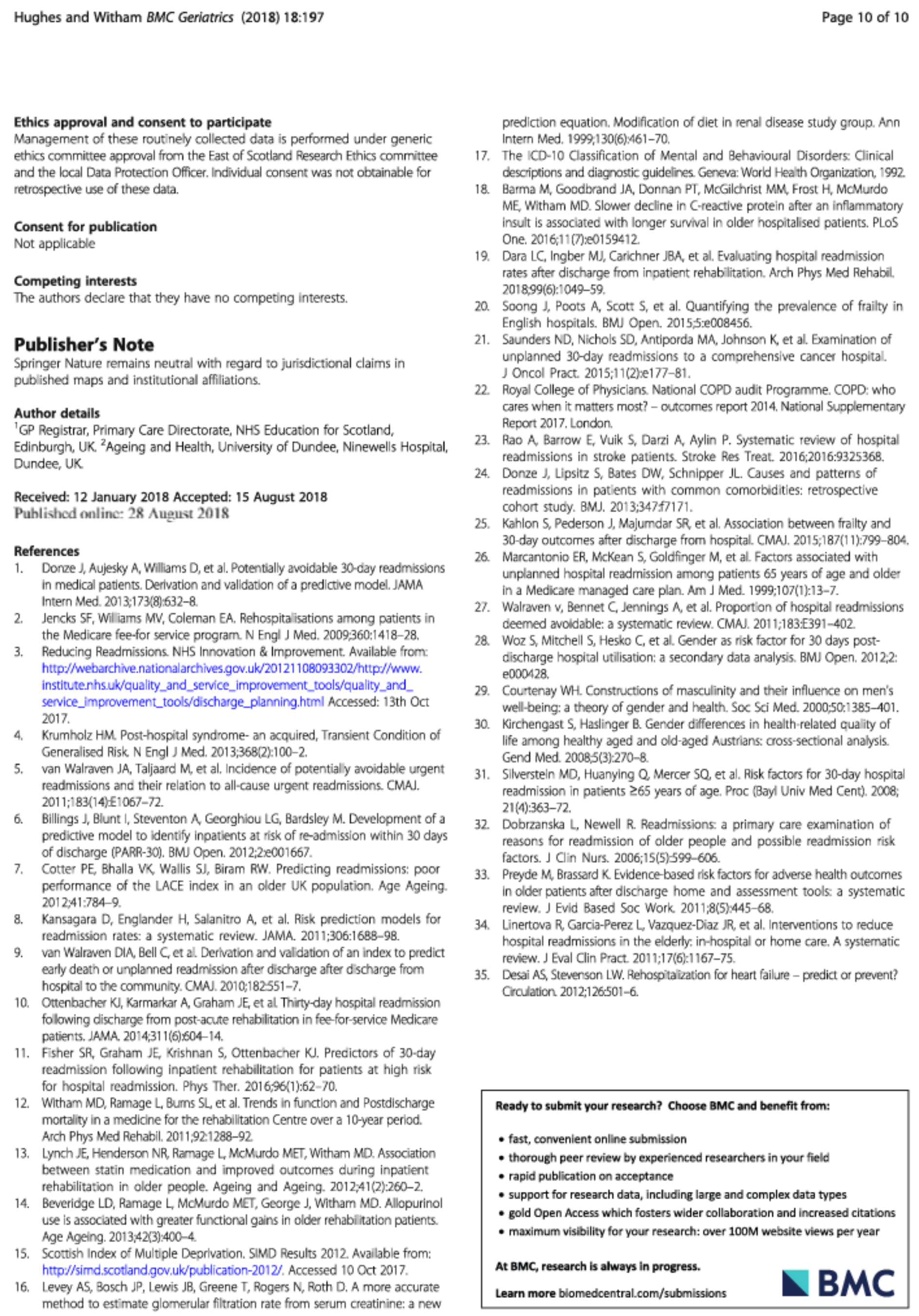
Availability of data and materials

Anonymised, linked routine healthcare data used in this analysis are held by the Health Informatics Centre (HIC), University of Dundee, in a Safe Haven environment. These data are not permitted to leave the safe haven environment, but access may be granted as part of collaborative work with University of Dundee authors. HIC may levy a charge for access to these data within the Safe Haven.

Authors' contributions

LDH and MDW co-designed and performed the analysis, cowrote the manuscript and both critically revised the manuscript. Both authors agree to be accountable for all aspects of the work.



Ethics approval and consent to participate
Management of these routinely collected data is performed under generic ethics committee approval from the East of Scotland Research Ethics committee and the local Data Protection Officer. Individual consent was not obtainable for retrospective use of these data.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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Appendix B: Copyright permission information for four papers to enable inclusion in this PhD by Published Works

Paper 1: Hughes LD. Utilizing Clinical Practice Guidelines in Multimorbid Older Patients – A Challenging Clinical Dilemma. *Journal American Academy of Geriatrics.* **2012**. 60:2180-1.

Licensed Content Publisher: John Wiley & Sons

License Number: 5232081091026.

License Date: January 18th 2022

Paper 2: Hughes LD, McMurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to older people with multiple co-morbidities*. Age Ageing* **2013**; 42:62-69

Licensed Content Publisher: Oxford University Press

License Number: 5232081317606.

License Date: January 18th 2022

Paper 3: Hughes LD, Hanslip J & Witham MD. Centrally Active Prescribing for Nursing Home Residents-how are we doing? *European Geriatric Medicine* **2012**. 3(5)304–307

Licensed Content Publisher: Elsevier

License Number: 220118-019177

License Date: January 21st 2022

Paper 5: Hughes LD, Cochrane L, McMurdo MET & Guthrie B. Psychoactive Prescribing for Older People – What difference does 15 years make? *International Journal of Geriatric Psychiatry*. **2016**;31(1):49-57

Licensed Content Publisher: John Wiley & Sons

License Number: 5232090537477.

License Date: January 18th 2022

Appendix C: Experience and Career Aspirations

I have undertaken a research orientated path during and following medical school. I completed my undergraduate MBChB with distinction at the University of Dundee and undertook an intercalated BSc in Care of Older People at Napier University (Distinction and University Medal). I started my research journey early in undergraduate training, and I attended several research conferences in the first 2 years of my degree and developed some basic understanding of research and was inspired by several leading academics from Tayside and Lothian.

I subsequently started completing components of the Good Clinical Practice programme at the Tayside Medical Science Centre, which provided extremely useful foundations in research principles and ethical considerations. Following this, I was awarded summer scholarships in consecutive years in 2011 (Population Science Clinical Summer Scholarship) and 2012 (Carnegie Vacation Undergraduate Scholarship & Muir Russell Studentship) which enabled funded time working with academics in primary care and geriatric medicine. These programmes were complemented by formal research training in quantitative research and medical statistics which I have subsequently been able to develop and hone over time. There was ad-hoc training on other methodologies such as case reports, and narrative reviews delivered by academics during these programmes as well. Both funded scholarships led to peer-reviewed academic publications.

During this time, I was also developing research presentation skills, with oral presentations at the Peninsula Trauma and Emergency Care Conference (2011) and the 17th International Network for Psychiatric Nursing Research (2011), alongside poster presentations at the British Geriatrics Society (2011) and the Academic Training in Research in Undergraduate Medicine (2011). During my undergraduate training, I was awarded various prizes including the Royal Society of Medicine John Fry Prize in 2012 for clinical research performed in a Dundee nursing home as an undergraduate student[2].

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[2] Hughes, LD & Adams L. Maximising sensory awareness for patients with dementia. *British Journal of Mental Health Nursing*. **2012.** 1(4):239-245.

I strongly believe that research requires rigorous peer review and publication so that the academic community can read, assess and consider implementation of new findings, and was aware of this early on in my training. I took an opportunity to develop editorial skills and experience by becoming the inaugural Editor of the Scottish Universities Medical Journal in 2011-12 and continued as an associate editor for 2 years. This was a steep-learning curve, as I developed a peer-review process, contributed material regularly, developed a website and formatting system to develop the journal. This, alongside my own personal research experience and training, improved my understanding of editorial processes and the journey of publication from developing a research question to peer-reviewed publication. As a postgraduate, I regularly review manuscripts for multiple journals which has been an invaluable way to develop critical appraisal skills for different methodologies alongside broadening my research interests. Currently, I am an Associate Editor for the journal BMC Family Practice (and Joint-Editor for Multimorbidity Special Issue) and continue to utilise training resources provided by Springer (in particular around critical appraisal).

I completed my postgraduate training in general practice in Fife obtaining MRCGP in April 2020, becoming increasing involved in clinical audit and quality improvement programmes. I have furthered my interests in medicine for the elderly and healthcare management obtaining a post graduate clinical diploma in geriatric medicine (2017) and a postgraduate diploma in advanced primary care management (2020). The latter programme was extremely useful as I improved my understanding of relational approaches to change and innovation and adapted my critical appraisal skills to assess different options for development of primary care systems. As part of the programme, I completed projects looking at areas I had previously not investigated, such as leadership and management domains and considered commissioning in relation to service re-design. This was complemented further last year 2021 I completed the Edward Jenner programme run by the NHS Leadership Academy.

During my time as a registered PhD by Published Works student at Napier, I have completed several of the post-graduate teaching programmes about PhD viva process, placing research in context and using library resources fully. I have also thoroughly utilised the book by Susan Smith, *PhD by Published Work: A Practical Guide for Success*, as the way of writing the PhD is somewhat different from my previous endeavours. I had 1-day a week funded by National Education Scotland for 1-year, where I worked as a NES Academic GP Fellow at the University of St Andrews. As part of this I attended weekly meetings organised by the Population Science Division, which delivered training in several research methodologies alongside broader discussions about epidemiology and policy analyses.

My career aspiration is to become a senior clinical leader in primary care and contribute to improving the quality and impact of primary care provision for the community especially the elderly and vulnerable in society. I feel that my academic experience to date, and this PhD process has been invaluable in driving this aspiration towards reality. I aim to successfully apply for an NRS Career Research Fellowship at the end of the year to drive forwards further research around multimorbidity.

Appendix D: Research Training & Research Dissemination

Over the course of my registration as a PhD by Published Works candidate at Edinburgh Napier University, I have continued to train in research methods and have disseminated core messages from my PhD by Published Works.

Firstly, I have had several supervisory sessions with Iain Atherton (Director of Studies) discussing research methods and in particular the merits of certain methodologies in answering research questions. In relation to my PhD, we considered the strengths and limitations of the methods used, alongside what approaches may be more appropriate for future research questions of interest. This provided the basis for revisions to my thesis, with more discussion around research methodologies and ethical considerations (see Chapter 2). Exploratory discussions, and signposting to textbooks providing introductory analysis and background qualitative research has been really helpful as I shape my future research agenda. These supervisory meetings have built upon online training completed as an Editorial Board member for BMC Primary Care, *Focus on Peer Review Online Masterclass.* This programme reinforced points we considered in supervisory meetings around the appropriateness of certain research methods in relation to heterogeneous research topics, and the challenges of single-centre studies and case studies.

Secondly, I have completed the National Education Scotland, Scottish Improvement Leader (ScIL) Programme alongside other roles which have been placing my PhD findings into a real-work context. The ScIL Programme is a quality improvement course which has supported me in my role as a Clinical Lead for the Perth City Hospital @ Home service. Over the 9-month programme, I have been supported and been provided with useful training around the design, development and delivery of a quality improvement project. I have implemented the pilot project phase and evaluated the Perth City Hospital @ Home programme, with multimorbidity and themes from my PhD being a key part of this programme and indeed engagement work. The ScIL programme has provided an excellent foundation for practical clinical and managerial leadership and training within quality improvement methodology. Reflecting upon the similarities and differences between quality improvement and research methodologies have been beneficial as both will play an important aspect of my career development.

The ScIL programme complemented my active interest in the broader aspects of primary care delivery. Indeed, I am a member of the Fife Local Medicine Committee and this experience has been invaluable. I have seen the design and implementation of policies during the current pandemic and now have a deeper understanding of the structure and delivery of primary care services in a regional context. Themes identified within the thesis, particular around health inequality, patient centred care and de-prescribing have been really important as part of broader NHS Fife work-streams within the Fife Health & Social Care Partnership. On a national level, I serve on the British Geriatrics Society GP Working Group, with frailty and multimorbidity being a fundamental aspect of health policy discussions.

Thirdly, I have made efforts to disseminate aspects of my clinical research findings and PhD by Published Works narrative findings. This has included presenting conclusions from my guideline work to GP practice colleagues, alongside exploring how targeted adjustment of our chronic disease management annual reviews can address some of these challenges. This is the basis of practice quality improvement work and will be fed to the GP cluster quality improvement forum. I have presented overall summary of the PhD by Published Works to the University of St Andrews School of Medicine department and received some very helpful feedback regarding the development of further work. Indeed, I have been involved in some recent academic submissions around multimorbidity clustering.

Overall, I have developed a wide array of research skills during the near decade where I have been involved in clinical research the result of which can be seen within the papers themselves and narrative thesis. The process of completing the PhD by Published Works has provided an opportunity to reflect on my previous work and place it in a current context alongside considering the changes which have arisen over the period of time the work was published. Over my period of registration, this process alongside focused consideration of research methodologies have been helpful in developing me as a researcher and planning my next steps towards academic development.

I aim to successfully apply for an NRS Career Research Fellowship at the end of the year to drive forwards further research around multimorbidity. Research ideas include exploring the perceived challenges by GPs of managing patients with multimorbidity and performing de-prescribing within 10-minute consultation, out of hours interactions for patients with complex multimorbidity by analysing free-text consultations notes and using patient vignette to explore GP (de)-prescribing decisions and referral decisions for patients with multimorbidity.

Appendix E: Curriculum Vitae

Name	Lloyd D Hughes
Date of Birth	14th August 1989
Job Title	General Practitioner
GMC Number:	7451823
Email	Lloyd.Hughes@nhs.scot

Personal Profile

I am a primary care physician who is committed to a career that encompasses research focused upon improving the delivery of high-quality care to all but especially the elderly in society. My current goals are to complete a PhD by Published Works and undergo further research training in qualitative research methodology, with the aim of moving into medical leadership and management.

Current Employment

1) **General Practitioner (Partner):** Tayview Medical Practice, NHS Fife [April 2022- Present]

2) **Clinical Lead for Primary Care & Preventative Healthcare in Forensic & Rehabilitation Psychiatry**: Stratheden Psychiatric Hospital, NHS Fife [February 2024 – Present]

3) **Communication Skills Clinical Tutor & Honorary Clinical Lecturer**: University of Dundee (May 2020 – Present)

4) **Honorary Clinical Lecturer:** University of St Andrews (August 2022 – Present)

Professional Membership

- Membership of Royal College of General Practitioners, UK - 2020

Previous Posts (most recent first)

- *GP with Special Interest in Geriatric Medicine & Clinical Lead for Perth City Hospital @ Home*, NHS Tayside [April 2022 – May 2023]

- *Salaried General Practitioner: Primary Care Emergency Service*, NHS Tayside [May 2020 – February 2023]

- *National Education Scotland Academic GP Fellow***,** University of St Andrews (August 2021 – July 2022)

- *Salaried GP, East Practice Arbroath, NHS Tayside (May 2020 - December 2021)*

- *Locum General Practitioner*, *multiple sites across NHS Tayside & NHS Fife. (May 2020 to March 2022)*

- *General Practice Specialty Trainee. NHS Fife (Feb 2017 – April 2020)*

- *Medical Practitioner, Care of the Elderly. NHS Fife (Feb 2019 – April 2020)*

In my GPST3 year, I worked 4 days in general practice and 1 day as a medical practitioner in care of the elderly after arranging this post with geriatric medicine team in the locality. This extended my training my 3 months, but provided an excellent exposure to psychogeriatrics, Hospital @ Home care, liaison nursing home work, front door frailty teams and geriatric day hospital work.

- *Clinical Fellow in Geriatric Medicine & Stroke, NHS Lothian (August 2016 – Feb 2017)*

- *Academic Foundation Doctor 1+2, NHS Tayside (Aug 2014 – Aug 2016)*

Education & Qualifications

- ***Scottish Improvement Leader Programme –*** National Education Scotland. 2023.
- ***Certificate in Commissioning and Purchasing for Public Care –*** Institute of Public Care. 2023.
- ***The Edward Jenner programme –*** NHS Leadership Academy. 2021.
- ***Diploma in Advanced Primary Care Management*** – Healthcare Financial Management Association. 2020.

- ***Diploma in Geriatric Medicine*** – Royal College of Physicians London. 2017.
- ***University of Dundee Medical School*** (2008-2014) MBChB *Distinction*
- ***Edinburgh Napier University*** (2011/2012) - Intercalated BSc degree BSc Care of Older People *Distinction and University Medal*
- ***Diploma in Advanced Primary Care Management*** – Healthcare Financial Management Association. 2020.

Awards and prizes

- ***2019 Royal Society of Medicine General Practice with Primary Healthcare Section John Fry Prize - Runner-Up*** for work entitled, 'Characterising Nursing Home Residents & Reviewing GP In-Hour Unscheduled Visits To Nursing Homes in a Scottish GP Practice'.
- ***2015 Royal Society of Medicine Geriatrics & Gerontology Section - Shortlisted*** for the *Clinical Governance and Audit Prize* and awarded oral presentation.
- **2013 Ethicon Trophy, University of Dundee - Runner-Up** for work entitled 'Non-Pharmaceutical management of challenging behaviour in patients with dementia in a nursing home setting'.
- **2012 Royal Society of Medicine General Practice with Primary Healthcare Section John Fry Prize - Winner** for work entitled: 'Non-Pharmaceutical management of challenging behaviour in patients with dementia in a nursing home setting'. Invited oral presentation.
- ***2012 Peninsula Trauma and Emergency Care Conference Undergraduate Essay Competition – Winner*** for essay entitled 'Recognising the challenges of providing quality emergency care to an ageing population'. Invited oral presentation at conference.
- ***2012 Substance Misuse Management in General Practice Undergraduate UK Essay Prize - Runner-Up*** for essay entitled 'How should healthcare students view addiction?'
- ***2011 Academic Training in Research in Undergraduate Medicine (Edinburgh) - Awarded the 'Best Medical Poster' prize***

Scholarships & Studentships

- ***2012 Carnegie Vacation Undergraduate Scholarship*** and the ***Muir Russell Studentship*** to study cumulative drug prescribing in older patients in NHS Tayside. ***2011 'Population Science Clinical Summer Scholarship'*** (University of Dundee) - Awarded after competitive process. This enabled me to carry out a 6-week research project entitled: 'Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to older people with multiple co-morbidities.'

Committee Roles

- GP Co-Lead for the Community and Primary Care Group (CPCG) within the British Geriatrics Society. October 2022 - Present
- Member of the GP with Special Interest in Geriatric Medicine Group (British Geriatrics Society) 2018 – Present
- Elected Associate in Training Committee Member. RCGP Scotland AiT / First5 Committee. Dec 2019 – Dec 2020
- Member of the Fife Local Medicine Committee Ltd. Dec 2019 - Present

Editorships & Journal Reviewer

- Associate Editor for BMC Primary Care (June 2020 – October 2023)

Selected Peer reviewed Publications

1. **Hughes LD** (2024). Commentary on: Are multimorbidity patterns associated with fear of falling in community-dwelling older adults? ***Journal of Frailty, Sarcopenia and Falls***. Accepted In-Press
2. Fagbamigbe AF, Agrawal U, Azcoaga-Lorenzo A, MacKerron B, Özyiğit EB, Alexander DC, Akbari A, Owen RK, Lyons J, Lyons RA, Denaxas S, Kirk P, Miller AC, Harper G, Dezateux C, Brookes A, Richardson S, Nirantharakumar K, Guthrie B, **Hughes LD**, Kadam UT, Khunti K, Abrams KR, McCowan C (2023). Clustering long-term health conditions among 67728 people with multimorbidity using electronic health records in Scotland. ***PLoS One***. 18(11):e0294666. PMID: 38019832

3. **Hughes LD** (2022). Exploring the Relationship between Falls in Long Term Care and Psychoactive Prescribing. ***J Frailty Aging.*** 11(4):416-419. PMID: 36346728
4. **Hughes LD** (2022). Understanding the processes behind the decisions – GPs and complex multimorbidity decision making. ***BMC Primary Care***. 23:162. PMID: 35761167
5. **Hughes LD** (2021). Changes in clinical manifestation of fibromyalgia syndromes after Alzheimer's disease diagnosis. ***Proc (Bayl Univ Med Cent),*** 34:4, 523-526. PMID: 34219947
6. **Hughes LD** & Keeble M (2019). Investing in Social Care to Reduce Healthcare Utilization: Important Considerations for Policy Makers. ***Br J Gen Pract.*** 70(690):4-5. PMID: 31879287
7. **Hughes LD**, Murphy F & Findlay D (2019). Assessment and Treatment of Depression for Patients with Dementia. ***Br J Hosp Med (Lond).*** 80 (3): 151-156. PMID: 30860908
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10. **Hughes LD** & Love G (2018). Incidental Hip Fracture in Out-Patient Clinic – The Importance of Patient Centred Assessment. ***Journal of Primary Health Care Medicine***. 2018;10(2):176–178. PMID: 30068474
11. Goodbrand JA, **Hughes LD**, Cochrane L, Donnan PT, McGilchrist M, Frost H, McMurdo ME & Witham MD (2017). Association between bisphosphonate therapy and outcomes from rehabilitation in older people. ***Arch Gerontol Geriatr.*** 70:195-200. PMID: 28214400
12. **Hughes LD**, Raitt N, Riaz MA, Baldwin SJ, Erskine K, Graham G. Primary Care Hypnotic and Anxiolytic Prescription - Reviewing Prescribing Practice Over Eight Years (2016). ***Journal of Family Medicine and Primary Care.*** 5(3): p.652-657. PMID: 28217600
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14. **Hughes LD** (2014). The Transplant Patient and Transplant Medicine in Family Practice ***Journal of Family Medicine and Primary Care.*** 3:345-54. PMID: 25657941
15. **Hughes LD**, Zammit K & Cordina J (2014). Restraint and the older patient: complicated practical medicine. ***British Journal of Nursing*** 23(3): 130-1 PMID: 24526018
16. **Hughes LD**, McMurdo MET, Guthrie B (2013). Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to older people with multiple co-morbidities. ***Age Ageing*** 42(1): 62-69 PMID: 22910303
17. **Hughes LD** & Pearson A (2013). Encouraging Healthy Ageing - a Vital Part of NHS Reform. ***British Journal of Nursing*** 22(3): p.174-178 PMID: 23411827
18. **Hughes LD** (2013). Changes in the clinical manifestation of fibromyalgia in an individual with dementia. ***Journal American Academy of Geriatrics*** 61 (12) p.2260-2261 PMID: 24329842
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